

# Simultaneous ST-elevation in lead augmented vector right (aVR) and III in non-ST-elevation acute coronary syndromes

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**Background:** The value of ST-elevation in lead augmented vector right (aVR) remains controversial in clinical practice. This study aimed to investigate the association of simultaneous ST-elevation in lead aVR and III with angiographic findings and clinical outcomes in patients with non-ST-elevation acute coronary syndromes (NSTEACS).

**Methods:** In this observational study, patients who had been diagnosed with NSTEACS and presented with ST-elevation in lead aVR and without ST-elevation in any other two contiguous leads were enrolled from January 2018 to June 2019. Demographic, baseline clinical, angiographic and interventional characteristics as well as clinical outcomes were collected and recorded on standardized case report forms.

**Results:** A total of 157 patients meeting the criteria were finally enrolled in this study and classified into two groups according to the presence of ST-elevation in lead III. Patients in the two groups were similar in average age and previous history of hypertension, diabetes mellitus, hyperlipidemia, chronic kidney disease, stroke, and peripheral vascular diseases (all P>0.05). Patients with ST-elevation in lead III tended to present with myocardial hypertrophy in the echocardiography (P=0.02). The cases with ST-elevation in lead III showed higher high sensitivity troponin T (hs-TnT; P=0.08) and creatinine kinase MB isoenzyme (CK-MB; P<0.01) whereas those without ST-elevation in lead III showed higher N-terminal pro brain natriuretic peptide (NT-proBNP; P=0.02). Of note, patients with ST-elevation in lead III presented with more ST-depression in multiple leads [especially in lead I, augmented vector left (aVL), V3–V6] as well as higher degree of ST-depression (all P<0.05) and were more likely to develop multi-vessel and left main trunk (LM) lesions (P=0.04), with 20% of the cases having a LM lesion and 60% having triple vessel lesions. Patients with ST-elevation in lead III were at increased risk of 3-year major adverse cardiovascular events (MACEs), despite no significant statistical difference between the two groups (hazard ratio =1.29; P=0.26).

Conclusions: The NSTEACS cases with simultaneous ST-elevation in lead III and aVR tended to present

T-depression, and more LM or multi-

with more multiple leads with ST-depression, higher degree of ST-depression, and more LM or multivessel lesions, suggesting a broader range of severe myocardial ischemia. The concurrent presentation of STelevation in lead III and aVR may play a vital role in the diagnosis, risk-stratification, and prediction of poor prognosis during the management of NSTEACS patients.

**Keywords:** Simultaneous ST-elevation in augmented vector right and III (simultaneous ST-elevation in aVR and III); coronary angiography; non-ST-elevation acute coronary syndromes (NSTEACS)

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# Introduction

The electrocardiogram (ECG) at admission plays a vital role in the early risk stratification and effective management of patients diagnosed with non-ST-elevation acute coronary syndromes (NSTEACS), which comprise heterogeneous groups with variable prognosis (1). The role of ST-elevation in the lead augmented vector right (aVR) in predicting the clinical outcomes remains controversial and is often ignored in clinical practice in the past. In recent years, studies have increasingly suggested that ST-elevation in the lead aVR is an important signal indicating left main or 3-vessel disease, urging doctors to initiate antithrombotic therapies and identify those potential high-risk patients requiring urgent revascularization (2-5). Isolated ST-elevation in

## Highlight box

#### Key findings

 Simultaneous ST-elevation in lead III and augmented vector right (aVR) in non-ST-elevation acute coronary syndromes (NSTEACS) patients were associated with more multiple leads with STdepression, higher degree of ST-depression and more left main or multi-vessel lesions, indicating a vital sign of broader range of severe myocardial ischemia during the management of NSTEACS patients.

#### What is known and what is new?

- The role of ST-elevation in the lead aVR in predicting the clinical outcomes remains controversial and is often ignored in clinical practice.
- Simultaneous ST-elevation in the lead III and aVR may be a vital sign of more severe myocardial ischemia during the management of NSTEACS patients.

