Predictive value of ST-segment deviation in aVR in patients suffering from acute coronary syndrome
A retrospective cohort study
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Abstract
Changes in the ST-segment in aVR of electrocardiogram have been used to predict the morbidity of left main and/or 3-vessel disease (LM/3-VD) in patients with acute coronary syndrome (ACS). However, the association with patient prognosis has rarely been reported.

A total of 274 patients diagnosed with ACS were retrospectively evaluated following allocation into 1 of 3 groups: the ST-segment elevation (STE) group ≥ 0.05 mV, ST-segment depression (STD) group ≥ 0.05 mV, and the Isoelectric group in aVR. A comparison of clinical characteristics, coronary angiography results, major adverse cardiovascular events (MACE), and GRACE risk score was made.

Patients in the STE and STD groups were older and had a lower LVEF, a greater number of MACE and higher GRACE risk score, compared with patients in the isoelectric group. Patients in the STE group had significantly greater morbidity due to LM/3-VD than did the non-STE groups. In addition, as the amplitude of STE in aVR increased, the number of MACE, GRACE risk score, and the incidence of LM/3-VD increased. Furthermore, after adjusting for other clinical factors, multivariate statistical results indicated that STE ≥ 0.05 mV in aVR was the only predictor of LM/3-VD, whereas STD ≥ 0.05 mV was not. It was found that STE or STD ≥ 0.05 mV in aVR was an independent predictor of MACE.

STE ≥ 0.05 mV in aVR is associated with LM/3-VD. Furthermore, ST-segment deviation in aVR may have prognostic value of MACE and associated with higher GRACE risk scores in patients with ACS.

Abbreviations: ACS = acute coronary syndrome, AMI = acute myocardial infarction, AUC = area under the curve, CI = confidence interval, ECG = electrocardiogram, GRACE = Global Registry of Acute coronary Events, LAD = left anterior descending branch, LCX = left circumflex branch, LDL-C = low-density lipoprotein cholesterol, LM/3-VD = left main and/or three-vessel disease, LVEDD = left ventricular end-diastolic diameter, LVEF = left ventricular ejection fraction, MACE = major adverse cardiovascular events, NSTEMI = non-ST-segment elevation myocardial infarction, OR = odds ratio, RCA = right coronary artery, ROC = receiver operating characteristic, SBP = systolic blood pressure, STD = ST-segment depression, STE = ST-segment elevation, STEMI = ST-segment elevation myocardial infarction, UA = unstable angina.

Keywords: acute coronary syndrome, aVR, GRACE risk score, MACE, prognosis

1. Introduction
Acute coronary syndrome (ACS) is a common acute and severe disease and a common cause of angina pectoris and even sudden cardiac death. As a noninvasive and rapid method of patient evaluation, an electrocardiogram (ECG) is commonly used in the clinical diagnosis of ACS, especially for the diagnosis of acute myocardial infarction (AMI), assisting in the identification of culprit lesions to determine the best course of treatment. However, only recently has the use of ECG for analysis of lead aVR been used as an approach used to predict culprit lesions and to provide a prognosis for patients diagnosed with ACS.

Researches have reported that ST-segment elevation (STE) in aVR is correlated with higher morbidity due to left main and/or 3-vessel disease (LM/3-VD), poor prognosis for large infarcts, and low left ventricular ejection fraction (LVEF) in ACS. Determination of Global Registry of Acute Coronary Events (GRACE) risk score has proven to be an accurate method of predicting poor prognosis in patients with ACS and has also been used to estimate the probability of all-cause mortality from hospitalization to 1-year following discharge. Both STE in aVR and high GRACE score are known to have prognostic value. However, the clinical value of lead aVR has often been apparently underestimated, from the lack of reports of the use of GRACE risk score and major adverse cardiovascular events...
2. Methods

2.1. Study design, population, and variables

A single-center retrospective investigation of 274 consecutive patients admitted to the coronary care unit of our hospital between January 2018 and June 2020 was conducted. All patients selected had undergone selective coronary angiography were diagnosed with ACS within 24 hours of the onset of symptoms. The diagnosis of ACS met the criteria of the American College of Cardiology.\[10\] Patients with incomplete clinical data, previous coronary artery bypass grafting (CABG), pacemaker implantation, rheumatic heart disease, cardiomyopathy, myocarditis, pericardial disease; left bundle branch block, atrial fibrillation, pre-excitation syndrome, or another distinct heart disease were excluded. The study was approved by the Ethics Committee of the First Affiliated Hospital of Guangxi Medical University. Written informed consent was obtained from all patients.

