ORIGINAL ARTICLE

Clinical Significance of ST Elevation in Lead aVR in Acute Pulmonary Embolism

Leili Pourafkari, M.D.,*† Samad Ghaffari, M.D.,* Arezou Tajlil, M.D.,* Fariborz Akbarzadeh, M.D.,* Farin Jamali, M.D.,* and Nader D. Nader, M.D., PH.D.†

From the *Cardiovascular Research Center, Tabriz University of Medical Sciences, Tabriz, Iran; and †Anesthesiology Department, University at Buffalo, Buffalo, NY, USA

Background: Prognostic stratification of patients with acute pulmonary embolism (PTE) is crucial in identifying patients who would benefit from more aggressive treatment. We aimed to examine the value of ST elevation in lead aVR (ST_{EaVR}) in predicting hospital mortality following PTE.

Materials: Two hundred patients with a diagnosis of PTE were allocated into two groups based on the presence or absence of ST_{EaVR}. Multivariate logistic regression analysis was used to investigate the role of “ST_{EaVR}” in relation to the other risk factors in predicting prognosis of PTE.

Results: Out of 200 patients, 24 (12.0%) had ST_{EaVR}. Patients with ST_{EaVR} were more likely to present with hypotension and tachycardia than those who did not have this electrocardiographic finding. A total of 33.3% of patients with ST_{EaVR} and 13.1% of those without ST_{EaVR} died during hospitalization. ST_{EaVR} had a low sensitivity of 25.8% but a high specificity of 90.5% for predicting hospital mortality. Odds ratio for hospital mortality was 3.32 for ST_{EaVR} with 95% confidence interval of 1.28–8.64 ($P = 0.017$) in univariate analysis. In multivariate analysis shock was the strongest predictor of hospital mortality.

Conclusion: The presence of ST_{EaVR} is indicative of hemodynamic instability, thereby having the ability to predict poor outcome. However, its impact on hospital mortality disappears when the presence of shock on admission is factored in the prediction model.

Ann Noninvasive Electrocardiol 2017;22(2):e12368, <https://doi.org/10.1111/anec.12368>

pulmonary embolism; electrocardiography; hospital mortality

Acute pulmonary embolism (PTE) is a common fatal event worldwide that needs immediate diagnosis and appropriate treatment.¹ The choice of a proper therapeutic approach in treating patients with acute PTE is highly dependent on the risk of complications and mortality.^{1,2} For this reason, different scoring systems are developed to prognosticate the patients suffering an acute PTE.^{3–5} However, electrocardiography (ECG), an easily accessible diagnostic modality, in risk stratification of patients with acute PE, is highly underutilized in clinical settings.^{6–8}

Although prognostic value of several common ECG patterns is investigated in patients with PTE,^{6,7} the prognostic role of the changes in lead aVR is not well described.⁸ However, with

increasing evidence that findings in lead aVR reveal important clinical information in various diseases, a few studies have been carried out to determine the prognostic value of ST segment elevation in this lead (ST_{EaVR}) following an acute PTE.^{9–13} While the results of these studies imply that ST_{EaVR} is suggestive of a more severe course of pulmonary embolism, the independency of its impact is a matter of controversy.^{9,11,14} In this context, it is worthwhile to determine whether this electrocardiographic finding independently provides further information for predicting hospital mortality in patients with confirmed diagnosis of PTE.

Based on these facts, we conducted a cohort cross-sectional study to evaluate the independent

Address for correspondence: Nader D. Nader, M.D., Ph.D., F.A.C.C., F.C.C.P., University at Buffalo, Buffalo, 252 Farber Hall, Main Campus, 3435 Main Street, Buffalo, NY 14214, USA. Tel: +17163457909 Fax: +17168293640; E-mail: nnader@buffalo.edu

Conflict of interests: None

Funding: None

© 2016 Wiley Periodicals, Inc.
DOI: 10.1111/anec.12368

significance of STE_{aVR} in predicting hospital mortality of patients who were admitted with acute PTE. We also investigated the association of STE_{aVR} with transthoracic echocardiographic (TTE) evidence of right ventricular enlargement/dysfunction. We hypothesized that the presence of STE_{aVR} was associated with significant right heart failure, and thereby contributing to higher hospital mortality rates.

METHODS AND MATERIALS

The design of the study was reviewed and approved by institutional review board at Tabriz University of medical sciences. The study was exempted from informed consent due to its non-interventional design and minimal risk to the patients. However, during all study stages, complete patients privacy was maintained.

