Risk Factors for Nonischemic St-segment Elevation in Patients With Electrocardiographic Left Ventricular Hypertrophy

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Abstract

Background ST-segment elevation (STE) is not a specific change for ST-segment elevation myocardial infarction (STEMI). This may lead to a mistaken diagnosis of STEMI and false-positive cardiac catheterization laboratory activation. We aimed to investigate risk factors for STE secondary to electrocardiographic LVH in order to provide more information for differential diagnosis.

Methods A total of 1,590 inpatients with electrocardiographic LVH without confounding factors (such as myocardial infarction) were enrolled in this study. Data on potential risk factors and patient characteristics were collected. Logistic regression analysis and receiver operating characteristic curve (ROC) were used to identify the risk of STE in patients with LVH.

Results After reviewing the ECGs, 1590 cases of electrocardiographic LVH were divided into an ST-segment elevation group (STE group, 81 cases) and non-ST segment elevation group (1509 cases). Eighty-seven cases were randomly selected from the non-ST segment elevation group to form a new non-ST segment elevation group (non-STE group, 87 cases) for further analysis. The mean age of the 168 participants (119 men, 70.83%) was 62.33 ± 16.27. Multivariate analysis showed that stroke, infection, and the value of S_{V1}+R_{V5} were significantly associated with STE secondary to LVH. The area under the receiver operating characteristic curve showed that the optimal value of S_{V1}+R_{V5} cut-off for predicting STE was 4.805 (sensitivity: 40.74%; specificity: 80.46%; AUC: 0.634; 95% CI: 0.550–0.719; $P < 0.05$).

Conclusions A value of S_{V1}+R_{V5} larger than 4.8 mV, stroke, and infection are independent risk factors for STE in patients with electrocardiographic LVH.

Background

ST-segment elevation myocardial infarction (STEMI) is usually caused by unstable plaque rupture of the coronary arteries, resulting in myocardial necrosis in the corresponding perfusion area, and is one of the most common fatal chest pains in the emergency department [1–4]. Rapid diagnosis and shortening of reperfusion therapy time are essential for reducing mortality and improving outcomes in STEMI patients [1,5]. The diagnosis of STEMI is based primarily on symptoms, electrocardiograms (ECG), and myocardial markers [1,5]. ECG is a powerful clinical tool to assist physicians in arriving at the correct diagnosis and determining proper therapy, in particular the reperfusion therapy [6]. The typical ECG changes of myocardial infarction are characterized by ST-segment elevation (STE). However, ECG is an imperfect tool in this setting [6]. STE is not a specific for a change in SETMI. STE can also appear in benign, nonischemic presentations, such as electrocardiographic left ventricular hypertrophy (LVH) [7,8]. Patients with electrocardiographic LVH can develop complex ST-T changes (including STE), which may lead to a mistaken diagnosis of STEMI [9–14]. Previous studies have shown that electrocardiographic LVH is the most significant independent risk factor in leading to a mistaken diagnosis of STEMI and false-positive cardiac catheterization laboratory activation. [11,12].

Current guidelines fail to provide a fast and effective method to identify STEMI in patients who have combined electrocardiographic LVH with STE [1]. Most studies look for ECG characteristics and clinical features of STEMI patients combined with LVH to help identify cases of myocardial infarction [6,15–17]. To date, no clinical studies have been conducted to investigate the clinical features of electrocardiographic LVH in patients with STE when myocardial infarction is excluded. The aim of this study was to investigate the risk factors for STE secondary to electrocardiographic LVH in order to provide information that can be used for differential diagnosis.

Method

Study Population A retrospective analysis was carried out for patients with electrocardiographic LVH at the First Affiliated Hospital of Shantou University Medical College between July 2015 and June 2017. Inclusion criteria included: (1) an ECG that conformed to Sokolow-Lyon criteria: $R_{V5} + S_{V1} \geq 4.0$ mV (males), $R_{V5} + S_{V1} \geq 3.5$ mV (females) [18]; (2) a patient age older than 18 years. Exclusion criteria included: (1) confounding factors that may affect the ST-segment, such as acute myocardial infarction, old myocardial infarction, conduction block, ectopic rhythm, pacemaker implantation, myocarditis, pericarditis, congenital heart disease, or cardiomyopathy; (2) ECGs where the $R_{V5} + S_{V1}$ could not be measured, such as ventricular fibrillation, ventricular flutter, continuous pacing rhythm, and cardiac arrest.