The clinical data of each patient at admission were obtained from hospital records and included gender, age, history of diabetes mellitus, hypertension, hyperlipidemia, smoking status, systolic blood pressure (SBP), heart rate, Killip classification, and MACE in hospital. The types of MACE recorded for all patients included severe left heart failure (NYHA grades III and IV), cardiogenic shock, acute left heart failure, cardiac death, and malignant arrhythmias (ventricular tachycardia, ventricular fibrillation, and other arrhythmias that could affect hemodynamics). Blood samples were obtained from each patient and Troponin I, creatinine, and low-density lipoprotein cholesterol (LDL-C) levels measured after admission. Transthoracic echocardiography during hospitalization was performed in a standard manner, whereby left ventricular end-diastolic diameter (LVEDD) and left ventricular ejection fraction (LVEF) were calculated.

ST-segment deviation in aVR was considered significant if it was ≥0.05 mV above or under the isoelectric line measured 20 ms after the J point. Depending on the ST-segment deviation in aVR, patients were divided into 1 of 3 groups, as follows: (1) STE Group, where STE ≥ 0.05 mV; (2) Isoelectric group; (3) STD Group, where STD ≥ 0.05 mV. Medical history and noninvasive diagnostics data (laboratory results, echocardiography, and resting ECG) in addition to coronary angiography were analyzed for each patient. To further analyze the influence of the amplitude of STE on prognosis and scale of disease in blood vessels in patients with ACS, the STE group was subdivided into 2 subgroups: STE ≥ 0.05 and < 0.1 mV, and STE ≥ 0.1 mV in aVR.

All patients underwent coronary angiography when hospitalized when presenting with ACS. All coronary angiographies were analyzed by 1 experienced cardiologist who was blinded to all subsequent results. The lesions of left main trunk (LM), left circumflex branch (LCX), left anterior descending branch (LAD), and right coronary artery (RCA) were observed. Stenosis of more than 70% of the lumen diameter in any 1 major epicardial artery or of more than 50% in the left main coronary artery was considered significant. The GRACE risk scores were calculated on admission. The GRACE risk model consisted of the following predictors at admission: age, systolic blood pressure, heart rate, Killip classification, ST-segment deviation, cardiac arrest, levels of creatinine, and presence of myocardial injury markers.

2.2. Statistical analysis

Quantitative variables are expressed as the means ± standard deviation (SD), while categorical variables are expressed as frequencies and percentages. Groups were compared using a Student t-test or ANOVA test for continuous variables and using a Chi-square test or Fisher exact test for categorical variables. Logistic regression analysis was performed to assess independent predictors of LM/3-VD and in-hospital MACE. The receiver operating characteristic (ROC) curve was performed, then area under ROC curve (AUC) was calculated. Double-tailed P values < .05 were considered statistically significant. All the statistical analyses were performed using SPSS (Version 24.0, IBM Corp.)

3. Results

3.1. Clinical characteristics of the study population

A total of 274 consecutive patients were selected for the present study who had presented with ACS, including 209 males and 65 females, with a mean age of 65.3 ± 10.1 years, of which 157 cases were diagnosed with ST-segment elevation myocardial infarction (STEMI), 34 cases with non-ST-segment elevation myocardial infarction (NSTEMI), and 83 cases with unstable angina (UA), as displayed in Table 1. There were 160 (58.4%) patients in the STE group, 81 (29.6%) patients in the Isoelectric group, and 33 (12.0%) patients in the STD group, among whom 95 (59.4%), 65 (80.2%), and 31 (93.9%) had suffered AMI, respectively. There were no statistical differences between the 3 groups in terms of mean age, proportions of males and females, history of hypertension, and diabetes mellitus, smoking status, blood pressure, or heart rate. Lipid levels (LDL-C, cholesterol), serum creatinine, and LVEDD were similar in the 3 groups. However, compared with the STD and Isoelectric groups, a greater proportion of the STE group was in Killip Class ≥ 2 and had a lower left ventricular ejection fraction. In addition, patients with ST-segment deviation in aVR were older, had more MACE (Table 2), and had a higher GRACE risk score. In summary, ST-segment deviation indicated poor prognosis.