Inclusion Criteria and Definitions

Medical records of 200 consecutive patients, who were admitted to the main university-affiliated heart center with a confirmed diagnosis of acute PTE from 2012 to 2014, were reviewed. The diagnosis of PTE was confirmed with computed tomography angiography (CTA) in all patients. All patients underwent ECG recording upon admission and TTE by an experienced cardiologist. Standard 12-lead ECG was recorded on admission using a paper speed of 25 mm/s and standardization of 10 mm/1 mV. The primary independent variable STE_{aVR} was defined as ST segment elevation of 1 mm or more from the J point on admission ECG in aVR lead. ECGs of patients were investigated to determine the presence of atrial fibrillation (AF), right bundle branch block (RBBB), P-pulmonale, S1Q3T3 pattern, and right axis deviation in frontal and precordial leads. During two-dimensional TTE the presence of right ventricular dysfunction and right ventricular enlargement were specifically sought. Tricuspid annular plane systolic excursion (TAPSE) was used for grading right ventricular dysfunction. Normal TAPSE was considered 2.4–2.7 cm, with lesser values indicating mild (2.0–2.3 cm), moderate (1.5–1.9 cm), and severe (<1.5 cm) RV dysfunction. Cutoff of 3.3 cm at mid right ventricular level was used for the definition of right ventricular enlargement. Furthermore, right

ventricular diastolic diameter, right ventricular systolic pressure, and left ventricular ejection fraction were measured by TTE examinations and were recorded for each patient.

Exclusion Criteria

Patients with ECG evidence of left bundle branch block or nonspecific intraventricular conduction delay, history of myocardial infarction, coronary artery bypass grafting, or pacemaker implantation were excluded. Additionally, those with a diagnosis of chronic obstructive pulmonary diseases or chronic thromboembolic pulmonary embolism were also excluded from this study.

Protocol for Thrombolytic Therapy

Patients were treated based on therapeutic protocol of our hospital under direct supervision of a clinical cardiologist. Patients with hemodynamic instability, syncope on presentation, or history of recent syncope, as well as patients with positive cardiac troponin-I (cTNI) in the presence of severe right ventricular dysfunction received unfractionated heparin coupled with intravenous thrombolytic therapy with 1.5 million units of streptokinase over 2 hours unless the risk of bleeding outweighed the benefits of thrombolytic therapy. In stable patients, low molecular weight heparin or unfractionated heparin was administered. After 48 hours of treatment with anticoagulants, warfarin was initiated to achieve the target international normalized ratio ranging between 2.0 and 3.0.

Study Design and Primary Study Outcome

Patients were allocated into two groups based on the presence or absence of STE_{aVR}. Baseline demographic characteristics of patients as well as clinical, ECG, TTE, and therapeutic data were compared in patients with and those without STE_{aVR}. Hospital mortality was the main primary endpoint of this study while hospital length of stay and evidence for right ventricular dysfunction were considered the secondary endpoints. The impact of STE_{aVR} on the primary and secondary endpoints was determined.

Statistical Analysis and Sample Size Determination

Sample size was determined using an online calculator (<http://powerandsamplesize.com/Calculators/>) and a three-times increase in the mortality of the first 100 patients admitted with PTE (pilot project). This rate of the increase in hospital mortality was comparable to those reported by Kukla et al. who also reported a three-times increase in mortality from 6.9% to 16.5%. The ratio of patients with STE_{aVR} to those without STE_{aVR} was 1:8 in our study; therefore the required sample size with alpha error of 0.05 and power of 0.80 was 20 patients with STE_{aVR}. From the total of 200 patients, there were 24 who had STE_{aVR} finding in their admission ECG. Data were transferred into an Excel worksheet and were analyzed with statistical software PASW Statistics SPSS Version 22.0 (IBM Inc. Chicago, IL, USA). Continuous variables were presented as the mean $\pm$ standard deviation and categorical variables were stated as frequencies and percentages. Chi-square analysis or Fisher's exact test was used as appropriate to compare the frequencies of categorical variables. Comparison of continuous variables between study groups were made with the use of independent *t*-test. Logistic regression analysis was used to determine the independent role of STE_{aVR} in predicting hospital mortality. Two-way analysis of variance is used to examine the interaction between hypotension and right ventricular dysfunction on the effect of STE_{aVR} on mortality rate. Multivariate regression analysis was performed with adjustment for age, gender, and the presence of hypotension at presentation. Receiver operative characteristics curves were plotted to calculate the sensitivity and specificity for prediction of mortality by STE_{aVR}. Statistical significance was defined as $P < 0.05$.

