

Predictive Value of Electrocardiogram for the Occurrence of Major Adverse Cardiac Events in Patients with Pulmonary Embolism

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Abstract

Background

Pulmonary embolism (PE) is one of the most prevalent cardiovascular diseases worldwide. A few studies have advocated the applicability of electrocardiogram (ECG) for the determination of prognosis of PE patients. Considering the low-cost and wide availability of ECG we aimed to investigate the association of selected ECG parameters with the occurrence of major adverse cardiac events (MACE) in PE patients.

Methods

In this study, 733 adult patients admitted with a definite diagnosis of acute PE were included from a registry of PE patients in a tertiary heart center. The patients' clinical records were retrospectively reviewed, and demographic information, ECG abnormalities as well as the data on MACE (including hypotension, mechanical ventilation, Syncope, cardiogenic shock, or in-hospital mortality) were extracted.

Results

A total of 177 patients (24.1%) had MACE. Right bundle branch block (RBBB), incomplete RBBB, S1Q3T3, ST elevation in leads V1 or III, QR wave in lead V1, and inverted T wave in lead V1 to V4 were more frequently detected in the ECGs of patients who developed MACE (P values = 0.006, 0.030, 0.001, 0.001, 0.042, 0.001, and 0.001, respectively). The results of multivariate regression analysis demonstrated that ST-elevation in aVR (OR = 3.87, 95%CI = 2.32–6.44, P = 0.001) and S1Q3T3 (OR = 2.04, 95%CI = 1.22–3.43, P = 0.007) were independent predictors of MACE in PE patients. The sensitivities of ST elevation in the aVR lead and S1Q3T3 were 53.1% and 59.9%, and specificities were 79.7% and 68.1%, respectively.

Conclusion

Some ECG parameters including S1Q3T3 and ST elevation in aVR are independent predictors of MACE in patients with PE. Investigating these parameters in ECG can be helpful in the determination of the prognosis of PE patients.

Introduction

Pulmonary embolism (PE) is one of the most prevalent cardiovascular diseases with an incidence of 39–115 per 10,000 population (1–3). Thrombolytic drugs are administered in patients with PE presenting with cardiogenic shock. However, low molecular weight or unfractionated heparin are considered as the therapeutic choices for hemodynamically stable patients (1). Therefore, an optimal selection of therapies for PE patients relies on risk stratification and identifying those in need of more aggressive types of treatment to improve prognosis.

Right ventricular dysfunction determined by transthoracic echocardiography or elevated biomarkers (cardiac troponin or natriuretic peptide) have been suggested by some studies to have a significant association with prognosis in PE patients (4–6). However, transthoracic echocardiography is not widely available in all centers and interpretation is largely operator-dependent.

About 70 percent of patients with PE have abnormal electrocardiograms (ECG)s, which comprise a wide range of changes including arrhythmia (supraventricular or ventricular tachycardia), conduction abnormalities (right bundle branch block [RBBB]), deviation of the electrical axis of the heart (left or right axis deviation [LAD and RAD]), changes in the P-wave shape, QRS wave amplitude, and QT dispersion (7). Previous studies have investigated various ECG parameters in the diagnosis of PE, but the results were not consistent (8–10). Therefore, ECG findings are not currently considered specific for the diagnosis of PE. However, some studies have advocated the applicability of ECG for the determination of PE prognosis. In a study carried out by Akgüllü et al., QT interval dispersion and P wave dispersion were significantly associated with early death in acute PE (11). Moreover, Escobar et al. proposed that sinus tachycardia and atrial arrhythmia were independent predictors of a poor prognosis in hemodynamically stable PE patients (12). Considering the low cost and wide availability of ECG, we aimed to investigate some parameters of ECG that have been previously underappreciated in PE patients and to examine their association with the occurrence of major adverse cardiac events (MACE).