#### What is the implication, and what should change now?

 We should pay more attention to simultaneous ST-elevation in the lead III and aVR during the management of NSTEACS patients. the lead aVR together with multi-lead ST depression was added to the 2013 American College of Cardiology Foundation/American Heart Association (ACCF/AHA) guideline for the management of ST-elevation myocardial infarction (STEMI) as a potential STEMI (6), which is also indicated in the 2017 European Society of Cardiology (ESC) guideline for STEMI (7) and 2020 ESC guideline for non-ST-elevation myocardial infarction (NSTEMI) (8). However, other study indicated that ST-elevation in aVR did not yield any additional prognostic information beyond comprehensive risk assessment (9). Harhash et al. reported that ST-elevation in aVR with multi-lead ST depression was associated with acute thrombotic coronary occlusion in only 10% of patients (10). A majority (63%) of patients presented with ST-elevation in other leads besides aVR but none were diagnosed with STEMI who have two contiguous leads with ST-elevation (4). We considered the controversial results partially due to the heterogeneity of the study population and various management of these high-risk patients in different centers. Besides, the controversy may highlight the complexity of ECG changes with clinical outcomes. There is a need for more evidence to gain a deeper knowledge of the predictive value of STelevation in aVR in the diagnosis and risk stratification of NSTEACS. In previous management of NSTEACS, we have recognized that some patients presented with STelevation in lead aVR accompanied with ST-elevation in lead III (which is the nearest lead to aVR), but without STelevation in lead II and aVF. The value of ST-elevation in lead aVR and III simultaneously remains unknown. This study aimed to investigate the association of simultaneous ST-elevation in lead aVR and III with angiographic findings and clinical outcomes in patients with NSTEACS, compared to ST-elevation in lead aVR but not in III. We present this article in accordance with the STROBE reporting checklist (available at https://jtd.amegroups.com/

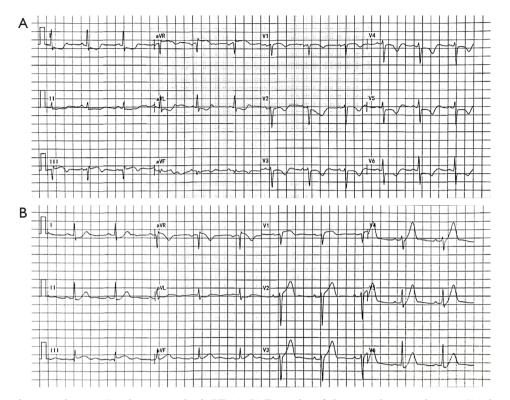


Figure 1 Electrocardiogram showing ST-elevation in lead aVR. (A,B) Examples of electrocardiogram showing ST-elevation in lead aVR without ST-elevation in any other two contiguous leads. aVR, augmented vector right; aVL, augmented vector left; aVF, augmented vector foot.

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# Methods

# Study design and population

This is a single-center, retrospective, observational cohort study. From January 2018 to June 2019, patients with acute chest pain admitted to the emergency room of Zhongshan Hospital Fudan University, diagnosed with NSTEACS, presented with ST-elevation in lead aVR, and without ST-elevation in any other two contiguous leads (*Figure 1A,1B*) were enrolled in this study. The exclusion criteria included tachycardia and serious medical conditions (not resulting from coronary artery disease), such as pulmonary emboli, subarachnoid hemorrhage, aortic dissection, sepsis, hypoperfusion, shock, hypoxemia, and so on. Those who refused to undergo coronary angiography and lost to follow up were also excluded from this study. Finally, a total of 157 patients were enrolled and divided into two groups according to the presence of ST-elevation in lead III (*Figure 2*). All the participants were followed up for 3 years via phone call every year. Demographic, clinical, and angiographic characteristics as well as clinical outcomes [major adverse cardiovascular events (MACEs), the composite of all-cause death, nonfatal myocardial infarction, and stroke] were collected on standardized case report forms. All ECG and echocardiographic data were evaluated according to the guidelines by the doctors from the ECG and Echocardiography Department of Zhongshan Hospital, who were blind to clinical data and outcomes. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013) and was approved by the Ethics Committee of Zhongshan Hospital Fudan University (No. B2018-263). Individual consent for this retrospective analysis was waived.

# Angiographic data

Coronary arteries were cannulated through a radial approach with 6 F catheters and recorded at a rate of 30 frames/second. Significant stenosis was defined as

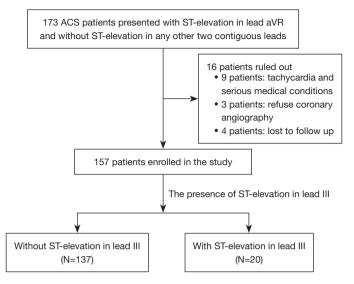


Figure 2 Flowchart of patient enrollment. ACS, acute coronary syndromes; aVR, augmented vector right.

