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What's The Predictive Value of Fragmented QRS in Mortality for Chronic phase of Pulmonary Thromboembolism?

Abdulla ARSLAN[1], Fatih AYTEMİZ[2], Barış DÜZEL[3], Gokmen AKKAYA[4], Umut KOCABAŞ[5], Nezihi BARIŞ[6]

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[1] Abdulla ARSLAN; Baskent University Istanbul - 0000-0003-2355-3524 - Apaslan@Msn.Com; Cardiology
[2] Fatih AYTEMİZ - Manisa City Hospital - 0000-0002-9143-7819 - Aytemiz83@Gmail.Com; Cardiology
[3] Barış Düzel – Mersin City Hospital - 0000-0002-0675-0377 - Drbarisss@Hotmail.Com; Cardiology
[4] Gökmen AKKAYA- İzmir Tepecik Education And Research Hospital - Akkayagokmen@Gmail.Com; 0000-0002-0509-1971; Cardiology
[5] Umut KOCABAŞ - Baskent University, 0000-0001-6424-9399 - Cardiology
[6] Nezihi BARIŞ- Dokuz Eylül University; Cardiology

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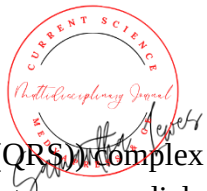

Abstract

Presence of fragmented QRS (F(QRS)) complex in a 12-lead electrocardiogram (ECG) has been shown to be the defect of the intramyocardial conduction. F(QRS) on ECG is related to high mortality rate in patients with acute coronary syndrome and pulmonary thromboembolism. There is no information about the mortality of chronic pulmonary embolism among patients with F(QRS). The aim of this study is to evaluate the patients who has already diagnosed with pulmonary thromboembolism (PTE) associated with fragmented QRS on ECG and to decide the effects of all-cause mortality in long term follow-up.

Method

In this observational, single-centre study we analyzed patients with PTE, retrospectively. The study group was consisted of patients who have already diagnosed with PTE and admitted to any department of Dokuz Eylul university hospital in 2013. If the patient diagnosed with a pulmonary emboli in his last admission, named as acute PTE, on the other hand, if previously diagnosed before last admission, it is named as chronic PTE. Overall 191 patients who met the criteria were included in the study. The ECGs were obtained from medical records. The patients were kept in follow-up for 5 years and their survival time checked from the government death notification system.

Results

We had analyzed 191 patients (%45 male, average age 67,36±15,97). During 5-year follow-up period, all-cause mortality rate was %55 (106/191). F(QRS) morphology was present in %55 (106/191) of the patients. Study population among patients with F(QRS) morphology, all-cause mortality rate was %59 (62/106). Although all-cause mortality rate for 5 year follows up period was higher in patients with F(QRS) it was not statistically significant (p=0,317).

Conclusion

The presence of fQRS on the surface ECG in patients with acute PTE is associated with increased mortality rates in long term. In the early examination of the patients with pulmonary embolism, ECG findings therefore should be considered either. Although it is not statistically significant, the patients in our cohort with F(QRS) morphology on the ECG proved higher mortality in 5-year follow-up period.

Keywords: *Fragmented QRS, pulmonary thromboembolism, long-term mortality*

Introduction

VTE (venous thromboembolism), is the most frequent disease after myocardial infarction and stroke among cardiovascular disease. VTE, includes deep vein thrombosis (DVT) and pulmonary thromboembolism (PTE) and the most life-threatening part is PTE (1). PTE is reported to manage hospitalization, morbidity and mortality in more than 250,000 patients annually (2). The mortality rate of PTE is approximately 25-30% in untreated patients, but in treated patients the mortality rate drops to 2-8%. Therefore, research focuses on risk classification to find high-risk patients and develops several prognostic markers such as clinical parameters, ECG parameters, imaging of the right ventricle (RV) by echocardiogram or computed tomography (CT), and laboratory biomarkers as well as various assessment scores to start the proper treatment as soon as possible (3). Besides these variables, ECG abnormalities in PTE are increasingly reported, and mounting data have recommended that ECG plays a great crucial role in the prognostic assessment of PTE patient population, due to its quickly and easily reachable (4-6).