Electrocardiographic features were collected by experienced cardiovascular physicians. ST-segment elevation is defined as an STE that appeared in any ECG lead and an elevation amplitude greater than 0.05 mV [1]. According to the STE status in the electrocardiogram, participants were divided into an STE group and non-STE group. Eighty-seven patients were randomly selected from the non-STE group by computer to form a new non-STE group for analysis.

Data collection Clinical data of patients in the STE group and new non-STE group were collected. We considered the following covariates as potential confounders: gender, age, fever (body temperature greater than 38°C), infection (required antibiotic treatment), acute chest pain, stroke (cerebral hemorrhage, cerebral infarction), biliary system disease (cholecystitis, biliary obstruction), history of hypertension, history of diabetes, history of coronary heart disease, smoking history, heart rate, blood pressure, white blood cells, hemoglobin, platelets, serum potassium ions, serum sodium ions, serum calcium ions, alanine acid transaminase (ALT), serum creatinine, cardiac enzymes (kinase isoenzyme (CK-MB), cardiac troponin I (cTnI)) and $S_{V1} + R_{V5}$ values. This study was approved by the Ethics Committee of the First Affiliated Hospital of Shantou University Medical College.

Statistical analysis Continuous variables are expressed as mean ± SD or medians (interquartile range) as appropriate. Categorical variables are presented as absolute values and proportions. Continuous variables were compared using one-way analysis of variance. Categorical variables were compared using the $\chi 2$-test or Fisher's exact test, as appropriate. Logistic regression analysis was used to estimate odds ratios (OR) for STE and their corresponding 95% confidence intervals (CI). Univariate regression analysis was performed to evaluate the association between clinical variables and STE secondary to LVH.

Variables that were statistically significant in the univariate analysis were entered into a multivariable logistic model. The area under the receiver operating characteristic curve (AUC) was determined to assess the discriminative ability of clinical variables in predicting STE. All statistical analyses were performed using SPSS Statistics version 23.0 (IBM Corporation, Armonk, NY, USA) and Heml 1.0 (Huazhong University of Science and Technology, Hubei, China). An α level of 0.05 was deemed significant for all analyses.

Results

Baseline characteristics A total of 67,589 electrocardiograms from the First Affiliated Hospital of Shantou University Medical College between July 2015 and June 2017 were collected. After screening based on our inclusion and exclusion criteria, 21,054 inpatient ECGs were enrolled for further analysis. After reviewing the ECGs, 1590 cases of electrocardiographic LVH, but without confounding factors, were collected and divided into an ST-segment elevation group (STE group, 81 cases) and non-ST segment elevation group (1509 cases). Eighty-seven cases were randomly selected from the non-ST segment elevation group to form a new non-ST segment elevation group (non-STE group, 87 cases) for analysis. The detailed process for participants selection is detailed in Fig. 1.

The clinical characteristics are shown in Table 1. The mean age of the 168 participants (119 men, 70.83%) was 62.33 ± 16.27 years. There were significant differences in ratio of fever, stroke, infection, heart rate, and S_{V1}+R_{V5} between STE and non-STE groups ($P < 0.05$, Table 1). Comparing with the non-STE groups, the ratio of fever, stroke, heart rate and infection were higher in the STE group. Other factors such as gender ratio, age, biliary tract disease, acute chest pain, history of hypertension, history of diabetes, history of coronary heart disease, and smoking history did not have significant difference between the STE group and non-STE group.