Methods

In this study, 1,064 patients (age range: 18–80 years) admitted with a definite diagnosis of acute PE between April 2011 and April 2017 were included from a registry of PE patients in a tertiary heart center (center name hidden for peer review). The diagnosis of patient must have been confirmed by computed tomography (CT) scan or lung perfusion scan to be included in our study. The exclusion criteria were antiarrhythmic medication use such as digoxin, severe metabolic diseases such as hypokalemia, myocardial infarction, heart failure, angina pectoris, sepsis, congenital heart disease, cor pulmonale, presence of left bundle branch block (LBBB) in admission ECG, pacemaker, and lack of an interpretable standard ECG in the first 24 hours of the onset of symptoms.

The study was conducted in accordance with the declaration of Helsinki. The protocol of the study was approved by the medical ethics committee of the university (university name hidden for peer review). Written informed consent was obtained from all patients for entering their data into the registry of patients with pulmonary embolism.

Measurements and definitions

The patients' clinical records were retrospectively reviewed, and demographic information, including age and gender, were recorded in the prepared checklists. Data on MACE was extracted from patients' files. MACE was defined as the occurrence of at least one of the following events:

- Hypotension: Systolic blood pressure (BP) less than 90 mmHg

- Mechanical ventilation
- Syncope: A transient loss of consciousness due to insufficient blood flow to the brain
- Cardiogenic shock: A significant reduction in BP (systolic BP < 90 mmHg) lasting more than 30 minutes and accompanied by symptoms of end-organ hypoperfusion
- In-hospital mortality due to PE complications.

ECG analysis

We analyzed the patients' ECG, which was obtained in the first 24 hours since the onset of symptoms using a supine, standard 12-lead ECG at 25 mm/s paper speed, and 10 mm/mV amplitude by MAC 500 ECG machine (GE medical system, USA). The investigations of ECG parameters were conducted manually with the help of a magnifying glass by two experienced cardiologists who were blind to the clinical data of the patients. Three consecutive beats were investigated for the analyses, where at least 10 leads were analyzable.

The following ECG changes were recorded in the checklist: ST-T changes in precordial leads, S1Q3T3, RBBB, incomplete RBBB (iRBBB), ST elevation in lead V1, ST elevation in lead III, ST elevation in lead aVR, low voltage QRS, QR wave in lead V1, and inverted T wave in leads V1 to V4.

Inverted T wave was defined as a T wave > 2 mm below the isoelectric line in two or more adjacent leads (V1 to V4).

Statistical analysis

The analysis was performed by Stata version 16 (StataCorp, USA). The Kolmogorov-Smirnov test was used to analyze the normality of quantitative variables. For those variables with normal distribution, we made comparisons between two groups by independent-sample t-test, and the descriptive statistics were presented as mean \pm SD. For numeric variables that were not normally distributed, we made comparisons between two groups by the Mann-Whitney U test, and the descriptive statistics were presented as median (25–75 percentiles). To analyze categorical data, we used a chi-square test and reported the Kappa value, and the descriptive statistics were presented as frequency (percentages). Multiple logistic regression analysis was performed to investigate the association between study variables and the occurrence of the MACE.

Furthermore, we used the receiver operating characteristic (ROC) curve to determine the area under the curve (AUC). Accordingly, the sensitivity, specificity, likelihood ratio (+), likelihood ratio (-), positive predictive value, and negative predictive value were reported. The P values less than 0.05 were considered as statistically significant.

Results

Of 1,064 patients with PE included in the study 331 patients were excluded (aged over 80 years in 107 patients, lack of CT angiography or perfusion scan in 110 patients, low EF in 41 patients, LBBB in 28 patients, non-interpretable ECG in 14 patients, acute on chronic PE in 14 patients, permanent pace maker in 5 patients, digoxin use in 4 patients, cor pulmonale in 2 patients, congenital heart disease in 2 patients, other critical diseases in 2 patients, and recent myocardial infarction (MI) and septic embolism in 2 patients). The final population consisted of 733 PE patients with a mean age of 57.60 ± 15.73 years. Of these, 379 patients (51.7%) were male, and 354 patients (48.3%) were female.