Fragmented QRS (fQRS) complexes on resting 12-lead ECG, proving the deterioration in myocardial electrical activation due to myocardial ischemia and scar has been reported as a useful marker in prognostic evaluation of various cardiovascular pathologies including ischemic or nonischemic dilated cardiomyopathy, coronary artery disease, arrhythmogenic right ventricular cardiomyopathy, Ebstein anomaly, and Brugada syndrome (7,8). Several large-scale studies have shown that the presence of fQRS in coronary artery disease is associated with myocardial scarring and necrosis tissue, and increased undesirable cardiac events and mortality in these patients (9). However, there is no information in the literature about the predictive value of fQRS detected in ECG in patients with chronic PTE in terms of mortality, morbidity or hospitalization.

The aim of this study was to evaluate whether patients with acute or chronic PTE patients have a fQRS parameter in their ECG and to decide if there is a difference in their mortality and to decide if patients with risk of mortality can be found in such patients.

Methods

Patient Population

Our study group consisted of patients who were admitted to any clinic, outpatient clinic or emergency department of Dokuz Eylul University Faculty of Medicine (DEUTF) in any time of 2013 and diagnosed with acute or chronic pulmonary thromboembolism. Between January 1, 2013, and December 31, 2013, all patients with International Statistical Classification of Diseases and Related Health Problems (ICD) code I26 in the digital system were examined. The records of 255 patients that found were analyzed retrospectively. Patient data computerized tomography and reports were obtained from the imaging archive, ECGs from the patient files and life information had looked from the government death notification system with patient's identity (ID) numbers. 30 patient's QRS duration were over the 120 msec, 14 patients who had not clear diagnosis were excluded from the study group. The ECG of 3 patients could not be reached and these patients were excluded from the study. In totally 9 Patients, who have a history of coronary artery disease, a history of aortic dissection, a history of pacemaker implantation and a pacemaker rhythm were excluded. PTE was obtained in the acute or chronic period by scanning the patients' registration dates and archive information.

Electrocardiogram Analysis and Definition of fQRS

The 12-lead ECGs of patients who were included to the study were evaluated by two independent cardiologists blinded to the patients' clinical outcomes. QRS fragmentation phenomenon was recently described by Das M et al. in a standard surface 12-lead ECG (10). fQRS is defined as the presence of a different RSR's pattern in two consecutive leads, corresponding to the major coronary artery region, regardless of the Q wave with a QRS duration of less than 120 msec in the standard ECG. These phenomenon includes an added R wave (R′), notching of the R wave, notching of the downstroke or upstroke of the S wave, or the presence of 1 R′ in more than two contiguous being anterior (V1–V5), inferior (II, III, aVF), or lateral (I, aVL, V6) myocardial segments. ("Fragmented QRS Complex Predicts In-Hospital Adverse Events and Long ...") Fragmentation in one derivation didn't accept.

CT Pulmonary Angiography Protocol

Contrast-enhanced chest tomography images of the patients in 2013 were evaluated. Both the reports and the images were checked by two independent cardiologists blinded to the patients' clinical outcomes. In these patients, PTE evaluated as a main, lobar, segmental and subsegmental pulmonary embolism.