 $\geq$ 70 narrowing in reference to the diameter of the adjacent normal segment of the coronary artery. Multi-vessel lesions were defined as significant stenoses involving three main epicardial coronary arteries, namely the left anterior descending (LAD), left circumflex (LCX), and right coronary (RCA) arteries. Angiographic data were interpreted at the core lab by two operators, who were blind to clinical data and outcomes.

# Statistical analysis

All the statistical analyses were conducted using Stata version 11.0 (StataCorp., College Station, TX, USA). Baseline characteristics between two groups were compared using the chi-square test for categorical variables and the Wilcoxon test for continuous variables. The hazard ratio (HR) and P value of developing 3-year MACE were calculated from Cox proportional hazard regressions, with adjustment for age, sex, body mass index (BMI), smoking status, systolic blood pressure, diabetes status, and total cholesterol. A P value <0.05 was considered statistically significant.

# Results

A total of 157 patients meeting the criteria were finally enrolled in this study. They were classified into two groups according to the presence of ST-elevation in lead III in ECG, including 137 patients (87.3%) without STelevation in lead III and 20 patients (12.7%) with ST- elevation in lead III.

# Demographic and clinical characteristics

There were more males in the group with ST-elevation in lead III (with ST-elevation in lead III vs. without STelevation in lead III: 90.0% vs. 68.6%, P=0.36). Patients in the two groups were similar in the average age and previous history of hypertension, diabetes mellitus, hyperlipidemia, chronic kidney disease, stroke, and peripheral vascular diseases. More patients without STelevation in lead III had undergone percutaneous coronary intervention (PCI) previously (with ST-elevation in lead III vs. without ST-elevation in lead III: 5.0% vs. 25.5%, P=0.03). Interestingly, patients with ST-elevation in lead III were more likely to present with myocardial hypertrophy in the echocardiography (with ST-elevation in lead III vs. without ST-elevation in lead III: 60.0% vs. 33.6%, P=0.02). Patients with ST-elevation in lead III showed higher high sensitivity troponin T (hs-TnT) (with ST-elevation in lead III vs. without ST-elevation in lead III: 0.21±0.03 vs. 0.12±0.04 ng/mL, P=0.08) and creatinine kinase MB isoenzyme (CK-MB) (with ST-elevation in lead III vs. without ST-elevation in lead III: 45.85±11.56 vs. 25.79±2.23 U/L, P<0.01), whereas those without STelevation in lead III showed significantly higher N-terminal pro brain natriuretic peptide (NT-proBNP) (with STelevation in lead III vs. without ST-elevation in lead III: 701.55±146.07 vs. 2,288.74±400.24 pg/mL, P=0.02). These

Table 1 Baseline characteristics in enrolled patients with and without ST-elevation in lead aVR

Baseline characteristics	Without ST-elevation in lead III (n=137)	With ST-elevation in lead III (n=20)	P value
Male, n (%)	94 (68.6)	18 (90.0)	0.36
Age (years), mean ± SD	67.9±1.0	69.1±2.8	0.43
Previous history, n (%)			
Hypertension	94 (68.6)	12 (60.0)	0.30
Diabetes mellitus	47 (34.3)	3 (15.0)	0.07
Hyperlipidemia	4 (2.9)	2 (10.0)	0.17
Chronic kidney disease	9 (6.6)	3 (15.0)	0.18
Stroke	14 (10.2)	0 (0.0)	0.14
Peripheral vascular diseases	8 (5.8)	1 (5.0)	0.68
PCI	35 (25.5)	1 (5.0)	0.03
Myocardial hypertrophy, n (%)	46 (33.6)	12 (60.0)	0.02
Thickness of IVS (mm), mean $\pm$ SD	10.8±0.1	11.9±0.4	0.88
Left ventricular ejection fraction (%), mean $\pm$ SD	57.8±9.2	54.4±10.5	0.25
Heart failure (EF <50%), n (%)	23 (16.8)	5 (25.0)	0.36
Aortic stenosis (moderate and severe), n (%)	3 (2.2)	0 (0.0)	0.56
Left ventricular high voltage, n (%)	19 (13.9)	5 (25.0)	0.17
Heart rate (beat per minute), mean $\pm$ SD	88.5±1.9	81.3±3.1	0.07
Sinus rhythm, n (%)	123 (89.8)	18 (90.0)	0.66
Atrial fibrillation, n (%)	14 (10.2)	2 (10.0)	0.66
Cardiac markers			
Hs-TnT (ng/mL), mean $\pm$ SD	0.12±0.04	0.21±0.03	0.08
Hs-TnT positive, n (%)	84 (61.3)	16 (80.0)	0.14
CK-MB (U/L), mean ± SD	25.79±2.23	45.85±11.56	<0.01
NT-proBNP (pg/mL), mean ± SD	2,288.74±400.24	701.55±146.07	0.02

