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Original Article

Prognostic value of fragmented QRS in acute pulmonary embolism: a cross-sectional-analytic study of the Iranian population

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Abstract: Background: Acute Pulmonary embolism (APE) is considered one of the deadliest cardiovascular diseases. Electrocardiographic (ECG) abnormalities in pulmonary embolism (PE) are increasingly reported. A growing number of studies have recommended that ECG plays a crucial role in the prognostic assessment of PE patients. However, there is scarce data on the prognostic importance of fragmented QRS (fQRS) on outcomes in patients with APE. This study aims to investigate the prognostic value of fQRS in APE patients. Materials and Methods: This is a cross-sectional-analytic study. This study included 280 patients diagnosed with APE admitted to Shahid Madani hospital, Tabriz, Iran. Computed tomography pulmonary angiography (CTPA) was used to diagnose APE. A checklist was prepared for all patients, demographic, clinical characteristics, and Major Adverse Cardiopulmonary events (MACPE), including in-hospital mortality, need for thrombolysis, mechanical ventilation, and surgical embolectomy, were recorded. Patients were divided into two groups: patients who manifested fQRS on their ECG and patients who did not; Then, demographic, clinical characteristics, and MACPE were compared in the two groups, as mentioned earlier. Furthermore, all statistical analyses were carried out using SPSS software. Results: 48 patients (17.14%) had fQRS(+) on their ECG, and 232 patients (82.86%) did not have it on their ECG. In data analysis, 22 patients (8.7%) had in-hospital mortality, 35 patients (13.9%) needed thrombolysis, nine patients (3.9%) required mechanical ventilation, and 13 patients (5.1%) needed surgical embolectomy. fQRS was not significantly associated with in-hospital mortality (P = 0.225), need for thrombolysis (P = 0.684), mechanical ventilation (P = 1.000), and surgical embolectomy (P = 1.000). Demographic and clinical characteristics were also similar in both groups. Conclusions: This study does not support the idea that fQRS on ECG is a valuable predictor of in-hospital mortality, the need for thrombolysis, mechanical ventilation, and surgical embolectomy.

Keywords: Fragmented QRS (fQRS), acute pulmonary embolism (APE), prognostic value

Introduction

Acute pulmonary embolism (APE) has been reported as a global crisis as it is able to cause significant morbidity and mortality rates. APE diagnosis is generally a challenging issue, and considering clinical manifestations is essential in this regard [1]. The most common symptoms are Dyspnoea, chest pain, and cough, while fever, tachycardia, abnormal pulmonary signs, and peripheral vascular collapse are also the most frequently observed physical findings. Cyanosis, hemoptysis, syncope, and the different clinical symptoms of acute cor pulmonale can seldom be present. Local disturbances in pulmonary circulation, pleural involvement, or impaired coronary circulation can probably cause pain. If small distal pulmonary artery (PA)

embolization occurs, pulmonary infarction and the following pleural irritation will produce chest pain. In addition, typical angina may appear because of RV ischemia in central PE cases.

The diagnosis can become more complicated if a patient has a history of pulmonary disease or heart failure; because deteriorating dyspnoea may be the only symptom indicative of PE, which makes it more difficult to be quickly diagnosed [2]. The most important predictive factors of mortality are blood pressure drop and shock, which occur only in 20 percent of the patients; accordingly, in the case of the standard hemodynamic profile, other findings should be evaluated carefully to estimate the probability of complication development and death [3, 4]. Electrocardiographic changes may be observed in acute pulmonary embolism, including arrhythmia (sinus tachycardia, atrial fibrillation, atrial flutter), P wave changes, QRS morphology, and axis deviation, non-specific ST segment and T wave changes in suitable side leads, S113T3 complex (S wave in the lead I, Q wave in lead III and T wave in lead III) and complete/incomplete right bundle branch block (RBBB) [5]; all of which are not cutting edge diagnostic hallmark due to a high degree of overlap with other cardiovascular events.

In such a fatal situation, individual diagnostic tests, each on their own, may lead to the maladministration of suspected PE cases. Consequently, integrated diagnostic approaches that offer a combination of different diagnostic tests are preferred, which can result in a lower risk of severe complications [6].