RESULTS

General and Clinical Characteristics

From 200 patients admitted with PTE, 24 (12.0%) had STE_{aVR} (>1 mm). Average age of the patients (61.0 ± 17.5 years) was similar in both groups. While female gender comprised slightly less than one half of all patients (47.5%), they were more likely to have STE_{aVR} compared to men (20.0% vs 4.8% $P = 0.001$). There was no difference in the frequency of comorbid coronary risk factors, for

example, hypertension, hyperlipidemia, and diabetes, between the two groups (Table 1). Among identifiable risk factors for PTE, history of recent immobilization was significantly higher in patients with STE_{aVR} (62.5% vs 31.4%, $P = 0.005$). From the presenting symptoms, tachycardia and shock (systolic blood pressure < 90 mmHg) were more common in patients with STE_{aVR} (79.2% vs 47.7%, $P = 0.008$ and 25% vs 9.8%, $P = 0.041$, respectively). Although, the frequencies for tachypnea, dyspnea on exertion or at rest, pleuretic chest pain, and syncope were comparable in both groups (Table 1). Thrombolytic treatment was offered to 42 (21.0%) patients with comparable distribution among those with or without STE_{aVR}. Minorities of patients were treated with digitalis; calcium channel blockers and beta-adrenergic blocking drugs which were equally distributed with regard to the presence of STE_{aVR} (Table 1).

Association between Other Electrocardiographic Findings and STE_{aVR}

The presence of ST segment elevation in lead aVR was associated with other electrocardiographic findings either due to similar direction of the injury vector or the extent of right side strain. There was no significant difference in prevalence of right bundle branch block (RBBB), atrial fibrillation, S1Q3T3 pattern, qR wave in lead V₁, and P-pulmonale between the patients with STE_{aVR} and those without this ECG finding. In patients with STE_{aVR}, the likelihood of ST segment elevation increases by 24.8% in the limb lead III ($P = 0.002$). There were reciprocal changes associated with the presence of STE_{aVR} in the form of ST segment depression in lead I ($\rho = 0.248$; $P < 0.001$), lead II ($\rho = 0.165$; $P = 0.020$), lead aVL ($\rho = 0.243$; $P = 0.001$), lead aVF ($\rho = 0.142$; $P = 0.047$), and in precordial leads V₄ through V₆ (Table 2).

Echocardiographic Findings

Right ventricular diastolic diameter was similar in patients with and those without STE_{aVR} (36.3 ± 6.9 mm vs 38.0 ± 7.9 mm; $P = 0.293$) as there was no correlation between the presence of right ventricular enlargement and STE_{aVR}. Similarly, prevalence of right ventricular dysfunction

Table 1. Comparison of Patients with and Those without ST Segment Elevation in Lead aVR for Baseline Characteristics, the Prevalence of Risk Factors, Clinical Manifestation, and Treatments Rendered

	(+) STE _{aVR} (N = 24)	(-) STE _{aVR} (N = 176)	ρ	P Value
Age	60 $\pm$ 16	61 $\pm$ 18		0.761
Female	19 (79.2%)	76 (43.2%)	0.233	0.001*
Massive pulmonary thromboembolism	23 (95.8%)	150 (86.2%)	0.092	0.187
Obesity (body mass index > 30 kg/m ²)	1 (4.2%)	5 (2.9%)	0.025	0.727
Use of oral contraceptive pill	0 (0.0%)	12 (6.9%)	-0.094	0.188
Deep vein thrombosis	2 (8.3%)	29 (16.6%)	-0.071	0.382
Recent immobility	15 (62.5%)	55 (31.4%)	0.212	0.003*
Past/current smoker	1 (4.2%)	38 (21.7%)	0.143	0.046*
History of neoplastic disease	1 (4.2%)	9 (5.1%)	-0.015	0.837
NY Heart Association functional class III & IV	0 (0.0%)	2 (1.1%)	-0.037	0.606
Hyperlipidemia	3 (12.5%)	13 (7.4%)	0.061	0.394
Diabetes	4 (16.7%)	17 (9.8%)	0.079	0.292
Stroke	0 (0.0%)	5 (2.9%)	-0.060	0.403
Clinical manifestations				
Dyspnea on exertion	18 (75.0%)	137 (78.7%)	-0.030	0.679
Tachypnea	18 (75.0%)	139 (79.9%)	-0.039	0.594
Tachycardia	19 (79.2%)	83 (47.7%)	0.205	0.004*
Dyspnea at rest	10 (41.7%)	81 (46.6%)	-0.032	0.670
Syncope	5 (20.8%)	20 (11.5%)	0.092	0.197
Systolic blood pressure < 90 mmHg (shock)	6 (25.0%)	17 (9.8%)	0.155	0.029
Pleuretic chest pain	2 (8.3%)	20 (11.5%)	-0.033	0.646
Hemoptysis	0 (0.0%)	5 (2.9%)	-0.060	0.403
Therapeutic modalities				
Thrombolytic therapy	8 (33.3%)	34 (19.5%)	–	0.179
Digitalis	2 (8.3%)	16 (9.1%)	–	0.627
Dobutamine	1 (4.2%)	0 (0.0%)	–	0.121
Calcium channel blockers	5 (20.8%)	16 (9.1%)	–	0.088
Beta-blockers	9 (37.5%)	52 (29.7%)	–	0.289