3.2. Coronary angiography results and comparison between the 2 subgroups

We wished to identify the cause of poor prognosis in patients with ST-segment deviation in aVR. As shown in Table 3, and confirmed by angiography, the number of cases of LM and LM/3-VD was found to be 47 (29.4%) and 79 (49.7%) in the STE group, 6 (7.4%) and 20 (24.7%) in the Isoelectric group, and 1 (3.0%) and 9 (27.3%) in the STD group, respectively. Patients in the STE group had a significantly higher proportion of LM lesions and LM/3-VD than did patients in the STD and Isoelectric groups. However, this relationship was not associated with the STD group. Besides, we found that there were no significant differences between the 2 subgroups in age, gender, smoking, diabetes mellitus, hypertension, lipid levels, serum creatinine, LVEF, and LVEDD, whereas as the amplitude of STE in aVR increased, Killip class ≥ II, LM/3-VD, MACE, and GRACE risk score increased (Table 4).

As shown in Table 5, after adjusting for other known CHD risk factors,\[10\] STE ≥ 0.05 mV in aVR was an independent predictor of LM/3-VD (OR: 2.67; 95% CI: 1.44–4.93; P < .05), whereas STD ≥ 0.05 mV was not. A logistic regression model was established, with mean age, smoking status, Troponin I, STEMI, Killip grade ≥ II, STE ≥ 0.05 mV in aVR and STD ≥ 0.05 mV in aVR used as independent variables, and MACE during hospitalization as dependent variables. The results indicate that both STE and STD ≥ 0.05 mV in aVR were independent predictors of MACE (OR: 7.16; 95% CI: 1.95–26.39; P < .05 for the STE group and OR: 10.01; 95% CI: 2.26–44.36; P < .05 for the STD group, Table 6).
**Table 1**

Clinical characteristics of the study population (n = 274).

|                          | STE Group, STE ≥ 0.05 mV (n = 160) | Isoelectric group (n = 81) | STD Group, STD ≥ 0.05 mV (n = 33) | P       |
|--------------------------|-----------------------------------|---------------------------|-----------------------------------|---------|
| Mean age                 | *64.08 ± 0.50                      | 59.11 ± 10.45             | *64.39 ± 13.05                    | .002    |
| Gender (male)            | 115 (71.9%)                       | 68 (84.0 %)               | 26 (78.8 %)                       | .107    |
| AMI                      | *94 (58.8%)                       | 66 (81.5%)                | 31 (93.9%)                        | .000    |
| STEMI                    | *69 (43.1%)                       | 59 (72.8%)                | 29 (87.9%)                        | .000    |
| NSTEMI                   | 25 (15.6%)                        | *7 (6.8%)                 | 2 (6.1%)                          | .149    |
| UA                       | *66 (41.3%)                       | 19 (18.5%)                | 2 (6.1%)                          | .000    |
| Smoking                  | 76 (47.5%)                        | 52 (64.2%)                | 19 (57.6%)                        | .044    |
| Diabetes mellitus        | 32 (20.0%)                        | 15 (18.5%)                | 9 (27.3%)                         | .563    |
| Hypertension             | 90 (56.3%)                        | 40 (49.4%)                | 20 (60.6%)                        | .462    |
| Heart rate (bpm)         | 81.68 ± 16.02                     | 77.90 ± 15.77             | 80.36 ± 15.80                     | .217    |
| SBP (mm Hg)              | 134.94 ± 27.41                    | 137.20 ± 23.63            | 127.67 ± 28.09                    | .046    |
| Killip class ≥ II        | *33 (20.6%)                       | 6 (7.4%)                  | 2 (6.1%)                          | .022    |
| Cholesterol (mmol/L)     | 5.15 ± 1.37                       | 5.00 ± 1.29               | 4.66 ± 1.09                       | .120    |
| LVEF (%)                 | 3.29 ± 0.99                       | 3.12 ± 0.93               | 3.12 ± 0.93                       | .346    |
| Creatinine (μmol/L)      | 110.25 ± 122.60                   | 113.00 ± 143.73           | 126.85 ± 137.37                   | .803    |
| Troponin I (ng/mL)       | 3.07 ± 3.76                       | 3.34 ± 3.42               | *6.80 ± 3.39                      | .000    |
| LVEDD (mm)               | 51.07 ± 5.75                      | 49.81 ± 4.86              | 50.12 ± 5.17                      | .210    |
| LVEF (%)                 | *48.14 ± 10.08                    | 51.15 ± 8.21              | 47.88 ± 8.16                      | .049    |
| GRACE risk score         | *151.22 ± 36.60                    | 136.06 ± 26.01            | *155.58 ± 35.25                   | .002    |