aVR, augmented vector right; SD, standard deviation; PCI, percutaneous coronary intervention; IVS, interventricular septum; EF, ejection fraction; Hs-TnT, high sensitivity troponin T; CK-MB, creatinine kinase MB isoenzyme; NT-proBNP, N-terminal pro brain natriuretic peptide.

results suggested a potentially more severe and urgent myocardial injury in the cases with ST-elevation in lead III. Meanwhile, higher NT-proBNP levels and relatively higher percentage of hypertension, diabetes, stroke, peripheral vascular diseases, and previous history of PCI indicated chronic rather than acute onset of the disease with more complications in the patients without ST-elevation in lead III (*Table 1*).

# ECG characteristics

There was no significant difference in the degree of ST-

elevation in lead aVR. As for the ST-segment changes in lead III, the patients with ST-elevation in lead III presented with ST-elevation of 1.28±0.75 mm while those without ST-elevation in lead III presented with ST-depression of 0.97±0.58 mm in 58 (42.3%) patients. We also investigated the ST-segment changes in other leads besides lead aVR and III. More patients showed ST-depression in lead augmented vector left (aVL) and V2 in the group with ST-elevation in lead III. Of note, we identified a higher percentage with ST-depression in multiple leads (especially in the lead I, aVL, V3–V6) and a higher degree of ST-depression in the group with ST-elevation in lead III, suggesting a broader

range and more severe myocardial ischemia and a potential role of ST-elevation in lead III in predicting multi-vessel lesions and left main trunk (LM) lesion. Besides, we also recognized ST-elevation in other leads except lead aVR and lead III in a few cases. A total of four cases showed ST-elevation in lead aVL but not in lead III, which did not occur in the cases with ST-elevation in lead III. STelevation in V1 occurred in 16 cases (11.7%) without STelevation in lead III and 5 cases (25.0%) with ST-elevation in lead III, without statistical difference between the two groups. A total of 10 cases (7.3%) without ST-elevation in lead III and 1 case (5.0%) with ST-elevation in lead III presented with ST-elevation in lead V2 (*Table 2*).

# Angiographic and interventional characteristics

More patients with ST-elevation in lead III tended to develop multi-vessel and LM lesions. Some 20% of the cases had LM lesion and 60% of the cases had triple vessel lesions in the group with ST-elevation in lead III. There was no significant difference in the occurrence of the single LAD, LCX, or RCA lesion between the two groups. These results added the evidence of the ST-elevation in lead III in predicting the multi-vessel and LM lesions (*Table 3*). More patients with ST-elevation in lead III underwent emergent PCI (<24 hours, in NSTEACS cases with extremely-highrisk and high-risk features according to guidelines). The percentages of intervention of different target vessels were similar between the two groups. Besides, 5 patients (3.6%)

Table 2 ST-elevation or depression in different leads

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 (*Table 3*).

#### Follow-up

All the participants were followed up for 3 years. Patients with ST-elevation in lead III were at increased risk of 3-year MACE (HR =1.29; P=0.26). The mortality rate in-hospital and out-of-hospital were similar between the two groups. More patients with ST-elevation in lead III experienced non-fatal myocardial infarction, suggesting more severe coronary lesions, consistent with previous findings (*Figure 3, Table 4*).

# Discussion

Over the past two decades the critical role of lead aVR has attracted increasing interest due to its possible association with left main or triple-vessel coronary artery disease or, as emphasized more recently, potential left main or proximal LAD occlusion. However, the sensitivity and specificity of lead aVR in the diagnosis remains controversial (11-13), urging us to conduct further investigation to gain a deeper knowledge of ST-elevation in aVR.