Asterisks signify statistically significant with a confidence interval of 95%.

was not associated with STE_{aVR} after PTE. Pulmonary pressures were uniformly high in all patients with PTE (52 $\pm$ 16 mmHg) as calculated by tricuspid valve regurgitation gradient. Right ventricular systolic pressures were 48 $\pm$ 14 mmHg in patients with STE_{aVR}, which were similar to those of 55 $\pm$ 16 mmHg in patients without STE_{aVR} (P = 0.445). There was no significant difference in left ventricular ejection fraction in patients with and those without STE_{aVR} (Table 3).

Clinical Outcome and Hospital Mortality

Thirty-one patients (15.5%) died during the course of their hospitalization, and the frequency

of death was also higher in patients with STE_{aVR} (33.3% vs 13.1%; P = 0.017). Peak concentrations of cTNI were comparable between survivors and those who died in the hospital (0.89 $\pm$ 2.14 vs 0.29 $\pm$ 0.83 ng/mL; P = 0.172). The presence of STE_{aVR} did not demonstrate any correlation with the peak concentrations of cTNI in the plasma (P = 0.347). Among eight patients with STE_{aVR} in whom thrombolysis was utilized, four (50%) did not survive. On the other hand, only three (8.8%) of cases without STE_{aVR} who received thrombolytic therapy did not survive (P = 0.017). Duration of hospital stay was 10.4 $\pm$ 10.7 days in all patients and since most of deaths occurred within short time after admission; duration of hospitalization was not significantly different among the

Table 2. Concomitant Electrocardiographic Findings Related to the Presence of ST Segment Elevation in Lead aVR (ST_EaVR)

	(+) ST _E aVR (N = 24)	(-) ST _E aVR (N = 176)	ρ	P Value
Right bundle branch block	3 (12.5%)	14 (8.0%)	0.053	0.436
Atrial fibrillation	3 (12.5%)	9 (5.1%)	0.101	0.161
S1Q3T3	7 (29.2%)	31 (17.6%)	0.096	0.175
Axis deviation	3 (12.5%)	49 (27.8%)	–	0.206
qR wave	3 (12.5%)	14 (8.0%)	0.052	0.440
P-pulmonale	4 (16.7%)	49 (28.2%)	–0.085	0.326
ST elevation of one millimeter or more				
Lead I	0 (0.0%)	2 (1.1%)	–0.037	0.602
Lead II	2 (8.3%)	4 (2.3%)	0.115	0.153
Lead III	5 (20.8%)	6 (3.4%)	0.248	<0.001*
Lead aVL	0 (0.0%)	1 (0.6%)	–0.026	0.713
Lead aVF	0 (0.0%)	3 (1.7%)	–0.046	0.522
Lead V ₁	2 (8.3%)	12 (6.8%)	0.019	0.792
Lead V ₂	1 (4.2%)	17 (9.7%)	–0.063	0.377
Lead V ₃	0 (0.0%)	14 (8.0%)	–0.102	0.152
Lead V ₄	0 (0.0%)	6 (3.4%)	–0.065	0.360
Lead V ₅	0 (0.0%)	3 (1.7%)	–0.046	0.520
Lead V ₆	0 (0.0%)	2 (1.1%)	–0.037	0.601
ST depression of 1 mm or more				
Lead I	5 (20.8%)	6 (3.4%)	0.248	<0.001*
Lead II	4 (16.7%)	8 (4.5%)	0.165	0.020*
Lead III	0 (0.0%)	6 (3.4%)	–0.065	0.360
Lead aVL	3 (12.5%)	2 (1.1%)	0.243	0.001*
Lead aVF	2 (8.3%)	3 (1.7%)	0.142	0.047*
Lead V ₁	0 (0.0%)	3 (1.7%)	–0.045	0.527
Lead V ₂	3 (12.5%)	8 (4.6%)	0.118	0.100
Lead V ₃	3 (12.5%)	7 (4.0%)	0.132	0.066
Lead V ₄	5 (20.8%)	7 (4.0%)	0.238	0.001*
Lead V ₅	4 (16.7%)	8 (4.5%)	0.171	0.016*
Lead V ₆	4 (16.7%)	5 (2.8%)	0.223	0.002*

Asterisks signify statistically significant with a confidence interval of 95%.

survivors and nonsurvivors. Similarly, the duration of hospital stay was similar between the group of patients with ST_EaVR and those without this finding (Table 4).