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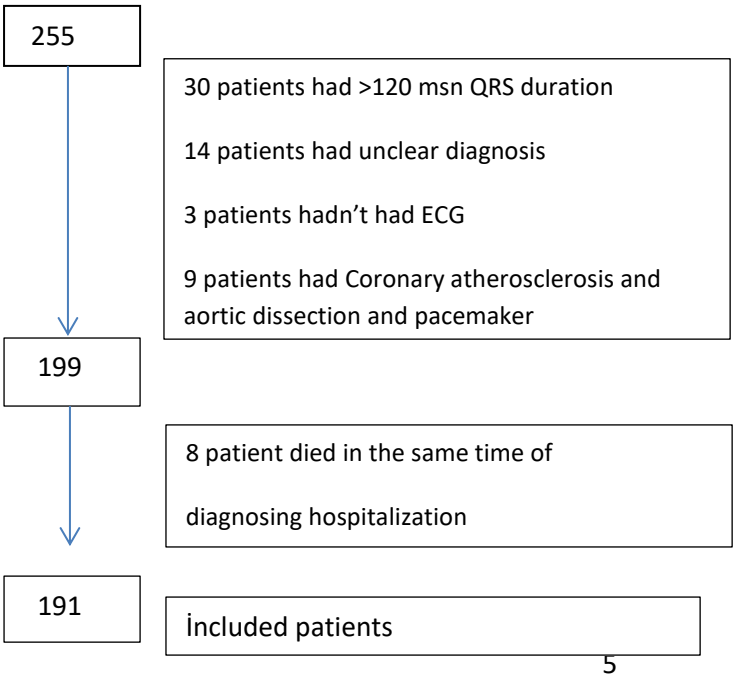
Echocardiographic Parameters

Echocardiography reports of the patients at the first admission time was obtained from the hospital report archive. In the reports of all patients included in the study we looked at: RV size and function as including tricuspid annular plane systolic excursion (TAPSE) were assessed with regarding current guidelines.(11,12) If Right Ventricular Ejection Fraction (RVEF) above from %50, it is evaluated as good, and if under %30 it is evaluated as bad function visually. And, for all the patient's tricuspid regurgitation degree and pulmonary arterial pressure looked up about current guideline (11). McConnell's sign was defined as hypokinesis of the mid-RV free wall with preserved motion of the RV apex(13). Left ventricular (LV) ejection fraction evaluated visually, but if there were unclear values, in that time it measured by using the biplane changed Simpson's method, and this is habit of Dokuz Eylul Cardiology department.

Definition of Mortality

In-hospital mortality and all cause death in-3 years was evaluated. Patients who could not be discharged at the first admission to the hospital were evaluated as an In-hospital mortality. After 3 years, until December 31, 2016, we looked at whether patients are alive or not by using the government system which was Death Notification System (DNS) with patient's ID numbers. All mortalities in this 3 years we picked up in group of all-cause mortality