According to medicine reference books, physicians use the Wells scoring system to estimate the risk of venous thromboembolism in a suspected subject; according which the first step is to measure the pre-clinical test probability of the disease. If the probability of deep vein thrombosis or pulmonary embolism is low (0-1) to moderate (2-6), the D-dimer test will be sufficient for the initial assessment. In this case, imaging diagnostic modalities will not be essential. An abnormal increased D-dimer blood level suggests further investigation using imaging techniques [7]. In addition to clinical probability tests, chest radiography, chest CT, lung scan, and blood analysis tests are non-imaging procedures that can be helpful.

The next step is reviewing treatment options and choosing the most beneficial one for the patient. In this stage, the venous thrombosis should be removed or resolved using drugs or surgery. Anticoagulants are the most commonly used drugs. A combination of Heparin or Fondaparinux and Warfarin is mostly recommended for patients. The aim is to keep INR in the 2-3 range and 2.5-3.5 if PE happens again. Duration of treatment ranges from 6 months to life-long based on the patient's situation [8]. The other option is thrombolysis. If a patient suffers from massive PE with unstable hemodynamics, thrombolysis can be beneficial as long as there is no contradiction. Patients with PE that have heart failure are also a group that can also benefit from this treatment [9]. Patients with contraindications for anticoagulation therapy or second emboli after treatment with anticoagulants are possible candidates for the placement of an Inferior vena cava filter, which may get removed as soon as the therapy with anticoagulants is a safe option for them [10]. Some patients should go under surgery. For example, chronic PE can raise pulmonary artery pressure and can be cured with a thromboendoarterectomy. Considering the poor long-term prognosis of surgery, it is not a common procedure for patients with PE [11]. Thus, the focus of recent studies has shifted to finding safer approaches such as EKGs' features.

Some studies investigated the clinical significance of fragmented QRS (fQRS) presence in ECGs and showed that fragmented QRS on a routine 12 lead surface electrocardiogram (ECG) could be a reasonable indication of the severity of cardiac involvement in different cardiac and systemic abnormalities. Fragmented QRS (fQRS) is defined as the presence of an R' wave, as well as the notching of an R or S wave in the company of narrow QRS. It indicates heterogeneous depolarization of the ventricular myocardium that can happen due to ischemia, fibrosis, or scarring. It may also demonstrate coronary microvascular dysfunction. It is a strong indicator of higher incidence rates of arrhythmias and sudden death in arrhythmic right ventricular dysplasia, Brugada syndrome, and acquired long QT syndrome. Its regression after cardiac resynchronization therapy shows reverse electrical remodeling. It has also been demonstrated to be indicative of myocardial involvement in congenital heart diseases and is

useful for diagnosing subclinical cardiac involvement in various systemic diseases [12]. According to a meta-analysis study on 1165 patients, fQRS was a statistically strong predictor of in-hospital mortality (OR: 2.92, 95% CI: 1.73-4.91; P < 0.001), all-cause-mortality at 2-year follow-up (OR: 4.42, 95% CI: 2.57-7.60; P < 0.001), and cardiogenic shock (OR: 4.71, 95% CI: 1.61-13.70; P = .005) in patients with pulmonary embolism [13].

Despite the poor sensitivity and specificity of ECG for diagnosing APE, it can play a crucial role in the prognostic assessment of patients dealing with Acute PE because of its ability to confirm other cardiovascular events like Acute coronary syndrome [14-20]. Also, doing an ECG test is low-cost, non-invasive, and available in every emergency room. Nevertheless, there is limited evidence on the prognostic value of fQRS in the detection of patients with Acute PE. Herein, we aimed to cross-sectionally investigate the prognostic importance of fragmented QRS in a population of 280-Iranian patients.

Method

Study population

In this study, we evaluated electronic documents of patients admitted to the Tabriz Shahid Madani cardiovascular, medical, and research centre with Acute Pulmonary Embolism (APE) diagnosis from March 2016 to September 2017. The inclusion criteria were considered as patients older than 18 years (>18) who were hospitalized in the mentioned medical and research center with the diagnosis of Acute Pulmonary Embolism (APE) according to the following criteria. The APE diagnosis was made using computed tomography pulmonary angiography (CTPA) and reviewed by at least two independent radiologists. A definite complete/partial filling defect in the pulmonary artery system in two consecutive CT sections was considered APE. Axial images were also used for diagnosis for discriminating clots from soft tissue if sagittal images were inadequate. Patients with a history of MI, paced rhythms, severe valvular heart disease, diastolic or systolic heart failure (CHF), LBBB, or RBBB were excluded. Finally, 280 cases were included in this study.