Table 1
Clinical characteristics of participants

Characteristic	Overall (n = 168)	STE Group (n = 81)	Non-STE Group (n = 87)	*P*
Sex, male (%)	119 (70.83)	55 (67.90)	64 (73.56)	0.420
Age, years	62.33 ± 16.27	61.99 ± 17.16	62.64 ± 15.49	0.795
Fever, n (%)	22 (13.10)	15 (18.52)	7 (8.05)	0.044
Acute chest pain, n (%)	12 (7.14)	8 (9.88)	4 (4.60)	0.304
Stroke, n (%)	32 (19.05)	22 (27.16)	10 (11.49)	0.011
Biliary system diseases, n (%)	3 (1.79)	3 (3.70)	0	0.110
Infection, n (%)	60 (35.71)	37 (45.68)	23 (26.44)	0.009
Hypertension, n (%)	118 (70.24)	53 (65.43)	65 (74.71)	0.189
Diabetes, n (%)	37 (22.02)	16 (19.75)	19 (21.84)	0.739
Coronary heart disease, n (%)	12 (7.14)	6 (7.41)	6 (6.90)	0.898
Smoking, n (%)	48 (28.57)	21 (25.93)	27 (31.03)	0.464
Heart rate (bpm)	84.95 ± 17.33	87.75 ± 19.88	82.34 ± 14.18	0.046
SBP, mmHg	150.40 ± 32.38	151.15 ± 34.09	149.70 ± 30.90	0.773
DBP, mmHg	86.48 ± 20.42	85.77 ± 23.40	87.15 ± 17.32	0.665
WBC, 10^9/L	9.95 ± 6.87	9.47 ± 4.57	10.41 ± 8.47	0.376
Hb, g/L	115.35 ± 31.83	119.46 ± 34.60	111.48 ± 28.65	0.106
PLT, 10^9/l	222.31 ± 90.31	212.49 ± 88.85	231.66 ± 91.22	0.172
Serum K^+, mmol/L	3.87 ± 0.63	3.83 ± 0.62	3.90 ± 0.63	0.450
Serum Na^+, mmol/L	137.78 ± 5.00	137.33 ± 4.59	138.21 ± 5.27	0.254
Serum Ca^+, mmol/L	2.16 ± 0.20	2.16 ± 0.24	2.15 ± 0.17	0.744
Alanine acid transaminase, U/L	17.00 (11.75-27.00)	18.50 (13.00-29.75)	16.50 (11.00-26.25)	0.735

Data given as mean ± SD, median (IQR), or n (%). *P*-value of < 0.05 was considered significant

Ck-MB, creatine kinase isoenzyme-MB; DBP, diastolic blood pressure; SBP, systolic blood pressure; TNI, Troponin I; WBC, white blood cells; Hb, hemoglobin; PLT, platelets.

Characteristic	Overall (n = 168)	STE Group (n = 81)	Non-STE Group (n = 87)	*P*
Serum creatinine, μmol/L	114.00 (87.00-211.00)	116.00 (85.00-254.00)	111.50 (87.00-192.50)	0.805
CK-MB, ng/mL	1.80 (1.80–2.11)	1.80 (1.80–2.13)	1.80 (1.80–2.11)	0.842
cTnI, ng/mL	0.1 (0.1–0.21)	0.1 (0.1–0.25)	0.1 (0.1–0.18)	0.564
Positive cTnI, n (%)	8 (4.76)	5 (6.17)	3 (3.45)	0.484
S_{V1}+R_{V5}(mV)	4.59 ± 1.00	4.85 ± 1.17	4.35 ± 0.72	0.001
Data given as mean ± SD, median (IQR), or n (%). *P*-value of < 0.05 was considered significant				
Ck-MB, creatine kinase isoenzyme-MB; DBP, diastolic blood pressure; SBP, systolic blood pressure; TNI, Troponin I; WBC, white blood cells; Hb, hemoglobin; PLT, platelets.				

Association between clinical variables and STE Univariate regression analysis showed that the ratio of fever, stroke, infectious disease, heart rate, and value of S_{V1}+R_{V5} were significantly associated with STE (Table 2).

Table 2
Factors associated with STE in patients with LVH (univariable analysis)

Variables	Univariate	
	OR (95% *CI*)	*P*
Fever	2.60 (1.05, 6.75)	< 0.05
Heart rate	1.02 (1.01, 1.04)	< 0.05
S_{V1}+R_{V5}	1.80 (1.24, 2.60)	< 0.01
Infectious disease	2.34 (1.22, 4.47)	< 0.05
Stroke	2.83 (1.25, 6.44)	< 0.05
CI, confidence interval; a *p*-value of < 0.05 was considered significant. STE, ST-segment elevation; LVH, left ventricular hypertrophy; OR, Odds ratio.		

Multivariate logistic regression analysis Variables that were statistically significant in univariate analysis were entered into a multivariable logistic model. Stroke (*OR*, 3.11; 95% *CI*, 1.31–7.39; $p = 0.01$), infection (*OR*, 2.08; 95% *CI*, 1.05–4.12; $p = 0.04$), and value of S_{V1}+R_{V5} (*OR*, 1.88; 95% *CI*, 1.29–2.75; $p < 0.01$) remained independently associated with the outcome in our multivariable model (Fig. 2).

Optimal $S_{V1}+R_{V5}$ index cut-off for predicting STE The area under the receiver operating characteristic curve (ROC) showed that the optimal $S_{V1}+R_{V5}$ cut-off value for predicting STE in patients with LVH, as determined using the Youden index, was 4.805 (sensitivity: 40.74%; specificity: 80.46%; AUC: 0.634; 95% *CI*: 0.550–0.719; $P < 0.05$) (Fig. 3).