Figure 1. *Inclusion criteria*



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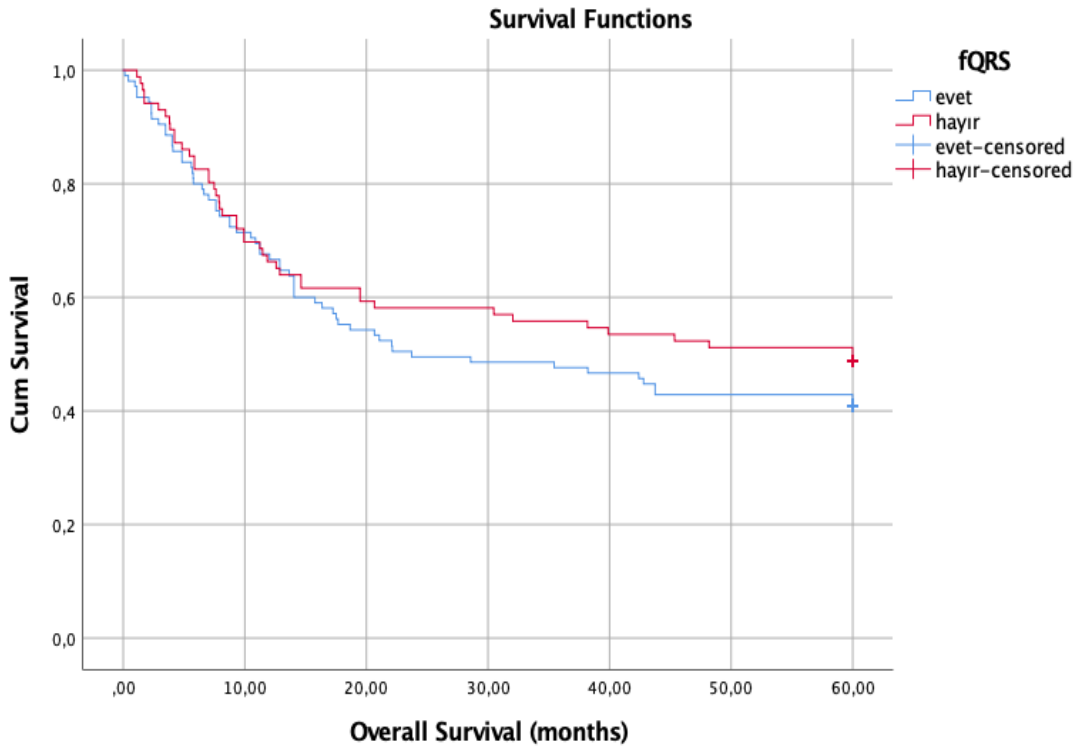
Clinical Outcome

In-hospital mortality was defined as death from any cause during hospitalization, Long-term all-cause mortality was decided as the occurrence of death with any cause during the follow-up 3 years.

Figure 2. *Overall Survival period*



Statistical Analysis

All data were recorded in SPSS 15.0 (Statistical Package for Social Sciences) statistics program. Percentages of categorical variables, mean values obtained by measurement, standard

deviations were shown. The significance of dependent variables was analyzed by chi-square and t test according to independent variables. Logistic regression analysis was used to predict the existence of the risk of the dependent variable according to the independent variables found to be significant in the univariate analysis. P values below 0.05 were considered significant in the analyzes.

Results

Patients Characteristics

A total of 199 patients (88male, %44,2; mean age 67,81±15,90) with diagnosis acute (30; %15,1) and chronic phase of PTE were enrolled, and followed up 36 months. Baseline characteristics, PTE anatomical classification, ECG, echocardiographic findings were proved in table 1-4.

Table 1. *Patients' baseline clinical traits*

	Patients n=191
Age	67,36±15,97
Female (%)	105 (55)
Hypertension (%)	144 (75,4)
Diabetes Mellitus (%)	65 (34)
Smoking[1] (%)	119 (62,3)
Cancer (%)	47 (24,6)

PTE: Pulmonary Thromboemboli,

[1] The patient that exposured to cigarette in any time in their life

Table 2. *Patient's electrocardiographic findings*

	Patients n=199

Average Heart Rate (bpm)	91,72±22,41
Average QT duration (msec)	391,88±46,7
Average QRS duration (msec)	93,25±12,99
Average PR duration[1] (msec)	156,6 ±35,1
fQRS positive (+) (%)	106 (55)
Right Axis (%)	31 (16,2)
S1Q3T3 + (%)	49 (25,7)
T wave negative (precordial derivations) (%)	43 (22,5)

[1] Without 20 Patients that had Atrial Fibrillation

Table 3. *Patients' echocardiographic findings*

	Patients n=199
LVEF[1] %	57,05±5,7
RV functions (%)	
Good	46,6
Moderate	46,1
Bad	7,3
PAP[2] Average	40,86±13,98
McConnell + (%)	23 (12)
D-shape LV (%)	45 (23,6)
TR[3] (%)	
Mild	43,5
Moderate	47,1
Severe	9,4

[1] LVEF: Left Ventricle Ejection Fraction
[2] PAP: Pulmonary Artery Pressure
[3] TR: Tricuspid Regurgitation

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Patients who had fQRS were 111 (%55,8) in all. The average of QRS was 93,42 (±13,09) msec. And there was %55,3 patients who had moderate or bad RV functions.