Instantly after the patient's admission, a 12-lead standard ECG was procured. All ECGs were evaluated by two cardiologists independently. Patients were divided into two groups based on the presence of fQRS on their ECGs: 1) patients with QRS fragmentation on ECG named fQRS(+); 2) patients without fQRS on ECG named fQRS(-) (fQRS criteria as defined above). Inter-observer or intra-observer variability was not assessed in ECG samples.

Ethical consideration

Patients' all personal data was restrictively preserved under the ethical codes of conduct by researchers. All patients gave their consent for participation in the study.

Demographic and clinical data, follow-up, and definitions

The follow-up process was conducted by reviewing patients' hospital medical records. Patients from centers dependent on Tabriz university of medical sciences with the diagnosis of acute pulmonary embolism based on computed tomography pulmonary angiography with no prior history of APE were included in this study.

Demographic and clinical information involving age, sex, blood pressure, smoking habits, diabetes mellitus, heart rate, and breathing rate were assessed. Instantly after admission, Ejection fraction values for the left ventricle were acquired via transthoracic echocardiography (TTE). These items were inspected in the two groups of participants with fQRS and without fQRS. Major adverse cardiopulmonary events (MACPE), such as in-hospital mortality events needed for surgery or thrombolysis and mechanical ventilation, were compared in the two groups of patients. In this study, in-hospital mortality was defined as death for any reason during hospitalization. Decision criteria for embolectomy Surgery, mechanical ventilation, or thrombolytic drug administration were defined according to cardiologists and cardiology residents. Cases presenting shock or hypotension alongside Acute PE were given IV thrombolysis (100 mg of recombinant tPA in 2 hours-long infusions) and intravenous UFH (unfractionated heparin). UFH administration protocol included an 80 U/kg bolus injection ensuing in an infusion rate of 18 U/kg/h. Measurement of aPTT (activated partial thromboplastin time was done four to six hours after bolus injection and three hours after dose regu-

Table 1. Comparison of demographic and clinical characteristic between study groups (n = 280)

Variables	*Group 1 (FQRS: n = 48)*	*Group 2 (non FQRS: n = 232)*	*P value*
Age	61.77±18.07	59.61±17.20	0.180
Gender			0.464
Male	22 (45.8%)	125 (53.9%)	
Female	26 (54.2%)	107 (46.1%)	
Hypertension	10 (20.8%)	77 (33.2%)	0.171
Diabetes	7 (14.6%)	30 (12.9%)	0.655
Hyperlipidemia	2 (4.2%)	22 (9.5%)	0.420
Smoking	5 (10.4%)	28 (12.1%)	0.773
Heart rate on Admission (beats/min)			0.839
< 100	24 (50%)	113 (48.7%)	
≥100	22 (45.8%)	112 (48.3%)	
Respiratory rate on Admission (breaths/min)			0.376
< 20	18 (37.5%)	112 (48.3%)	
≥20	24 (50%)	95 (40.9%)	
Blood sugar (mg/dL)	127.45±55.79	131.76±70.00	0.975

lation to preserve aPTT elongation according to therapeutic heparin levels. Cases with normotensive state and low-risk Acute PE without severe renal conditions (creatinine clearance rate of less than 30 ml/min) were given 1.0 mg/kg of enoxaparin every twelve hours. Warfarin was used alongside the treatment with parenteral anticoagulants. Warfarin dose administration was adjusted to 2.5 INR (international normalized ratio).

Indicators of surgery or thrombolysis

Thrombolysis treatment is indicated for patients with massive pulmonary embolisms and unstable hemodynamic profiles. This procedure is also indicated for APE patients with a prior cardiac arrest history.

Due to poor prognosis in the long term, surgery intervention for pulmonary embolism is uncommon. Latest technology developments have made surgery an effective procedure for a specific group of patients. For example, patients suffering from chronic pulmonary embolism that show increased pulmonary artery pressure can be treated with thrombi endarterectomy [11].