Discussion

LVH alters the measurement of cardiac repolarization. Characteristic ECG changes associated with LVH including STE, prominent septal Q waves, T-wave inversion, and ST-segment depression, which may lead to misdiagnosis of acute myocardial infarction [6]. The presence of LVH, when associated with STE, has been demonstrated as a risk factor for false-positive ST-segment elevation myocardial infarction diagnoses, commonly leading to unnecessary reperfusion therapy [9–14]. Chest pain centers have been built in many countries. Chest pain centers have been shown to shorten the reperfusion therapy time, which is associated with better outcomes for myocardial infarction patients [3]. However, in order to shorten the reperfusion time, physicians at chest pain centers often do not have enough time for careful differential diagnosis [12]. Previous studies have shown that in the early stages of chest pain center construction, the incidence of false activation of cardiac catheterization laboratory increased, and the occurrence of false activation events was closely related to electrocardiographic LVH [12,14]. More seriously, previous publications have shown that LVH with STE is an independent risk factor for misdiagnosing STEMI in patients with aortic dissection [19,20]. Aortic dissection is a catastrophic disease with rapid onset, rapid progression, high mortality, and poor natural prognosis [19]. Patients with aortic dissection who are misdiagnosed as STEMI will lead to serious consequences [21,22]. Therefore, physicians should be keenly aware of the possibility of LVH confounding the ability to recognize true STEMI [6]. For patients with STE, physicians need to quickly identify patients with true STEMI for reperfusion treatment, while minimizing misdiagnosis of nonischemic diseases as STEMI to avoid iatrogenic damage. Thus, it is necessary to reduce misdiagnosis by finding a method that can be used to identify STE secondary to LVH and ischemic STE.

However, STEMI guidelines do not define STE diagnostic thresholds for LVH patients. The 2017 ESC Guidelines for the management of acute myocardial infarction indicate that STE is considered suggestive of ongoing coronary artery acute occlusion in the following cases: at least two contiguous leads with STE > 0.1 mV in all leads other than leads V_2-V_3, where the following cutoff points apply: STE > 0.2 mV in men ≥ 40 years, STE ≥ 0.25 mV in men < 40 years, or STE ≥ 0.15 mV in women [in the absence of LVH or left bundle branch block (LBBB)] [1]. The 2013 ACCF/AHA guidelines for the management of STE myocardial infarction define diagnostic STE, in the absence of LVH or left LBBB, as new STE at least 1 mm (0.1 mV) in two or more anatomically contiguous leads (with allowance of up to 1.5 mm (0.15 mV) in leads V_2–V_3 for women and 2 mm (0.2 mV) in the same leads for men) [23]. Interestingly, these guidelines define diagnostic thresholds in the absence of LVH, but the guidelines do not clarify how to

diagnose STEMI in the case of LVH, which might result in many unnecessary, potentially dangerous coronary angiographies.

Based on the deficiencies of current clinical guidelines, we need to find more methods to help clinicians make a differential diagnosis. There have been many studies looking for ECG characteristics and clinical features of STEMI patients with LVH to help identify cases of myocardial infarction. For example, a study by Armstrong et al. suggested using a ratio of ST-segment to R-S-wave magnitude ≥ 25% as a diagnostic criteria for STEMI to improve specificity of diagnosis in patients with anterior territory STE [17]. However, using these additional ECG diagnostic criteria and clinical features to identify STEMI may reduce the sensitivity of the ECG for STEMI diagnosis. To date, no clinical studies have been performed to identify independent predictors of STE in nonischemic patients with LVH. Therefore, we tried to investigate the risk factors for STE in patients with LVH but without STEMI in order to provide more information for differential diagnosis.