Our study demonstrated that the patients with STelevation in lead aVR and lead III tended to have more multi-vessel and left main lesions compared to those with ST-elevation in lead aVR but not lead III (70.0% vs. 47.4%, P=0.04). More patients in the group with ST-

ECG lead	Without ST-elevation in lead III (n=137)	With ST-elevation in lead III (n=20)	P value
Lead I			
ST-depression, n (%)	97 (70.8)	18 (90.0)	0.19
ST-depression (mm), mean $\pm$ SD	0.93±0.48	1.79±0.81	0.02
Lead II			
ST-depression, n (%)	115 (83.9)	15 (75.0)	0.52
ST-depression (mm), mean $\pm$ SD	1.23±0.67	1.14±0.63	0.91
Lead III			
ST-elevation, n (%)	0 (0.0)	20 (100.0)	-
ST-elevation (mm), mean $\pm$ SD	_	1.28±0.75	-
ST-depression, n (%)	58 (42.3)	0 (0.0)	-
ST-depression (mm), mean $\pm$ SD	0.97±0.58	_	_

Table 2 (continued)

Table 2 (continued)

ECG lead	Without ST-elevation in lead III (n=137)	With ST-elevation in lead III (n=20)	P value
Lead aVR			
ST-elevation, n (%)	137 (100.0)	20 (100.0)	-
ST-elevation (mm), mean $\pm$ SD	1.04±0.51	1.25±0.59	0.21
Lead aVL			
ST-elevation, n (%)	4 (2.9)	0 (0.0)	0.58
ST-elevation (mm), mean $\pm$ SD	0.875±0.25	-	-
ST-depression, n (%)	41 (29.9)	17 (85.0)	0.01
ST-depression (mm), mean $\pm$ SD	0.72±0.31	1.52±1.02	0.007
Lead aVF			
ST-depression, n (%)	82 (59.9)	8 (40.0)	0.52
ST-depression (mm), mean $\pm$ SD	1.03±0.59	1.18±0.59	0.64
Lead V1			
ST-elevation, n (%)	16 (11.7)	5 (25.0)	0.15
ST-elevation (mm), mean $\pm$ SD	1.31±0.57	1.4±0.55	0.98
ST-depression, n (%)	4 (2.9)	1 (5.0)	0.27
ST-depression (mm), mean $\pm$ SD	0.19±0.04	0.33±0.15	0.09
Lead V2			
ST-elevation, n (%)	10 (7.3)	1 (5.0)	0.58
ST-elevation (mm), mean $\pm$ SD	1.8±0.42	1±0.5	0.56
ST-depression, n (%)	24 (17.5)	10 (50.0)	0.01
ST-depression (mm), mean $\pm$ SD	1.56±0.86	2.17±1.22	0.12
Lead V3			
ST-depression, n (%)	69 (50.4)	12 (60.0)	0.56
ST-depression (mm), mean $\pm$ SD	1.88±1.12	3.08±2.06	0.004
Lead V4			
ST-depression, n (%)	112 (81.8)	15 (75.0)	0.43
ST-depression (mm), mean $\pm$ SD	2.16±1.26	3.33±2.08	0.002
Lead V5			
ST-depression, n (%)	122 (89.1)	18 (90.0)	0.92
ST-depression (mm), mean $\pm$ SD	2.20±1.34	3.00±1.80	0.03
Lead V6			
ST-depression, n (%)	122 (89.1)	18 (90.0)	0.92
ST-depression (mm), mean $\pm$ SD	1.86±0.10	2.67±1.18	0.01

ECG, electrocardiogram; SD, standard deviation; aVR, augmented vector right; aVL, augmented vector left; aVF, augmented vector foot.

Angiographic and interventional characteristics	Without ST-elevation in lead III (n=137)	With ST-elevation in lead III (n=20)	P value
Angiographic characteristics, n (%)			
LM lesions	14 (10.2)	4 (20.0)	0.18
Single LAD lesions	13 (9.5)	1 (5.0)	0.44
Single LCX lesions	12 (8.8)	1 (5.0)	0.49
Single RCA lesions	7 (5.1)	1 (5.0)	0.73
Multi-vessel lesions	62 (45.3)	12 (60.0)	0.16
Multi-vessel or LM lesions	65 (47.4)	14 (70.0)	0.04
Interventional characteristics, n (%)			
Emergent PCI	84 (61.3)	16 (80.0)	0.11
LM PCI	16 (11.7)	5 (25.0)	0.10
LAD PCI	47 (34.3)	6 (30.0)	0.70
LCX PCI	43 (31.4)	8 (40.0)	0.44
RCA PCI	26 (19.0)	7 (35.0)	0.10
Multi-vessel PCI	41 (29.9)	9 (45.0)	0.18
Elective PCI	25 (18.2)	3 (15.0)	0.72

LM, left main trunk; LAD, left anterior descending artery; LCX, left circumflex artery; RCA, right coronary artery; PCI, percutaneous coronary intervention.