Receiver operator characteristic analysis revealed that ST_EaVR was not a significant predictor of hospital mortality (Area under the curve AUC = 0.58 ± 0.06; P = 0.114). While ST_EaVR had a low sensitivity of 25.8%, it had a relatively high specificity of 90.5% and positive predictive value of 86.9%. Odds ratio (OR) for hospital mortality was 3.32 for ST_EaVR with 95% confidence interval (CI) of 1.28–8.64 (P = 0.017) in univariate

analysis. Nonetheless, its inclusion in a multivariate model along with gender, acute troponin leakage > 0.20 ng/mL, right ventricular dilatation, and presence of shock state, ST_EaVR was not independently associated with hospital mortality (OR = 2.31, 95% CI: 0.77–6.94; P = 0.137) (Table 5). Female gender was an independent predictor of mortality as it tripled the risk after an acute PTE. Additionally, right ventricular dilatation was an independent predictor of hospital mortality. Presenting at a state of shock was the strongest predictor of hospital mortality after PTE (AUC = 0.62 ± 0.06; P = 0.032). It carried a

Table 3. Echocardiographic Assessment of Both Right and Left Ventricles Comparing of Patients with and without ST Segment Elevation in Lead aVR

Echocardiographic Findings	(+) STE _{aVR}	(-) STE _{aVR}	ρ	P Value
Right ventricular dilatation	14 (58.3%)	104 (60.5%)	-0.001	0.828
Right ventricular diastolic diameter (mm)	36.4 $\pm$ 6.9	38.0 $\pm$ 7.9	-	0.293
Right ventricular hypertrophy	2 (9.1%)	5 (3.1%)	0.102	0.169
Right ventricular dysfunction	2 (8.3%)	26 (15.2%)	-0.061	0.822
Mild	15 (62.5%)	74 (43.0%)	-	0.283
Moderate	0 (0.0%)	8 (4.7%)	-	
Severe	2 (8.3%)	18 (10.5%)	-	
Right ventricular systolic pressure (mmHg)	48 $\pm$ 14	55 $\pm$ 16		0.445
Left ventricular hypertrophy	0 (0.0%)	5 (2.1%)	-0.062	0.406
Left ventricular ejection fraction (%)	51.3 $\pm$ 3.5	49.5 $\pm$ 8.1	-	0.538

Table 4. Comparison of Clinical Outcome and Mortality in Relation to ST Segment Elevation in Lead aVR with Univariate Odds Ratios for Predicting Study Outcomes

	(+) STE _{aVR}	(-) STE _{aVR}	Odds Ratio	P Value
Shock state on admission	6 (25.0%)	17 (9.8%)	3.08 (1.08–8.80)	0.036*
Cardiac arrest	9 (37.5%)	22 (12.6%)	4.15 (1.62–10.61)	0.003*
Cardiac troponin-I leak (>0.2 ng/ml)	3 (12.5%)	31 (18.0%)	0.65 (0.18–2.32)	0.506
Hospital mortality	8 (33.3%)	23 (13.1%)	3.32 (1.28–8.64)	0.017
Mortality in patients with no RV dysfunction	2 (28.6%)	5 (6.9%)	5.36 (0.82–34.94)	0.056
Hospital length of stay (days)	10.7 $\pm$ 11.3	8.4 $\pm$ 4.4	-	0.076

Asterisks signify statistically significant with a confidence interval of 95%.

sensitivity of 32.3% and a specificity of 92.2% in predicting hospital mortality. Since the state of shock correlated with the presence of STE_{aVR} ($\rho = 0.155$; $P = 0.029$), inclusion of shock in multivariate analysis effectively eliminated the significance of STE_{aVR} in predicting hospital mortality because of the existing covariance between these two factors (Table 5).

DISCUSSION

We demonstrated that female gender, the presence of STE_{aVR}, concomitant myocardial injury, the state of shock, and echocardiographic evidence of right ventricular dilatation were individually associated with poor hospital outcome. Female gender remained an independent predictor of mortality in our study. Although the rate of death following an acute PTE was originally reported to be higher in men,¹⁵ studies in the last two decades have demonstrated a fundamental shift in this pattern as the absolute rate of death is currently higher among women.^{16,17} Agarwal

et al.¹⁶ report a modest 9% increase in hospital mortality among female patients with acute PTE. The association was much stronger in our study as we report approximately 2.5 times higher death rates in women during hospitalization. In a recent report women have been different from male patients in terms of signs and symptoms on presentation, as well as, the extent and location of the culprit thrombus.¹⁸

Bedside electrocardiography is readily available and is routinely performed in every patient who is admitted to the emergency rooms with symptoms of acute PTE. Therefore, it is clinically important to identify an electrocardiographic marker, which can be used for the determination of the associated risks and prognosis. In line with this goal, certain ECG patterns, for example, S1Q3T3 and qR wave in lead V₁, are proposed to assist with diagnosis or risk assessment of acute PTE. All ECG findings suffer from low sensitivity and specificity in diagnosing acute PTE. Both S1Q3T3 pattern and the presence of qR wave in lead V₁ have low sensitivity and specificity in determining the clinical