Risk factors for STE After researching the literature, we collected and analyzed common potential risk factors that may affect the ST segment. According to multivariate logistic regression analysis, a value of S_{V1}+R_{V5} larger than 4.8 mV is an independent risk factor for STE in patients with electrocardiographic LVH. S_{V1}+R_{V5} is the main indicator of the Sokolow- Lyon standard in diagnosing LVH, which reflects the projection of the largest vector of the left ventricular depolarization on the horizontal plane [6,18]. Our study further finds that the value of S_{V1}+R_{V5} could not only be used to diagnose electrocardiographic LVH, but also that the magnitude of S_{V1}+R_{V5} is positively correlated with the risk of nonischemic STE. Therefore, LVH patients combined with STE and an elevated S_{V1}+R_{V5} (larger than 4.8 mV) should be highly suspect for the possibility of secondary nonischemic STE. Conversely, if STE occurs when S_{V1}+R_{V5} is not significantly elevated (less than 4.8 mV), then STEMI might be considered to avoid misdiagnosis and delaying primary angioplasty. To determine how the S_{V1}+R_{V5} performs to differentiate between ischemic STE and nonischemic STE secondary to LVH, a threshold of 4.8 mV was chosen by optimizing receiver operating characteristic (ROC) curves. For a patient with an S_{V1}+R_{V5} larger than 4.8 mV, physicians should be keenly aware of the possibility of nonischemic STE secondary to LVH. Otherwise, STEMI should be considered. The specificity is high (0.8) but the sensitivity is low (0.4) on the ROC curve. Given that missed diagnosis of STEMI could lead to serious consequences, high specificity is needed to minimize the possibility of missed diagnosis. Considering that the magnitude of S_{V1}+R_{V5} is an additional auxiliary differential diagnosis method, lower sensitivity is acceptable. Therefore, a value of S_{V1}+R_{V5} greater than 4.8 mV could be used for clinical differential diagnosis and is worth further research.

We also found that stroke is related with the incidence of STE in patients with LVH. Patients with stroke are more likely to have STE, and the incidence of STE is 2.11-fold higher than that without stroke. The mechanism is not clear. We believe this might be related to brain-heart interaction, a group of heart disease secondary to central nervous system disorders, such as stroke [24–26]. Previous publications have reported that ECG abnormalities in stroke occur in 70% -80% of cases, and are mainly represented as ST-T

abnormalities (including STE) [27–30]. In the current study, we found that superimposed stroke based on electrocardiographic LVH results in a significant increase in the incidence of STE.

Previous publications indicate that infection has important effects on the cardiovascular system. That pneumonia is a risk factor for acute cardiac complications has been documented thoroughly in several large cohorts [31,32]. Therefore, we included infection as a potential risk factor in the logistic regression analysis. According to the results of the multiple logistic regression analysis, patients combined with infection and electrocardiographic LVH are more prone to STE, and the incidence of STE is increased by 108% compared with non-infected patients. Several mechanisms, related to the systemic response to infection, can account for the ST-T change. Acute inflammation can influence cardiac metabolic supply-to-demand ratio, depress myocardial function and increase left ventricular afterload [32–34].

Given the high incidence of LVH, our findings have important implications. Clinicians need to realize the importance of secondary STE in patients with LVH and exercise appropriate clinical alertness to avoid misdiagnosing non-ischemic STE as ischemic STE. An adequate estimation of the risk of STE secondary to electrocardiographic LVH will require new strategies that adequately weigh clinical factors associated with non-ischemic STE in our study. We found that a value of S_{V1}+R_{V5} larger than 4.8 mV, stroke, and infectious disease are independent risk factors for STE in patients with LVH. Physicians should be keenly aware of the possibility of nonischemic STE secondly to LVH in patients with an S_{V1}+R_{V5} larger than 4.8 mV, or combined with infection or stroke to avoid false-positive cardiac catheterization laboratory activation. It should be emphasized that since we have eliminated other factors that may cause ST segment elevation, such as myocardial infarction, the myocardial enzymes in most of the cases we included are normal. Therefore, applying the conclusion of this research to cases with normal myocardial enzymes might have higher specificity.

Limitations First, we analyzed the clinical features of patients with STE caused by LVH to help differential diagnosis. However, we did not explore the clinical features of STEMI with LVH. However, risk factors, such as hypertension, diabetes, hyperlipidemia, and smoking history, have been identified as risk factors for STEMI [1]. These risk factors, which have been widely used to identify ischemic STE and STE secondary to LVH in clinical practice, may be important clinical features of STEMI in patients with LVH. Second, we did not collect cardiac ultrasound or magnetic resonance (MR) results from cases of electrocardiographic LVH to verify true LVH on structure [35]. However, previous studies have found that electrocardiographic LVH itself, not depending on structural hypertrophy, is a risk factor for misdiagnosis of STEMI [35]. Third, there are currently several ECG criteria available for the diagnosis of LVH, including the Sokolow-Lyon standard, Cornell standard, and Gubner-Ungerleider standard. This study only used the Sokolow-Lyon standard to diagnose ECG LVH. However, the Sokolow-Lyon criterion has a higher diagnostic specificity, which is recommended by the guidelines for hypertension [30,36]. Fourth, the potential influencing factors we included may not be comprehensive, and there may be other potential influencing factors for ST segment elevation that have not been included and analyzed. However, the factors we analyzed cover common clinical indicators and factors already mentioned in the literature.