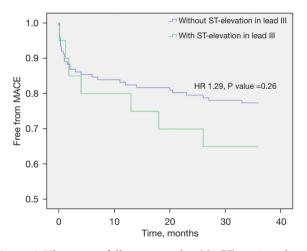


Figure 3 Three-year follow-up results. MACE, major adverse cardiovascular event; HR, hazard ratio.

elevation in lead III presented with ST-depression in multiple leads (especially in lead aVL and V2) and higher degree of ST-depression in lead I, aVL, and V3–V6. These results indicated a broader range of more severe myocardial ischemia in the cases with ST-elevation in lead III, probably due to higher percentage of left main lesion or triple-vessel lesions. Electrocardiographically, lead aVR is electrically opposite to the lateral or left-sided leads (I, II, aVL, V4-V6) and reflects electrical activity from the right upper portion of the heart. Lead III is the nearest to lead aVR, so we considered that the combination of STelevation in lead aVR and III could partially explain the increased possibility and degree of ST-depression in the lateral or left-sided leads. A previous study reported that the degree of ST-segment depression was associated with the diagnostic value and the prognosis (9). Our study showed no significant difference in the MACE and mortality rate between the two groups, possibly due to limited sample size and high percentage of timely emergent revascularization. Similar results were reported in a previous study that lead aVR could predict early revascularization but not long-term events (14).

In addition, our study demonstrated a higher percentage of previous PCI and higher NT-proBNP level in the cases without ST-elevation in lead III but similar percentages of other chronic diseases between the two groups, suggesting a possibly higher percentage of microvascular lesions and chronic myocardial ischemia in this group. On the contrary,

Table 4 Three-year follow-up results

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Clinical outcomes	Without ST-elevation in lead III (n=137)	With ST-elevation in lead III (n=20)	P value
In-hospital death, n (%)	6 (4.4)	1 (5.0)	0.90
Stroke, n (%)	5 (3.6)	1 (5.0)	0.77
Non-fatal myocardial infarction, n (%)	3 (2.2)	2 (10.0)	0.06
Out-of-hospital death, n (%)	17 (12.4)	3 (15.0)	0.75
MACEs, n (%)	31 (22.6)	7 (35.0)	0.23

MACEs, major adverse cardiovascular events.

the cases with ST-elevation in lead III presented with higher hs-TnT and CK-MB levels, indicating acute coronary lesions.

Interestingly, 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. Further studies are needed to clarify the underlying mechanism.

Previous research reported that ST-elevation in aVR with multi-lead ST depression was associated with acutely thrombotic coronary occlusion in only 10% of patients (10). The ST-elevation in lead aVR could be identified in the cases of atrioventricular-reentry tachycardia, pulmonary embolism, aortic dissection, cardiac shock, and so on (4,15-19). Therefore, we excluded patients with tachycardia and severe medical conditions in the enrollment of participants, which contributed to the presence of LM or multi-vessel lesions in half of the enrolled patients, a significantly higher proportion compared to previous reports. The major limitation of this study is small sample size and short-term follow-up. We are planning to design a larger sample investigation and longer-term follow-up in the future. In addition, lack of statistical significance in MACEs between two groups might indicate the complexity of correlation between ECG changes and clinical outcomes, urging us to explore a multifaceted approach to risk stratification and patient management in future studies.

# Conclusions

The NSTEACS cases with ST-elevation in lead III and

aVR tended to present with more multiple leads with STdepression and higher degree of ST-depression and have more left main or multi-vessel lesions, suggesting a broader range of severe myocardial ischemia. Simultaneous STelevation in the lead III and aVR may play a vital role in the diagnosis, risk-stratification, and prediction of poor prognosis during the management of NSTEACS patients.

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# Footnote

*Reporting Checklist:* The authors have completed the STROBE reporting checklist. Available at https://jtd. amegroups.com/article/view/10.21037/jtd-24-823/rc

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*Conflicts of Interest:* All authors have completed the ICMJE uniform disclosure form (available at https://jtd.amegroups. com/article/view/10.21037/jtd-24-823/coif). The authors have no conflicts of interest to declare.

*Ethical Statement:* The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013) and was approved by the Ethics Committee of Zhongshan Hospital Fudan University (No. B2018-263).

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