Table 4. *Anatomical and Hemodynamical classification of the patients who were diagnosed with PTE*

	Patients n=199
PTE anatomic localization	
Main PTE (%)	26 (13,6)
Lober PTE	67 (35,1)
Segmenter PTE (%)	79 (41,4)
Subsegmenter PTE (%)	19 (9,9)
Acute PTE[1] (%)	22 (11,5)
Thrombolitic Therapy (%)	13 (6,8)

[1] Acute PTE who had unstable hemodynamia

There were 30 patients (%15,1) evaluated as acute PTE because of their hemodynamic instability. And in this patients only 21 of them (%10,6) needed thrombolytic therapy.

Comparison between fQRS (+) and fQRS (−) Patient Groups

Table 5. *Comparison patients fQRS (+) and (-) groups*

	fQRS + (n=106)	**fQRS - (n=85)**	***p***
Age	68,21±15,98	66,31±15,98	0,416
Sex M/F %	49/56	37/49	0,662
Hypertension (%)	82 (78,1)	62 (72,1)	0,399
Diabetes Mellitus (%)	35 (33,3)	30 (34,9)	0,878
Cancer (%)	22 (21,0)	25 (29,1)	0,238
HBG (gr/dl)	11,72±1,98	11,90±1,87	0,530
WBC (x10^3/µL)	10,71±5,33	9,83±5,09	0,250
Troponin I (ng/ml)	0,17±0,51	0,13±0,44	0,507
Sinus Rhythm (%)	96 (91,4)	77 (89,5)	0,804