The investigated ECG parameters in PE patients are described in Table 1. The most common sign was the presence of an inverted T wave, which was seen in 306 patients (41.9%). Other common signs were S1Q3T3 in 283 patients (38.6%), ST elevation in aVR in 206 patients (28.2%), iRBBB in 138 patients (18.9%), and ST elevation in V1 in 123 patients (16.8%). In majority of patients (91.4%), the ratio of S wave to R wave in lead I was more than 1.

Table 1

ECG findings in included patients and with respect to the occurrence of major adverse cardiac events

ECG sign		Total	Major adverse cardiac events			
			Positive	Negative	Kappa value	P-value*
RBBB	Positive	56 (7.7)	22 (12.4)	34 (6.1)	0.82	0.006
	Negative	676 (92.3)	155 (87.6)	520 (93.9)		
iRBBB	Positive	138 (18.9)	43 (24.3)	94 (17)	0.79	0.030
	Negative	594 (81.1)	134 (75.7)	460 (83)		
S1Q3T3	Positive	283 (38.6)	106 (59.9)	177 (31.9)	0.23	0.001
	Negative	450 (61.4)	71 (40.1)	378 (68.1)		
Low voltage QRS	Positive	89 (12.2)	23 (13)	65 (11.7)	0.15	0.653
	Negative	643 (87.8)	154 (87)	489 (88.3)		
ST elevation in V1	Positive	123 (16.8)	45 (25.4)	78 (14.1)	0.12	0.001
	Negative	608 (83.2)	132 (74.6)	475 (85.9)		
ST elevation in III	Positive	24 (3.3)	10 (5.6)	14 (2.5)	0.44	0.042
	Negative	708 (96.7)	167 (94.4)	540 (97.5)		
ST elevation in aVR	Positive	206 (28.2)	94 (53.1)	112 (20.3)	0.31	0.001
	Negative	524 (71.8)	83 (46.9)	441 (79.7)		
ST depression in V1	Positive	10 (1.4)	0 (0)	10 (1.8)	-0.27	0.072
	Negative	720 (98.6)	176 (100)	543 (98.2)		
QR wave in V1	Positive	40 (5.5)	18 (10.3)	22 (4)	0.86	0.001

RBBB, Right bundle branch block; iRBBB, Incomplete right bundle branch block

	Negative	690 (94.5)	157 (89.7)	532 (96)		
R/S wave ratio in I	≤ 1	398 (94.7)	121 (94.5)	277 (94.9)	0.40	0.847
	> 1	22 (5.2)	7 (5.5)	15 (5.1)		
inverted T wave	Positive	306 (41.9)	95 (53.7)	210 (38)	0.12	0.001
	Negative	424 (58.1)	82 (46.3)	342 (62)		
RBBB, Right bundle branch block; iRBBB, Incomplete right bundle branch block						

A total of 177 patients (24.1%) had MACE. The mean age in the MACE and control (no MACE) groups was 56.77 ± 1.16 and 57.93 ± 0.68 years, respectively ($p = 0.408$). Also, 100 patients (56.5%) in the MACE group and 278 patients (50.3%) in the control group were male ($P = 0.167$).

RBBB, iRBBB, S1Q3T3, ST elevation in leads V1 or III, QR wave in lead V1, and inverted T wave in lead V1 to V4 were more frequently detected in the ECGs of patients who developed MACE (P values = 0.006, 0.030, 0.001, 0.001, 0.042, 0.001, and 0.001, respectively).

Logistic regression analysis showed that age ($P = 0.395$) and sex ($P = 0.150$) had no significant relationship with the occurrence of MACE.

The results of multivariate regression analysis on the relationship between the ECG signs and the occurrence of MACE are described in Table 2. ST-elevation in aVR (OR = 3.87, 95%CI = 2.32–6.44, $P = 0.001$) and S1Q3T3 (OR = 2.04, 95%CI = 1.22–3.43, $P = 0.007$) were independent predictors of MACE. Other ECG signs in patients with PE were not significantly associated with the occurrence of MACE.