Table 5. Univariate and Multivariate Analysis for the Predictors of the Hospital Mortality

Predictors	Univariate OR	P value	Multivariate OR	P Value
ST _{EaVR}	3.32 (1.28–8.64)	0.017*	2.31 (0.77–6.94)	0.137
S1Q3T3 ECG pattern	1.30 (0.51–3.28)	0.581		
qR Pattern in Lead V ₁	1.18 (0.32–4.37)	0.806		
Age (year)	1.02 (0.99–1.04)	0.220		
Female gender	2.70 (1.20–6.07)	0.017*	3.24 (1.24–8.49)	0.017
Previous/current smoking	0.39 (0.11–1.37)	0.142		
Coronary artery disease	0.68 (0.19–2.40)	0.545		
Diabetes mellitus	1.32 (0.41–4.21)	0.644		
Hyperlipidemia	0.76 (0.16–3.52)	0.724		
Dyspnea at rest	1.78 (0.82–3.87)	0.144		
Shock state on admission	5.64 (2.20–14.47)	<0.001*	6.38 (2.14–19.04)	0.001
Right ventricular dilatation	2.91 (1.12–7.51)	0.028*	4.20 (1.40–12.56)	0.010
Right ventricular systolic pressure	1.05 (0.98–1.12)	0.143		
Left ventricular ejection fraction	0.96 (0.88–1.04)	0.286		
Thrombolytic treatment	1.08 (0.83–2.70)	0.873		
Beta-blockers	0.91 (0.39–2.12)	0.893		
Acute troponin leak (>0.20 ng/ml)	2.29 (0.95–5.55)	0.066*	1.28 (0.44–3.74)	0.647
Multivariate logistic regression for hospital mortality (gender * ST _{EaVR} * RV dilatation * troponin leak)				
Female gender			2.74 (1.12–6.71)	0.027*
ST _{EaVR}			3.01 (1.06–8.52)	0.038*
Right ventricular dilatation			3.22 (1.18–8.77)	0.022*
Acute troponin leak (>20 ng/mL)			1.93 (0.72–5.21)	0.194

*Asterisks indicate the predictors that were selected to be included in multivariate analysis model based on a probability ≤ 0.100 .

outcome of acute PTE. In this study, we have shown that ST_{EaVR} is associated with higher frequency of cardiovascular collapse and hospital mortality even in patients receiving thrombolytic therapy. Despite a lower sensitivity, ST_{EaVR} is reasonably specific in predicting the occurrence of death within hospital. A similar association has been shown with cardiac arrest and the state of shock with systolic blood pressures less than 90 mmHg at the time of admission.

A few studies have recently investigated the relationship between ST segment changes in lead aVR and prognosis of patients with acute PTE.^{9,11,19} A recent meta-analysis about the prognostic value of various ECG findings in patients with acute PTE, identifies heart rates > 100 bpm and the presence of S1Q3T3 pattern, complete RBBB, T wave inversion in leads V₁ through V₄, atrial fibrillation, and ST_{EaVR}, as six electrocardiographic findings that predict the development of hemodynamic collapse or hospital death. Among

these factors, T wave inversion in leads V₂ and V₃, and ST_{EaVR} with respective odds ratios of 6.94, 7.07, and 5.24 have had the highest impact on poor hospital outcome.²⁰ However, the studies that are included in this meta-analysis, except for the study by Janata et al., focus on ST_{EaVR} in the context of other electrocardiographic findings. This method of predictive modeling is the most likely explanation for the higher cumulative odds ratio that is reported in this meta-analysis compared to our study.

In a research conducted by Kukla et al., ST_{EaVR} is reported in 45.5% of sample population and it is associated with a worse prognosis in the course of acute PTE. According to their results, ST_{EaVR} has a sensitivity of 66.7% and specificity of 57.3% for predicting hospital mortality.⁹ However, in our study, the presence of ST_{EaVR} has a sensitivity of 25.8% and specificity of 90.5% for predicting hospital mortality. In another study, ST_{EaVR} is detected in 35% of patients and is

associated with a poor prognosis only in a subset of patients with intermediate risk but not in all study populations.¹¹ However, it should be noted that in these studies, the association of STE_{aVR} with hospital mortality is only investigated individually.^{9,11} Aside from these two studies, which directly evaluate the prognostic value of STE_{aVR} in patients with acute PTE, there are some other reports that investigate various combinations of electrocardiographic patterns to predict the prognosis of patients with acute PTE.^{10,13,14,19,21} It has been demonstrated that the presence of STE in at least one of the leads III, aVR and V₁–V₄, or ST segment depression in at least two lateral leads is associated with a higher mortality in patients with intermediate risk in the univariate analysis.¹³