*P < .05 compared with the isoelectric group.

AMI = acute myocardial infarction, GRACE = Global Registry of Acute coronary Events, LDL-C = low-density lipoprotein cholesterol, LVEF = left ventricular ejection fraction, NSTEMI = non-ST-segment elevation myocardial infarction, SBP = systolic blood pressure, STD = ST-segment depression, STE = ST-segment elevation, NSTEMI = non-ST-segment elevation myocardial infarction, UA = unstable angina.

**Table 2**

Comparison of MACE in hospital among 3 groups of patients [N (%)].

| MACE                  | STE Group (n = 160) | Isoelectric group (n = 81) | STD Group (n = 33) | P       |
|-----------------------|--------------------|---------------------------|--------------------|---------|
| Cardiogenic shock     | 20 (12.5%)         | 1 (1.2%)                  | 7 (21.2%)          | .002    |
| NYHA grades III and IV* | 7 (4.4%)         | 1 (1.2%)                  | 0                  | .326    |
| Acute heart failure*  | 12 (7.5%)          | 1 (1.2%)                  | 0                  | .046    |
| Ventricular fibrillation | 15 (9.4%)   | 0                         | 6 (17.6%)          | .002    |
| III/atrioventricular block* | 3 (1.9%) | 0                         | 3 (8.8%)           | .02     |
| Cardiac death         | 15 (9.4%)          | 1 (1.2%)                  | 4 (11.8%)          | .04     |
| One of the above      | 41 (25.6%)         | 3 (3.7%)                  | 11 (33.3%)         | .000    |

*P < .05 using Fisher exact test for calculation.

MACE = major adverse cardiovascular events, NYHA = New York Heart Association, STD = ST-segment depression, STE = ST-segment elevation.

**Table 3**

Comparison of LM/3-VD in the 3 groups.

|                  | STE group (n = 160) | Isoelectric group (n = 81) | STD group (n = 33) | P       |
|------------------|--------------------|---------------------------|--------------------|---------|
| LM                | 47 (29.4%)         | 6 (7.4%)                  | 1 (3.0%)           | .000    |
| LM/3-VD           | *73 (40.7%)        | 20 (24.7%)                | 9 (27.3%)          | .000    |
| Two-vessel disease| 39 (24.4%)         | 23 (28.4%)                | 12 (36.4%)         | .349    |
| One-vessel disease| *42 (26.3%)        | 38 (46.9%)                | 12 (36.4%)         | .005    |

*P < .05 compared with the isoelectric group.

STD = ST-segment depression, STE = ST-segment elevation, LM = left main coronary artery, LM/3-VD = left main and/or 3-vessel disease.

3.3. ROC analysis to determine GRACE risk score and degree of STE for predicting MACE

As shown in Figure 1, the area under the ROC curve of GRACE for predicting MACE in all patients was 0.80 (P = .000, 95% CI: 0.73–0.87). The sensitivity and specificity of predicting MACE with GRACE value > 153 were 76% and 69%, respectively. The area under the ROC curve of STE ≥ 0.1 mV for predicting MACE was 0.62 (P = .000, 95% CI: 0.53–0.71). However, if the STE was ≥0.05 mV, but <0.1 mV, the area under the ROC curve was 0.48, which had no significant difference.