Statistical analysis

Continuous variables were indicated as mean ± SD, and categorical variables were designated as percentages. a *P*-value < 0.05 was accounted statistically noteworthy. Differences between cases and control participants were assessed using the two-sample t-test and the Mann-Whitney U test. Fisher's exact test or χ^2 test was utilized to compare categorical variables. Pearson correlation coefficients were calculated to determine the correlation between the variables' strength and type. The Chi-square test and t-test were utilized to compare and analyze categorical and continuous variables between the two groups, respectively. To evaluate the relationship between variables with the incidence of in-hospital adverse events and long-term all-cause mortality, univariate and multivariate Cox proportional hazard regression were respectively conducted. Kaplan Meier analysis was used for event-free survival in participants of two groups (with or without QRS). Statistical analyses were conducted using the SPSS statistical software (Version 23.0; SPSS Inc., Chicago, IL, USA).

Results

Patients characteristics

This study included 280 retrospectively followed cases diagnosed with APE. Patients were divided into two groups based on the presence of fQRs: fQRS(+) and fQRS(-). The patient's demographic and clinical data are presented in (**Table 1**).

Comparison between patients with fQRS(+) and fQRS(-)

Forty-eight of two hundred and eighty patients exhibited fQRS patterns based on previously

Table 2. The relationship of Major adverse cardiopulmonary events (MACPE) with the presence of Fragmented QRS (fQRS)

	FQRS [n (%)]			
MACPE events	Group 1 (FQRS)	Group 2 (non-FQRS)	Odds ratio (95% confidence interval)	*P* value
In-hospital mortality				
Yes	6 (14.3%)	16 (7.6%)	2.02 (0.74-5.51)	0.225
No	36 (85.7%)	194 (92.4%)		
Thrombolysis				
Yes	5 (11.9%)	30 (14.3%)	0.81 (0.29-2.22)	0.684
No	37 (88.1%)	180 (85.7%)		
Mechanical Ventilation				
Yes	1 (2.3%)	8 (4.3%)	0.61 (0.075-5.05)	1.000
No	41 (97.6%)	180 (95.7%)		
Embolectomy				
Yes	2 (4.8%)	11 (5.2%)	0.91 (0.19-4.23)	1.000
No	40 (95.2%)	199 (94.8%)		

mentioned criteria. Ten patients (20.8%) with fQRS(+) and 77 patients with fQRS(-) had hypertension, and no statistically significant difference was observed between the two groups. (*p* value: 0.171, **Table 1**). In the hemodynamic analysis of patients at admission, 137 patients had a heart rate below 100 bpm, 24 of these patients (50%) were in the fQRS(+) group. One hundred thirty-four cases had a heart rate of more than 100 bpm, 22 of whom had an fQRS pattern. No significant difference was observed during the analysis (*p* value: 0839, **Table 1**).

Clinical outcomes

Analysis of the in-hospital mortality rate between the two groups showed that six patients (14.3%) in the fQRS(+) and 16 in the fQRS(-) group had in-hospital death. In-hospital mortality rates of the two groups did not differ (*p* value: 0.225, **Table 2**).

5 fQRS(+) patients (11.9%) and 30 fQRS(-) patients (14.3%) underwent thrombolytic treatment. A *P*-value of 0.684 demonstrated an insignificant difference in the need for thrombolytic treatment administration. Amongst fQRS(+) patients, one (2.4%) and amongst the fQRS(-) group, eight (4.3%) received mechanical ventilation *p*-value was calculated to be one; therefore, it exhibited no substantial difference for the need to receive mechanical ventilation. Two patients (4.8%) with fQRS pattern and eleven (5.2%) without it were administered embolectomy *P*-value of one suggested no substantial difference between the two groups.