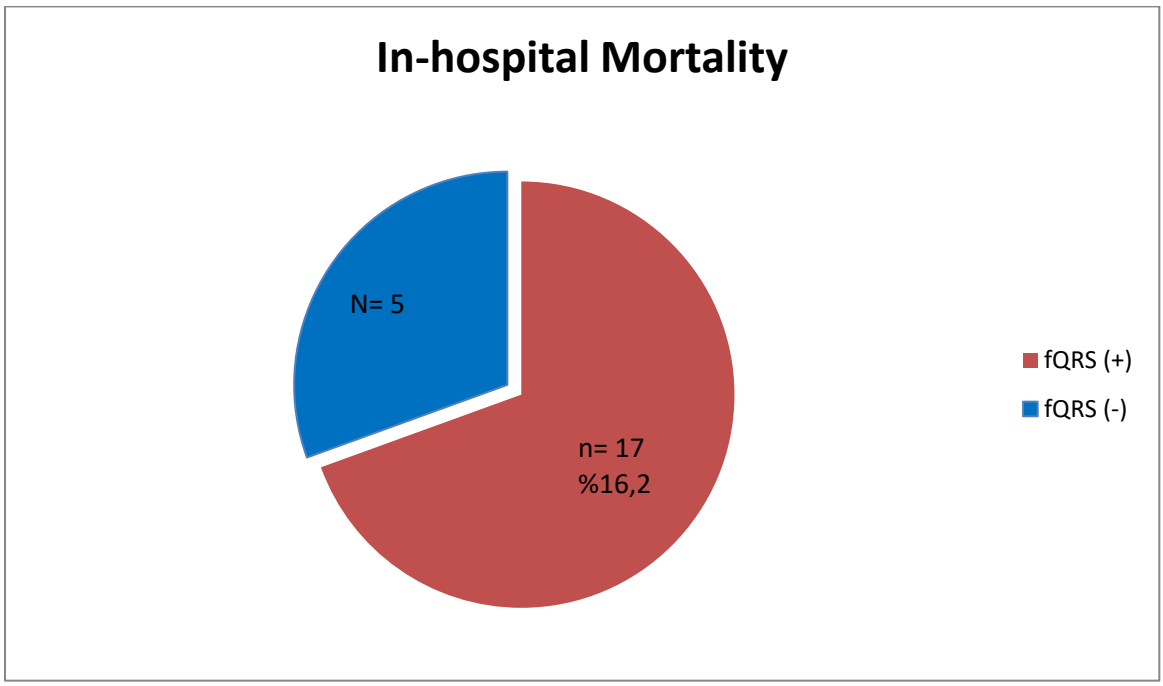
Average Heart Rate (bpm)	92,22±21,52	91,12±23,5	0,736
PR duration	**162,30±33,43**	**149,56±36,11**	***0,017***
QT duration	**402,05±44,46**	**379,48±46,64**	***0,001***
QRS duration	**98,01±11,81**	**87,44±12,02**	***0,001***
Right axis (%)	**25 (23,8)**	**6 (7)**	***0,002***
S1Q3T3 (%)	**35 (33,3)**	**14 (16,3)**	***0,008***
Twave Neg in precordial leads (%)	**32 (30,5)**	**11 (12,8)**	***0,005***
RV functions (%)			0,170
Good	46 (43,8)	43 (50)	
Moderate	48 (45,7)	40 (46,5)	
Bad	11 (10,5)	3 (3,5)	
LVEF (%)	57,40±5,73	56,63±5,71	0,355
PAP	42,14±15,97	39,30±10,95	0,163
McConnell Sign (%)	*17 (16,2)*	*6 (7)*	***0,073***
D-shape LV (%)	29 (27,6)	16 (18,6)	0,172
TRdegree (%)			0,109
Mild	42 (40)	41 (47,7)	
Moderate	49 (46,7)	41 (47,7)	
Severe	14 (13,3)	4 (4,7)	
Trombolitic	**11 (10,5)**	**2 (2,3)**	**0,04**
PTE anatomic localization (%)			0,182
Main PTE	19 (18,1)	7 (8,1)	
Lobar PTE	36 (34,3)	31 (36)	
Segmenter PTE	42 (40)	37 (43)	
Subsegmenter PTE	8 (7,6)	11 (12,8)	
Acute PTE	13 (12,4)	9 (10,5)	0,821
All cause of death (%)	**62 (59)**	**44 (51,2)**	**0,307**
Mortality in-hospital (%)	**17 (16,2)**	**5 (5,8)**	***0,038***

Based on the previously mentioned criteria, 111 patients (55.8%) demonstrated fQRS in ≥2 contiguous lead. fQRS were decided primarily in the V1–V2 (70 patients) and inferior leads (41 patients). QRS fragmentation was proved predominantly in the R wave (61 patients). Patients with fQRS had more frequent elevated cardiac Troponin I (cTnI), right bundle branch block (RBBB), S1Q3T3 sign,T wave negativity in precordial leads and right axis deviation, duration of PR, QT and QRS longer durations in ECG. fQRS(+) patients had taken more often thrombolytic therapy. 30 patients were accepted acute PTE, and only 19 of this patients had fQRS, there was not statistically signification.

Clinical Outcomes

A total of 31 patients were experienced mortality in-hospital. And 23 (%20,7) of them were fQRS positive. During the follow-up period, 46 patients died. Clinical outcomes were represented in Graphic 1and 2.

Graphic 1. *In-hospital mortality in F QRS positive and negative groups (p=0,038)*



During follow-up,36 months, all-cause mortality occurred more often in the fQRS (+) group, but it wasn't significant (P = 0.341) Graphic 2:

Graphic 2. *5-year follow-up all cause deaths in FQRS positive and negative groups(p=0,307)*