4. Discussion

The present study focused on understanding the predictive and prognostic significance of lead aVR in patients with ACS during hospitalization. In patients diagnosed with ACS, patients with ST-segment deviation in aVR were older and had lower LVEF, a greater number of MACE, and higher GRACE risk score compared with patients without ST-segment deviation, which indicated a poor prognosis. It was also clear from the results that STE ≥ 0.05 mV in aVR predicted greater morbidity due to LM/3-VD in comparison with the other groups. In addition, MACE, GRACE risk score, and the incidence of LM/3-VD were higher with increased ST-segment elevation in aVR. Furthermore, multivariate statistical results indicated that STE ≥ 0.05 mV in aVR was an independent predictor of LM/3-VD, but STD ≤ 0.05 mV was not. It was also found that ST-segment elevation or depression in aVR was an independent predictor of MACE. These results indicate that ST-segment deviation in aVR may be an important predictive tool for diagnosis and prognosis in ACS, offering potentially better treatment strategies for ACS-afflicted patients.

Lead aVR locates at the upper-right portion of the frontal 6-axis system, the direction of which is a +150° vector, while the opposite direction is located at a +30° vector, between I and II. It is directed precisely to the basal part of the interventricular septum and right ventricular outflow tract. Infarction in these critical regions often induces a change in the aVR ST-segment.[11] Tamura et al concluded that the possible mechanisms of STE in aVR are as follows: occlusion of the proximal LAD (especially a short LAD) resulting in transmural ischemia of the basal interventricular septum, large-diameter occlusions of the proximal right coronary artery (RCA) resulting in transmural ischemia of the right ventricular outflow tract, and mirror-like changes corresponding to the STD in leads I, II, aVL, and V4–V6 due to ischemia in the apical and lateral wall leads, and finally, ischemic changes in the subendocardial myocardium caused by LM/3-VD.[12]
In order to identify high-risk patients with ACS, Gorgels et al analyzed ECGs recorded in 113 patients with chest pain who underwent coronary angiography, the results showing that STE > 0.05 mV in aVR was associated with multivessel disease and was an important predictor of acute coronary lesions.[14] These results indicate that STE ≥ 0.05 mV in aVR plays an important role in predicting LM/3-VD. In the present study, compared with the non-STE groups, the STE group had a higher incidence of LM/3-VD (P < .05). The incidence of LM/3-VD increased as the amplitude of STE in aVR increased. These results were similar to those found in previous studies.[18,19] Patients with LM/3-VD not showing STE may be due to the presence of collateral circulation, small lesions, mild ischemia, and pseudoimprovement on ECG, although the lesions involved a wide range and severe stenosis. However, there were more patients with STE ≥ 0.05 mV in our paper than those reported by Barraés[18] (58% vs 48%). The main reason may be that the data were incomplete or the patients who had not received CAG after admission were excluded. Multivariate statistical analysis indicated that STE ≥ 0.05 mV in aVR was an important predictor of LM/3-VD (OR: 2.67, 95% CI: 1.44–4.93), consistent with the results of previous studies.[16,20,21]

STD in aVR was mostly caused by acute inferior wall myocardial infarction, and the infarcted vessels were mostly RCA and part of the LCX, but rarely observed in the LAD.[22] At present, it is believed that a possible mechanism for STD in aVR is left ventricular apical and inferior lateral wall transmural myocardial infarction. A recent study concluded that the cause was as follows: Severe stenosis or occlusion of the RCA with large posterior branches; severe stenosis or occlusion of the LCX which can affect blood perfusion of the obtuse ramus with large posterior branches; severe stenosis or occlusion of the RCA; severe stenosis or occlusion of the LCX; or posterior lateral ramus; occlusion of the LAD, especially at its distal end.[21] Kanie et al reported that STD ≥ 0.1 mV in aVR was associated with substantial impaired myocardial reperfusion.[24] An STE or STD ≥ 0.1 mV in aVR was shown to be independently associated with coronary complexity in ACS.[21] In the present study, the majority of the diseased vessels were either a RCA or LCX with high levels of myocardial enzyme in the STD group. There was 1 case in STD group with LM lesion, the reason was that long LAD occlusion affected inferior apical and inferior lateral wall myocardial ischemia.
But due to the small number of cases in this group, coronary complexity was not discussed in detail. Compared with the Isoelectric group, STD ≥ 0.05 mV in aVR did not significantly predict the presence of LM/3-VD.