Discussion

When a patient with signs and symptoms of acute pulmonary embolism refers to the emergency department, taking ECG is one of the first diagnostic procedures [2]. Several pieces of research have indicated the importance of typical and prevalent disorders of ECG in evaluating the prognosis of patients with acute pulmonary embolism. Recent studies have reported that different disorders of ECG in patients with acute pulmonary embolism may forecast hemodynamic instability, magnitude, dysfunction of the right ventricle, increased pulmonary artery pressure (PAP), cardiogenic shock, and mortality. One of the findings which have been highly considered in recent years is the presence of fQRS in the routine ECG taken in patients, which marks abnormal depolarization and is a sign of heterogeneity in the activity and delay in ventricular conduction and is caused by ischemia, fibrosis, and myocardial scarring [21]. Right ventricular transmural infarction despite open and healthy coronary arteries has been observed in the autopsy of patients who died from acute pulmonary embolism [22]; thus, it seems that fQRS in patients with acute pulmonary embolism is caused by right ventricular transmural infarction and is related to high mortality in this respect.

fQRS in some cardiovascular diseases such as coronary heart disease (CAD), Brugada, isch-

emic and non-ischemic cardiomyopathy, long QT syndrome, arrhythmogenic right ventricular dysplasia (ARVD), and Ebstein has been considered a predictive factor. However, few studies have been concerned with its predictive role in patients with acute pulmonary embolisms [16, 17, 19, 20, 23, 24]. This research was performed to determine the predictive value of fQRS in patients with acute pulmonary embolisms hospitalized at the Shahid Madani educational, medical, and research center of Tabriz.

In our study, fQRS in patients with acute pulmonary embolism was not related to hospital death; the need for thrombolytics, in need of an embolectomy, in need of mechanical ventilation, and in general, MACPE and its value as a predictive factor were inconspicuous. According to these results, the presence of fQRS in the ECG of these people may not be considered a predictive factor.

In their study, Kukla et al. observed that in patients with cardiogenic shock caused by acute pulmonary embolism, fQRS in V1 lead was not related to hospital death [25]. Also, in their study, Zhan et al. showed that fQRS in V1 lead is not related to the need for advanced treatments, need for inotropic, need for mechanical ventilation, need for thrombolysis, and need for surgical thrombectomy [26]. These results were consistent with our research results. However, on the other hand, Zhan et al. showed that there exist fQRS in baseline ECG of 20 percent of patients with pulmonary embolism, while in hemodynamic instability cases, this finding increased to 95 percent [27]. Also, Kukla et al. showed that fQRS in V1 lead predicts cardiogenic shock in patients with acute pulmonary embolism [25]. In Cetin et al.'s study, fQRS has been recognized as a predictive factor of cardiogenic shock, need for thrombolytic, hospital death, and mortality due to all reasons, and also as a factor for identifying patients at high risk of acute pulmonary embolism [21].

In Karaka et al.'s research, it was also observed that fQRS might be a valuable finding in predicting hospital death and mortality in the long term and identifying patients with a high risk of acute pulmonary embolism [28]. In the meta-analysis of some previous studies by Qaddoura et al., it was also indicated that fQRS could be used as a valuable finding and marker for predicting adverse consequences in patients with acute pulmonary embolism [13]. The results of the above studies were not consistent with our research. This incident may be due to several probable reasons, which are mentioned below.

Only the first ECG of the patient was considered in our analysis regarding fQRS, and other ECGs of the patient were not studied in this regard. As fQRS changes in ECG may also be observed transiently, thus this explanation might be a potential factor in acquiring different results.

The other reason which may be considered is that in the studies mentioned above, including Cetin, Kukla, and Zhan's studies [21, 25, 27], the definition of fQRS differed from the one in our study; in other words, the fQRS modified criteria were used in their study while in our study, a standard definition of fQRS was developed based on which our analysis was done. As we know, fQRS is a predictive factor for patients with a high risk of acute pulmonary embolism. Contrary to previous studies, the assessment of disease risk and severity of embolism was not performed in our research; thus, the low number of patients with high risk and massive embolism in this study might be another possible justifying reason for the observed results.

fQRS is also associated with myocardial scarring or fibrosis chronically. The presence of fQRS in ECG of APE patients is acute and reversible. Thus, the troubled differentiating of these two forms of fQRS in the first admission of patients could have also caused the seen differed results. Although in some limited studies about patients with acute pulmonary embolism, the presence of fQRS in ECG has been recognized as a predictive factor of hospital death and long-term mortality and an undesirable and predictive consequence of patients with high-risk, the results of our study showed the opposite. Therefore, more investigations on this matter are required.

Conclusions

This research showed that in patients with acute pulmonary embolism, fQRS in ECG does not have a significant relationship with hospital death, need for thrombolytic, need for mechanical ventilation, need for surgical embolectomy, and in general, MACPE.

Disclosure of conflict of interest

None.

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