More importantly, the factors we include in the analysis are easy to obtain, being routine indicators of clinical laboratory tests. Therefore, the potential influencing factors we discussed could be applied to different grades of hospitals, enabling our conclusions to have broader application.

Conclusion

Physicians should be keenly aware of the possibility of nonischemic STE secondary to electrocardiographic LVH. An S_{V1}+R_{V5} value larger than 4.8 mV, stroke, and infection are independent risk factors for STE in patients with electrocardiographic LVH.

Declarations

Ethics approval and consent to participate

The study was approved by the ethics committee of the First Affiliated Hospital of Shantou University Medical College. The need for consent was waived because of the retrospective data. Dr. Xiansheng Huang granted administrative permission to access the raw data.

Consent to publish

Not applicable.

Availability of data and materials

Raw data supporting the obtained results are available at the corresponding author.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

HG, WZ, XH and JZ contributed to the conception and design, analysis and interpretation of data, drafting of the manuscript. CN, ZC and SC contributed to the collection, analysis, and interpretation of the data. XH contributed to the conception and design and revised it critically for important intellectual content. All authors read and approved the final manuscript.

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Figures

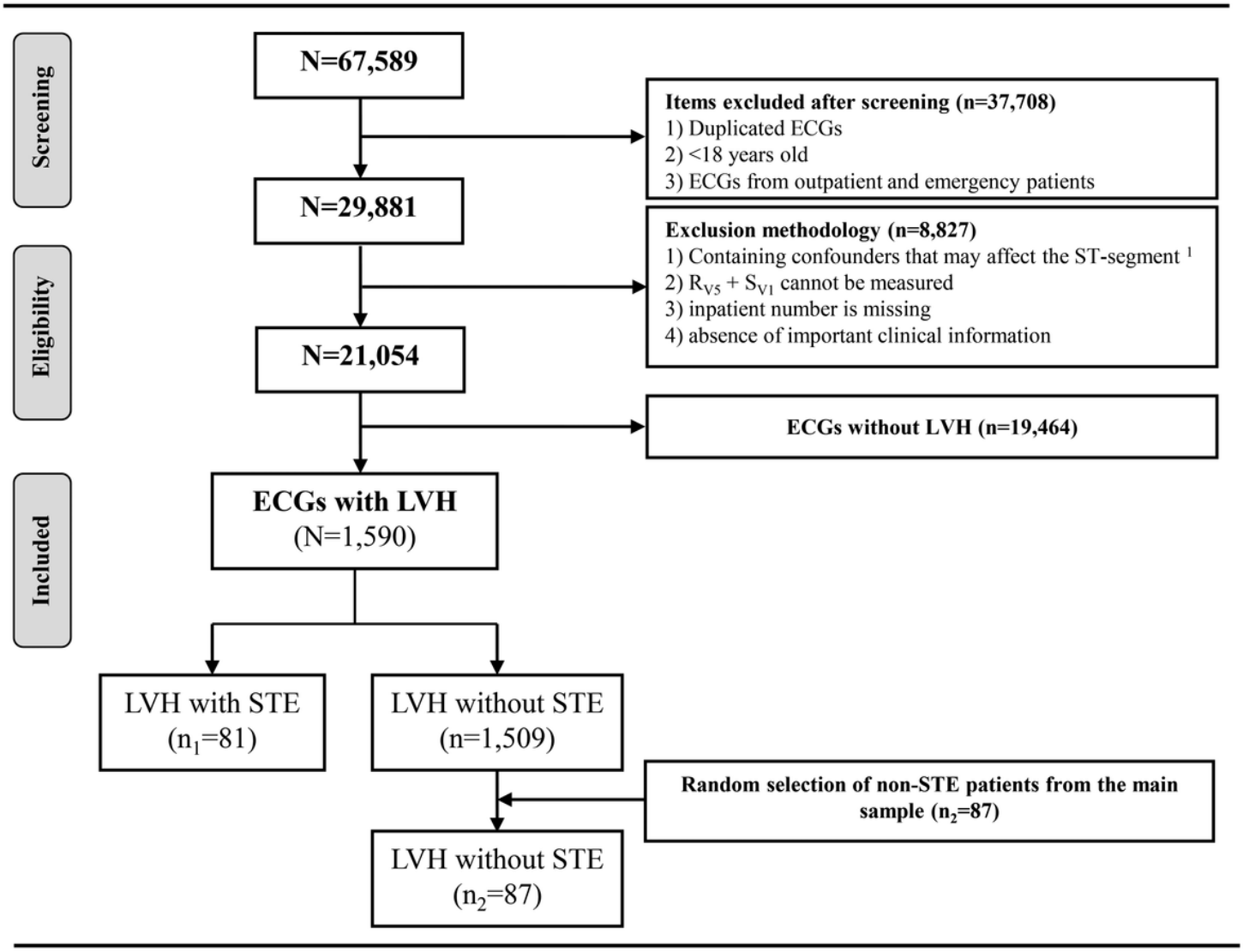

Figure 1

The complete procedure of the participants selection and exclusion. 1 Confounders including acute myocardial infarction, old myocardial infarction, conduction block, ectopic rhythm, pacemaker implantation, myocarditis, pericarditis, congenital heart disease, or cardiomyopathy. ECG= Electrocardiograph; LVH= left ventricular hypertrophy; STE= ST-segment elevation.

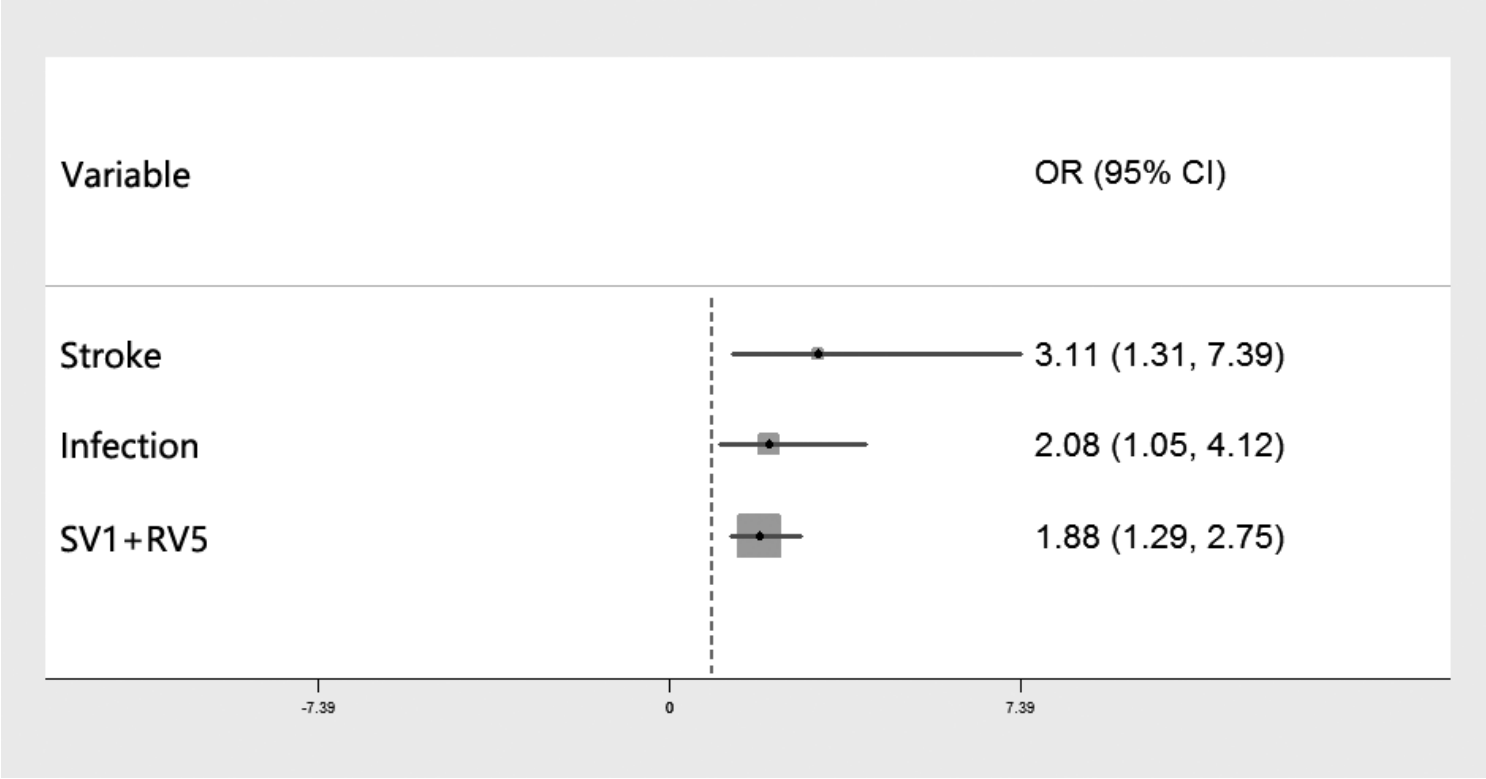

Figure 2

Multivariate logistic regressions analysis for STE secondary to LVH LVH= left ventricular hypertrophy; STE= ST-segment elevation.