Table 2

The results of multiple regression analysis of the association of ECG findings in included pulmonary embolism patients and the occurrence of major adverse cardiac events

ECG sign		95 % CI			
		Adjusted OR	lower	upper	P value
RBBB	Positive	1.48	0.71	3.08	0.286
	Negative	ref	-	-	
iRBBB	Positive	1.08	0.62	1.88	0.760
	Negative	ref	-	-	
S1Q3T3	Positive	2.04	1.22	3.43	0.007
	Negative	ref	-	-	
Low voltage QRS	Positive	1.09	52/0	2.25	0.814
	Negative	ref	-	-	
ST elevation in V1	Positive	1.12	0.7	1.78	0.634
	Negative	ref	-	-	
ST elevation in III	Positive	1.87	0.68	2.36	0.448
	Negative	ref	-	-	
ST elevation in aVR	Positive	3.87	2.32	6.44	0.001
	Negative	ref	-	-	
ST depression in V1	Positive	Empty	-	-	-
	Negative	ref	-	-	-
QR wave in V1	Positive	1.81	0.78	4.16	0.161
	Negative	ref	-	-	-
R/S wave ratio in I	1 \leq	ref	-	-	-
	1 $>$	77/1	64/0	88/4	0.161
inverted T wave	Positive	1.32	0.82	2.11	0.247
	Negative	ref	-	-	-

RBBB, Right bundle branch block; iRBBB, Incomplete right bundle branch block

The ROC curve was plotted for two variables that had a significant relationship with the occurrence of MACE (Fig. 1). The results of ROC analysis and the predictive values of ST elevation in the aVR lead and

S1Q3T3 for the occurrence of MACE are described in Table 3. The predictive values of ST elevation in the aVR lead and S1Q3T3 for the occurrence of MACE were moderate (the AUC for ST elevation in the aVR lead = 0.664, and for S1Q3T3 = 0.640). The sensitivity of ST elevation in the aVR lead and S1Q3T3 was 53.1 and 59.9%, and specificity was 79.7 and 68.1%, respectively.

Table 3
The prognostic power of ST elevation in aVR and S1Q3T3 for the occurrence of major adverse cardiac events

	Value (95% CI, Lower – Upper)	
	ST elevation in aVR	S1Q3T3
Sensitivity	53.1% (45.5% - 60.6%)	59.9% (52.3% - 67.2%)
Specificity	79.7% (76.2% - 83%)	68.1% (64.1% - 72%)
ROC area	0.66 (0.62 - 0.70)	0.64 (0.59 - 0.68)
Likelihood ratio (+)	2.62 (2.11 - 3.25)	1.88 (1.58 - 2.23)
Likelihood ratio (-)	0.588 (0.50 - .69)	0.58 (0.48 - 0.71)
Positive predictive value	45.6% (38.7% - 52.7%)	37.5% (31.8% - 43.4%)
Negative predictive value	84.2% (80.7% - 87.2%)	84.2% (80.5% - 87.4%)

Discussion

According to the guidelines of the European Society of Cardiology (ESC), the risk stratification and determination of the prognosis of the PE patients is necessary and can be helpful in choosing the best therapeutic strategy (1). However, the applicability of ECG changes for determining the prognosis of PE patients is under debate. Inverted T wave in precordial leads, S1Q3T3, and ST elevation in aVR were the most common ECG parameters in PE patients. These findings were also previously remarked as the most common ECG abnormalities in PE patients (9, 13–15). Furthermore, the results of the current study showed that some changes in ECG, including RBBB, iRBBB, S1Q3T3 sign, ST elevation in leads V1 and III, QR wave in lead V1, and inverted T wave in precordial leads were significantly more frequent in the MACE group than the control group. ST elevation in lead aVR and S1Q3T3 sign were associated with a higher risk of MACE during hospitalization. Although the sensitivity and positive predictive value of these changes were low, the specificity and negative predictive value were high. Therefore, these parameters in ECG can be considered as a cheap and widely available tool for rolling out the PE patients who are not at high risk of MACE. A similar study by Kukla et al. on 292 acute PE patients also reported that atrial fibrillation, S1Q3T3 sign, negative T waves in leads V2–V4, ST-segment depression in leads V4–V6, ST-segment elevation in leads III, V1 and aVR, QR in lead V1, RBBB, higher number of leads with negative T waves, and higher sum of the amplitude of negative T waves were more frequent in patients who experienced PE complications (7). Moreover, in multivariate analysis, ST-segment elevation in leads aVR