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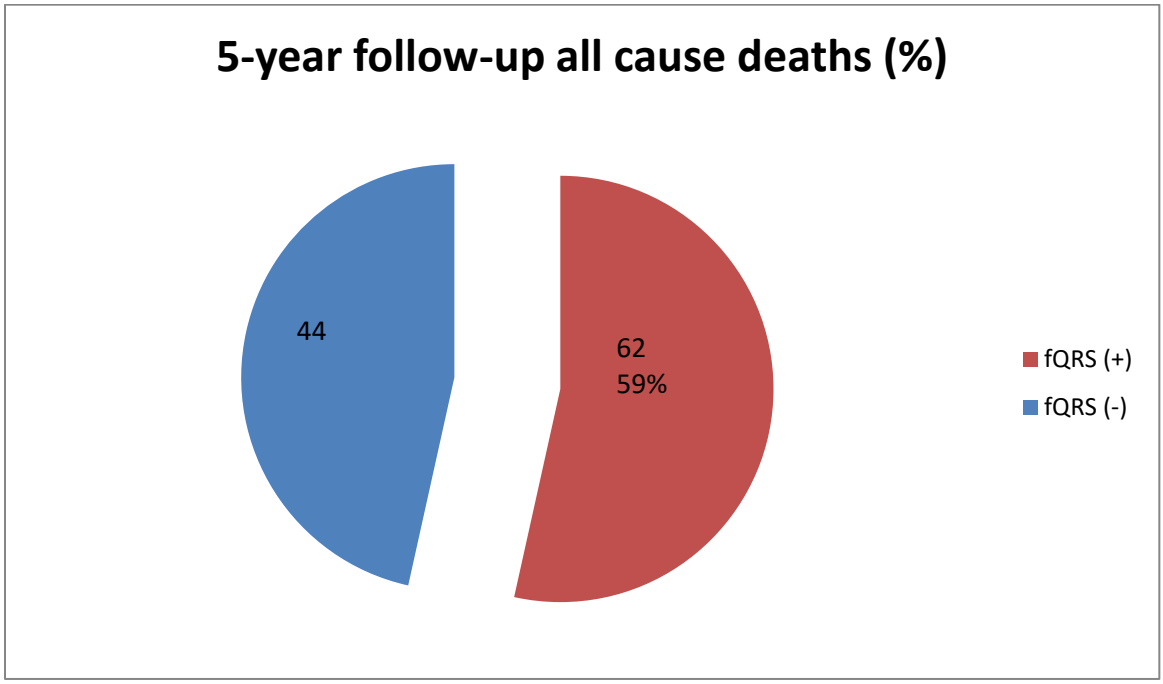

In the light of these findings, we used all this parameters (the patient's age, right ventricular function, McConnel sign presence and d-shape left ventricle presence, using lytic in treatment, PTE time and degree of tricuspid regurgitation) in regression analysis. In this analysis, fQRS, like all parameters except age after corrections, disappeared statistically in the in-hospital mortality.

Table 6. *Regression analysis*

	P value
Age	**0,037**
F QRS	0,204
Right ventricule functions	0,851
McConnel Sign	0,455
D-shape Sign	0,480
Therapy strategy	0,999
PTE time (acute/chronic)	0,999
Tricuspit regurgitation degree	0,262
P<0,05 values were acceptable.	

Discussion

The 12-lead ECG is among the most helpful and risky diagnostic tools for early diagnosis of pulmonary thromboembolism because of its non-invasive, inexpensive, fast and easily accessible results. A detailed evaluation of the ECGs to be obtained in patients suspected of PTE may strengthen the likelihood of PTE and may be interpreted in the short and long term. There is some thought that QRS wave may be important in finding risky patients with PTE [Fragmented QRS (fQRS+)], which is associated with intraventricular conduction defect. However, this data is not proven. There is no data on mortality in both acute and chronic PTE patients who have fQRS(+)

FQRS was detected in 55.8% of the patients in our study (111 patients). The exact frequency of f QRS is not known in patients with acute and chronic PTE in the literature. A recent study on acute PTE (14) showed a frequency of around 15% fQRS. In another study that they looked at fragmentation in only one derivation, V1 (15), the frequency was %9,8 in acute PTE patients. However, unlike these two studies, we think that the presence of chronic patients in our patient group increases this frequency.