When severe stenosis or occlusion occurs in LM or in the 3-vessels, patients mainly present with anterior wall or extensive anterior wall myocardial ischemia or infarction, often leading to cardiac arrest, acute heart failure, malignant arrhythmia, cardiogenic shock, or other serious hemodynamic disorders, which are associated with a high fatality rate. In 2016, Nabati et al found that STE ≥ 0.05 mV in aVR was associated with a higher 3-month mortality and often had a correspondingly higher Gensini score and multivessel lesions.²⁸ Barrabés et al examined 775 patients diagnosed with AMI, which aimed to investigate the prognostic value of STE in aVR, finding that patients with STE ≥ 0.05 mV in aVR displayed poor outcomes with higher morbidity due to heart failure and increasingly recurrent ischemic events, in addition to higher mortality during hospitalization, indicating that the observations may have been associated with high in-hospital and 1-year cardiovascular mortality in patients suffering from ACS.²⁷ Alherbish et al found that ST-segment deviation in aVR was independently correlated with an increase in 90-day rate of death.³⁰ In patients with inferior/posterior AMIs in addition to STD in aVR mostly displayed ST-segment changes in other leads, suggesting that STD ≥ 0.05 mV in aVR may be associated with a coronary artery that supplies a large area.²⁹ Consequently, an STE or STD ≥ 0.05 mV in aVR may lead to a poor outcome. In the present study, the prevalence of MACE was 41 (25.6%) in the STE group, 3 (3.7%) in the isoelectric group, and 11 (33.3%) in the STD group. Compared with the Isoelectric group, patients where STE or STD ≥ 0.05 mV had a higher prevalence of MACE and GRACE risk score. After adjusting for other clinical factors, STE and STD ≥ 0.05 mV in aVR remained independent risk factors for MACE, indicating poor outcome.

Determination of the GRACE risk score allows rapid cardiovascular risk assessment and has been widely used to predict the clinical prognosis of patients, also able to guide early risk stratification and intervention in patients suffering from ACS.³⁰ Early identification of patients with severe coronary artery disease and early use of invasive treatments may help reduce MACE in high-risk patients.³⁰ In our study, the ROC analysis found GRACE risk score had good predictive value for MACE (AUC = 0.80, 95% CI: 0.73–0.87, P = .000), with a sensitivity of 76% and specificity of 69% when it was in the average of ST deviation. So we used the GRACE risk score to evaluate prognosis in patients with ST-segment deviation in aVR, and found that STE ≥ 0.05 mV was consistent with a higher morbidity due to LM/3-VD, while also having a worse prognosis, higher GRACE risk score, and a greater number of MACE than patients in the non-STE groups.³¹ As the degree of STE in aVR increased, MACE, and GRACE risk score increased, suggesting severe ischemia in the basal part of the interventricular septum and the outflow tract of the right ventricle. Compared with STE ≥ 0.05mV and <0.1 mV, STE ≥ 0.1 mV had better predictive value of MACE (AUC: 0.62 vs 0.48). In addition, compared with patients in the Isoelectric group, patients in the STD group had more MACE and higher GRACE scores. Taken together, these data provide evidence that STE and STD ≥ 0.05 mV in aVR could assist in determining patient risk stratification and provide optimal management for patients suffering from ACS.

A limitation of the present study is the single-center retrospective analysis using a small number of patients. Thus, relative selective bias was inevitable. Therefore, we suggest that further studies are undertaken with a larger number of samples and longer follow-up time after discharge to help validate the results.

5. Conclusions
In conclusion, the results indicate that STE ≥ 0.05 mV in aVR is correlated with LM/3-VD. Furthermore, our results suggest that ST deviation in aVR may have prognostic value, indicative of more MACE and are associated with higher GRACE risk score in patients with ACS.

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Author contributions
Zhi-Yu Zeng contributed to conception and design of the study, data analysis, and interpretation. Ji-Ge Hong contributed to collection and assembly of data.

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