(OR 2.49; $p = 0.011$) was identified as an independent predictor of complications during hospitalization. Nevertheless, this study did not report the sensitivity and specificity of these parameters for predicting the occurrence of complications during hospitalization (7). Also, Janata et al. investigated 396 PE patients and revealed that ST elevation in aVR was the only significant predictor of mortality in the intermediate-risk group. However, this association was not detected in high-risk patients (16). In a larger study conducted on 508 PE patients, Geibel et al. demonstrated that the presence of at least one of the following ECG findings, besides hemodynamic instability, syncope, and pre-existing chronic pulmonary disease, was a significant independent predictor of early (30-day) mortality. These ECG findings were atrial arrhythmias, complete RBBB, peripheral low voltage, Q waves in leads III and aVF, and ST-segment elevation or depression over the left precordial leads. In this study, the association of ECG findings with in-hospital mortality was not evaluated individually (17). Moreover, some prior studies used a combination of different ECG signs to develop a scoring system. Toosi et al. investigated a 21-point system based on ECG changes in 159 acute PE patients and reported that having a score of ≥ 3 in this scale can predict the occurrence of right ventricular dysfunction with high sensitivity and specificity of 76 and 82 percent, complicated disease course with moderate sensitivity and specificity of 58 and 60 percent, and mortality incidence with moderate sensitivity and specificity of 59 and 58 percent, respectively (10). Iles et al. evaluated a similar 21-point scoring system based on ECG changes on 229 PE patients and reported that an ECG score of ≥ 3 predicted those with $> 50\%$ perfusion defect with a sensitivity of 70% (95% confidence interval [CI], 59 to 81%), and a specificity of 59% (95% CI, 51 to 67%) (18). Another study also used a 21-point ECG score to predict right ventricular dysfunction, and reported a sensitivity of 92% and a negative predictive value of 97%; similarly, complications during hospitalization were predicted with sensitivity and negative predictive value of 75% and 92%, respectively (19). These studies suggested that ECG can be considered as a useful tool for the determination of the prognosis of PE patients; however, none of them investigated the association of the ECG findings individually with PE prognosis.

As far as we investigated, our study was the largest study that evaluated the prognosis of PE patients based on their ECG findings. Moreover, we reported sensitivity, specificity, and predictive value as well as OR and 95% CI for each ECG abnormalities individually in order to better clarify the association of ECG findings with the occurrence of MACE to be used in the clinical setting. However, our study had some limitations. We did not evaluate the laboratory data, medical and drug history, clinical presentation, echocardiographic findings, and medications administered during hospitalization for all the patients. This was partially due to some missing data of the patients' files. As a result, we did not adjust the outcome for these confounding variables, which can be considered as a possible source of bias for our findings.

Moreover, we excluded the patients who had a positive history of taking antiarrhythmic medication such as digoxin, severe metabolic disease such as hypokalemia, myocardial infarction, heart failure, angina pectoris, sepsis, congenital heart disease, cor pulmonale, LBBB in admission ECG, and permanent pacemaker. These patients were excluded due to the possibility of ECG changes caused by these abnormalities that could interfere with the ECG changes due to PE. However, the exclusion of these patients can partially limit the generalizability of our findings as a considerable proportion of the PE patients have at least one of these abnormalities.

Conclusion

Some parameters of ECG, such as S1Q3T3 and ST elevation in aVR, are independent predictors of MACE in patients with PE. Investigation of these parameters in ECG can be considered as a cheap and widely available strategy for the determination of the prognosis of PE patients, in particular for rolling out those who have less possibility of experiencing MACE.

Declarations

Ethics approval and consent to participate: The study was conducted in accordance with the ethical guidelines of the declaration of Helsinki and the protocol was approved by the ethics committee of the university.

Consent for publication: Not applicable.

Availability of data and materials: All Data and material collected during this study are available from the corresponding author upon reasonable request.