Interestingly, when we further examine the association of STE_{aVR} with hospital mortality in context with other confounding factors, such as female gender, the presence of RV dilatation, and acute leakage of cardiac troponin, STE_{aVR} still comes out as an independent predictor of hospital mortality. Nevertheless, when multivariate analysis includes the presence of shock on admission, the predictive role of STE_{aVR} disappears as an independent factor. Since there is a significant association between the state of shock on admission and STE_{aVR} in our cohort, we believe that the covariance between these two factors is the main reason that STE_{aVR} loses its significance by inclusion of shock. Furthermore, we speculate that STE_{aVR} is merely an electrocardiographic manifestation of shock in patients with acute PTE. In a consensus by the European Society of Cardiologists, the presence of shock has been identified as an independent factor predicting hospital mortality in patients with PTE.¹ In the current study, we also show that patients admitted with systolic blood pressures less than 90 mmHg are more likely to succumb to death during the course of their hospitalization. In another study, Kukla et al.¹⁰ included different electrocardiographic findings in a multivariate analysis and found that STE_{aVR} is independently associated with the occurrence of complications during hospitalization but not with mortality. Nevertheless, in a subset of patients with cardiogenic shock, these authors do not report any significant association between STE_{aVR} and hospital mortality.¹⁴

We further report a significant rate of hospital mortality in patients who developed acute

dilatation of the right ventricle after PTE. This finding is in agreement with previous reports that have suggested right ventricular dysfunction and elevated pulmonary artery pressure as indicators of poor prognosis in acute PTE, particularly in those with concurrent hypotension.^{22,23} To understand any possible association between STE_{aVR} and RV dysfunction/dilatation, we have examined the correlation between echocardiographic evidence of RV strain and STE_{aVR}. Similar to the results reported by Kukla et al.,⁹ we failed to establish any association between the size of the right ventricle and STE_{aVR}. Such an association has been only reported in a single study by Janata et al.,¹¹ but it has not been reproduced by others.

On the other hand, our results suggest that the presence of STE_{aVR} is associated with ST depression in leads V₄–V₆ but not with electrocardiographic signs of right ventricular strain. This may suggest that the presence of STE_{aVR} is indicative of left ventricular ischemia rather than right ventricular failure. In a study by Zhan et al., ECG recordings of the patients with pulmonary emboli have been investigated at baseline and later during hemodynamic instability. They have shown that the occurrence of STE_{aVR} with concomitant STD in lead I/V₄–V₆ is more prevalent in the course of hemodynamic instability during hospitalization and described this pattern as a sign of subendocardial left ventricular ischemia.¹⁹ In another study, Zahn et al.²¹ evaluated a subset of patients with T inversion on ECG and found a higher rate of mortality in patients with concomitant subendocardial ischemic pattern.

It should also be noted that lead aVR is a calculated lead using lead I and II. Thus, ST elevation in lead aVR is always accompanied by ST depression in either lead I and/or lead II. Since the vectors in aVR are summation of these vectors, the information retrieved from this lead cannot be independent of the others and they will merely be an association. Consequently, although helpful, ST elevation in aVR cannot be expected to provide independent information that is not retrieved by careful analysis of the other leads in the electrocardiogram.

In summary, the presence of STE_{aVR} is indicative of hemodynamic instability, thereby predicting poor outcome and increase in hospital mortality. However, its impact on hospital mortality disappears when the presence of shock on

admission is factored in the prediction model. This is significant as an electrocardiographic indicator of cardiovascular collapse and cardiac arrest due to the extent of obstruction to the right ventricular outflow. This study has several limitations. Our population included patients stable enough to undergo imaging studies, for example, CT angiography or echocardiography. Consequently, we missed patients who presented with cardiac arrest or expired shortly after admission. Furthermore, due to a lack of any angiographic data, patients with unknown coronary artery disease may have been included in this study. Larger studies with consideration of hospital presentation delay would help in the better evaluation of electrocardiographic changes in the course of pulmonary emboli.