After assessment of echocardiographic and angiographic images, there was a higher rate of right ventricular functions, higher mean pulmonary artery pressures, and higher McConnell and d-shape left ventricular findings in the group with fQRS, but none were statistically significant. The left ventricular functions were similar between the Fragmented QRS group, and the group not detected. There is no study to compare these findings yet.

There was no significant difference in PTE localization between f QRS positive and negative groups. This suggests that fQRS has no predictive value for anatomic localization in PTE. However, in the treatment group, the group with fQRS(+) was found to have significantly more thrombolytic treatment. Although there were few patients in the two groups (17 (15.3%) versus 4 (4.5%),it was seen that the group with fQRS (+) had less hemodynamic stability and significantly more thrombolytic therapy was needed.

There are many studies suggesting that the presence of fQRS increases unwanted cardiac events including mortality (16,17). 186 patients with acute pulmonary embolism were found to be significantly higher in the group with fQRS(+) than in the in-hospital mortality and long-term mortality. (18). In our study, in-hospital mortality and all-cause deaths were evaluated after 3-year follow-up. And In-hospital mortality in patients with fQRS (+) was 20.7%, while in-patient mortality in patients without fQRS (-) was found to be 9.1% and the difference was statistically significant (p=0,025). Patients were followed up for 3 years after hospital discharge and mortality rates were measured. Mortality was seen in 98 (49.2%) of 199 patients during 3-year follow-up. Although the mortality rate was higher in fQRS (+) group, among the fQRS (+) and (-) groups after 3 years of follow-up, it was seen that the mortality rate was not found to be significant statistically.

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F QRS findings which were found to be significant in in-hospital mortality were analyzed by regression analysis statistically and we did this analysis after we corrected this parameters statistically age, right ventricular function, presence of McConnel mark, d-shape of left ventricle, lytic treatment, PTE time and tricuspid regurgitation degree. With this analysis, the statistical significance of fQRS in in-hospital mortality has disappeared and it is important to note that only age is effective.

Clinical Implications

Considering the association of FQRS with worse clinical outcomes, the evaluation of fQRS complex in ECG admission may be useful in finding patients at higher risk for adverse events and mortality. These patients may be followed up more closely at shorter intervals. Although further evaluation with prospective randomized trials is needed, the presence of fQRS should be considered in the decision-making process of thrombolytic therapy. At the same time, the data on whether adverse cardiac events will develop more often is unclear as to the presence of fQRS in the ECG of patients with already have diagnosis of PTE, who are currently being admitted to the hospital for any reason.

Limitations

Patients included in our study group were collected from a single center. In addition, in patients analyzes, only mortality rates were examined in 3 years follow-up and the rates of major cardiovascular side effects (MACE) could not be reached because they could not be accessed from their files.

Conclusions

Pulmonary embolism is a clinical condition that is still in great difficulty in the diagnosis despite developing technology and innovations. The 12-lead ECG is currently the first, fastest, most important and inexpensive diagnostic tool for the diagnosis and differential diagnosis of pulmonary embolism. In conclusion, the presence of fQRS complex, as a simple and possible ECG marker, appears to be a novel predictor of in-hospital adverse events and long-term all-cause mortality in PTE patient population. And this parameter may use the identification of patients whom at higher risk for mortality and individualization of therapy. In patients with a diagnosis of pulmonary embolism, the presence of fQRS on the surface ECG may help to prove to the clinician that patients have greater risk of in-hospital mortality. In addition, it should not be overlooked that patients with fQRS need more thrombolytic therapy for treatment selection. We think that new, larger studies are needed to investigate the relationship between the presence

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of fQRS with clinical, echocardiographic and angiographic findings and to investigate in-hospital mortality and long-term follow-up.

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