Conflicts of interest/Competing interests: None declared.

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Authors' contributions: Conceptualization: FS, EJ, SG; Methodology: FS, SM, SRSE; Formal analysis and investigation: SG, FS, SRSE; Writing (original draft preparation): SRSE, FS; Writing (review and editing): FS, EJ, SG, SM; Funding acquisition: SG; Resources: FS, SG; Supervision: SG, EJ

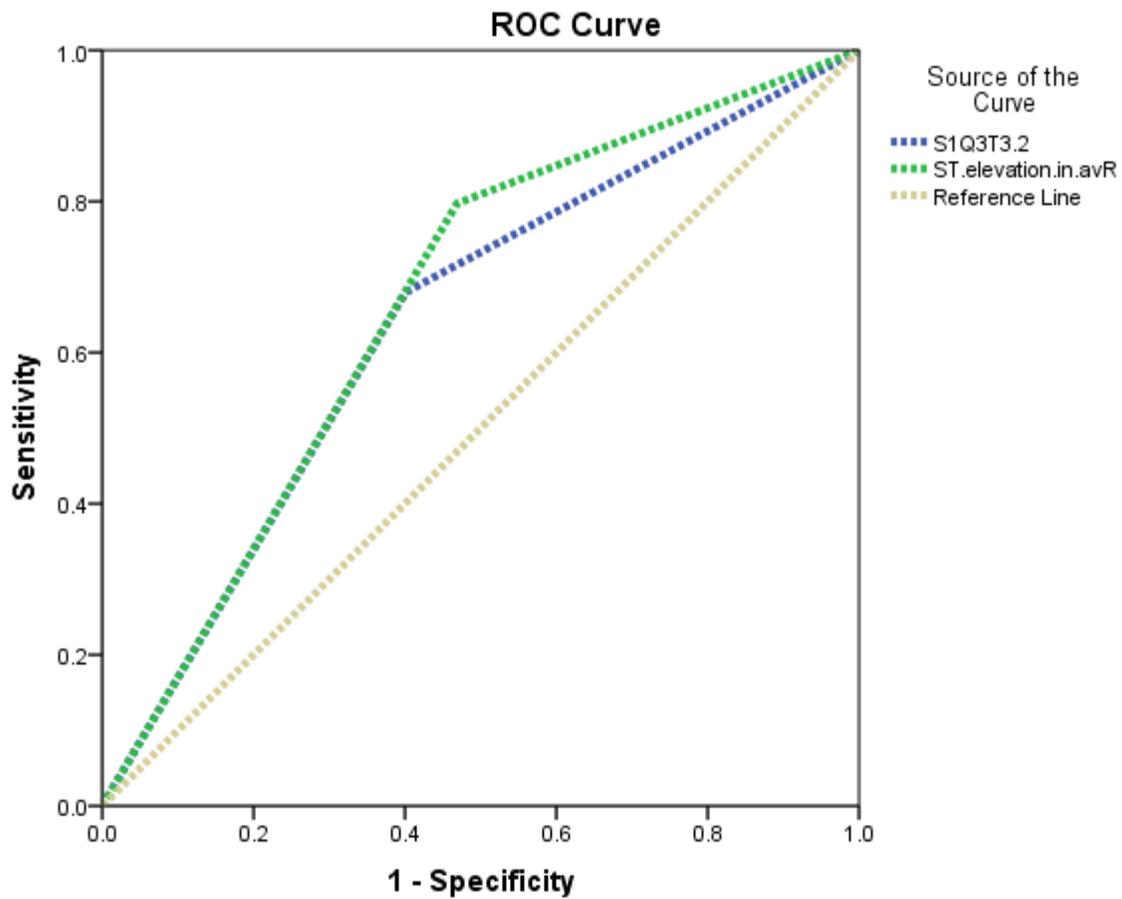
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Figures



Diagonal segments are produced by ties.

Figure 1

ROC curve for the prognostic value of S1Q3T3 and ST elevation in aVR lead for the occurrence of major adverse cardiac events in patients with pulmonary embolism