Acknowledgments: *The work was presented as a brief abstract in 2015 NYSSA 69th Post Graduate Assembly in December 2015 in New York, USA.*

REFERENCES

- Konstantinides SV, Torbicki A, Agnelli G, et al. 2014 ESC guidelines on the diagnosis and management of acute pulmonary embolism. *Eur Heart J* 2014;35:3033–3069, 69a–69k.
- Carson JL, Kelley MA, Duff A, et al. The clinical course of the pulmonary embolism. *N Engl J Med* 1992;326:1240–1245.
- Gibson NS, Sohne M, Buller HR. Prognostic value of echocardiography and spiral computed tomography in patients with pulmonary embolism. *Curr Opin Pulm Med* 2005;11:380–384.
- Kostrubiec M, Pruszczyk P, Bochowicz A, et al. Biomarker-based risk assessment model in acute pulmonary embolism. *Eur Heart J* 2005;26:2166–2172.
- Aujesky D, Obrosky DS, Stone RA, et al. Derivation and validation of a prognostic model for pulmonary embolism. *Am J Respir Crit Care Med* 2005;172:1041–1046.
- Kostrubiec M, Hryniewicz A, Pedowska-Wloszek J, et al. Is it possible to use standard electrocardiography for risk assessment of patients with pulmonary embolism? *Kardiol Pol* 2009 Jul;67:744–750.
- Kanbay A, Kokturk N, Kaya MG, et al. Electrocardiography and Wells scoring in predicting the anatomic severity of pulmonary embolism. *Respir Med* 2007;101:1171–1176.
- Digby GC, Kukla P, Zhan ZQ, et al. The value of electrocardiographic abnormalities in the prognosis of pulmonary embolism: A consensus paper. *Ann Noninvasive Electrocardiol* 2015;20:207–223.
- Kukla P, Dlugopolski R, Krupa E, et al. The prognostic value of ST-segment elevation in the lead aVR in patients with acute pulmonary embolism. *Kardiol Pol* 2011;69:649–654.
- Kukla P, Dlugopolski R, Krupa E, et al. Electrocardiography and prognosis of patients with acute pulmonary embolism. *Cardiol J* 2011;18:648–653.
- Janata K, Hochtl T, Wenzel C, et al. The role of ST-segment elevation in lead aVR in the risk assessment of patients with acute pulmonary embolism. *Clin Res Cardiol* 2012;101:329–337.
- Zhong-qun Z, Chong-quan W, Nikus KC, et al. A new electrocardiogram finding for massive pulmonary embolism: ST elevation in lead aVR with ST depression in leads I and V4 to V6. *Am J Emerg Med* 2013;31:456. e5–e8.
- Kukla P, McIntyre WF, Fijorek K, et al. Use of ischemic ECG patterns for risk stratification in intermediate-risk patients with acute PE. *Am J Emerg Med* 2014;32:1248–1252.
- Kukla P, McIntyre WF, Fijorek K, et al. Electrocardiographic abnormalities in patients with acute pulmonary embolism complicated by cardiogenic shock. *Am J Emerg Med* 2014 Jun;32:507–510.
- Lilienfeld DE. Decreasing mortality from pulmonary embolism in the United States, 1979–1996. *Int J Epidemiol* 2000;29:465–469.
- Agarwal S, Clark D 3rd, Sud K, et al. Gender disparities in outcomes and resource utilization for acute pulmonary embolism hospitalizations in the United States. *Am J Cardiol* 2015;116:1270–1276.
- Horlander KT, Mannino DM, Leeper KV. Pulmonary embolism mortality in the United States, 1979–1998: An analysis using multiple-cause mortality data. *Arch Intern Med* 2003;163:1711–1717.
- Deng X, Li Y, Zhou L, et al. Gender differences in the symptoms, signs, disease history, lesion position and pathophysiology in patients with pulmonary embolism. *PLoS ONE* 2015;10:e0133993.
- Zhan ZQ, Wang CQ, Nikus KC, et al. Electrocardiogram patterns during hemodynamic instability in patients with acute pulmonary embolism. *Ann Noninvasive Electrocardiol* 2014;19:543–551.
- Shopp JD, Stewart LK, Emmett TW, et al. Findings from 12-lead electrocardiography that predict circulatory shock from pulmonary embolism: Systematic review and meta-analysis. *Acad Emerg Med* 2015;22:1127–1137.
- Zhan Z-Q, Wang C-Q, Wang Z-X, et al. Significance of ST-segment deviation in patients with acute pulmonary embolism and negative T waves. *Cardiol J* 2015;22:583–589.
- ten Wolde M, Söhne M, Quak E, et al. Prognostic value of echocardiographically assessed right ventricular dysfunction in patients with pulmonary embolism. *Arch Intern Med* 2004;164:1685–1689.
- Trujillo-Santos J, den Exter P, Gómez V, et al. Computed tomography-assessed right ventricular dysfunction and risk stratification of patients with acute non-massive pulmonary embolism: Systematic review and meta-analysis. *J Thromb Haemost* 2013;11:1823–1832.
- Zhong-qun Z, Bo Y, Nikus KC, et al. Correlation between ST-segment elevation and negative T waves in the precordial leads in acute pulmonary embolism: Insights into serial electrocardiogram changes. *Ann Noninvasive Electrocardiol* 2014;19:398–405.