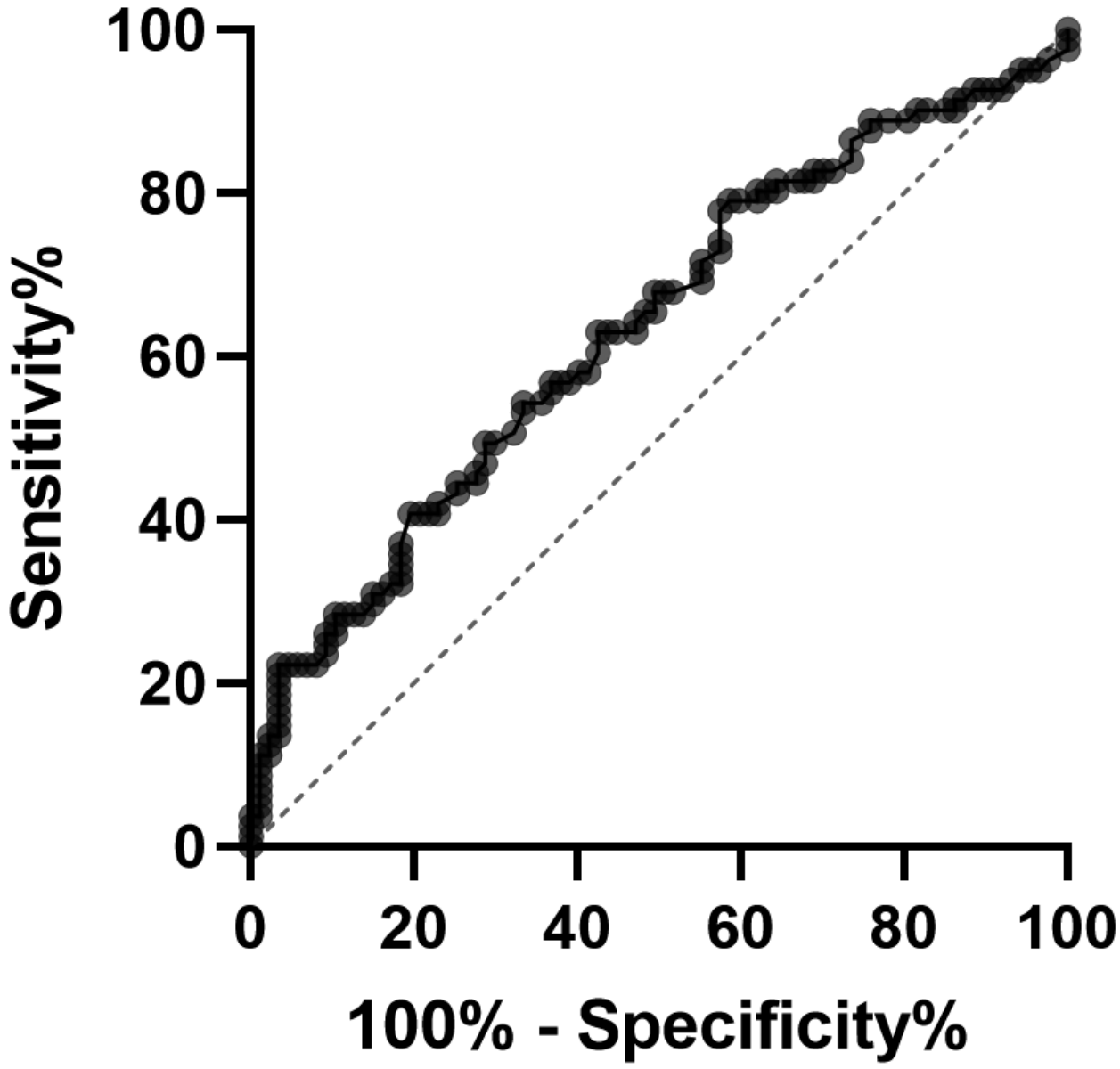

Figure 3

Receiver operator characteristic (ROC) curve for SV1+RV5 predicting STE in patients with LVH LVH= left ventricular hypertrophy; STE= ST-segment elevation.