



Fragmented QRS formation and its predictors in patients with breast cancer receiving anthracycline-based chemotherapy

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Introduction

Fragmented QRS (fQRS), defined as the presence of an additional R wave (R'), R wave or the S wave notching, or the presence of more than one R' wave in two consecutive leads in the electrocardiography (ECG), has been shown to be associated with myocardial scar tissue [1]. Significant association was found between myocardial scar detected by myocardial single-photon emission computed tomography (SPECT) imaging and fQRS [1]. The clinical implications of this relationship between scar tissue and fQRS have also been studied in several studies. In patients with coronary artery disease (CAD), fQRS has been shown to be associated with all-cause mortality and cardiac events [2].

Anthracycline-based chemotherapy (AbC) is used in about 32% of patients with breast cancer, despite the new treatment modalities being developed [3]. Anthracyclines can cause damage to DNA by forming reactive oxygen radicals (ROS) and as a result, anthracycline-induced cardiotoxicity (AiC) may occur [4,5]. fQRS, an indicator of scar tissue, may be associated with cardiotoxicity that occurs after cancer treatments. But, there is no study that examines the relationship between AbC treatment and fQRS formation.

Bilirubin is known to have cardioprotective effects due to its endogenous antioxidant properties and it has been shown that high total serum bilirubin levels are associated with reduced risk of cardiovascular disease [6,7]. In a study, inverse relationship was found between pre-AbC serum bilirubin levels and deterioration in post-cancer treatment left ventricular ejection fraction (LVEF) [8]. However, the association between formation of fQRS and bilirubin level in patients receiving AbC was not investigated.

In this study, we aim to evaluate fQRS formation and its predictors in patients with breast cancer receiving AbC. Since we think that fQRS may be associated with AiC, clarifying the predictors of fQRS may contribute to treatment management of this patient group.

Material and methods

This is a retrospective cohort study evaluating the fQRS formation and its predictors in breast cancer patients receiving AbC. Between October 2010 and October 2017, a total of 515 patients who were diagnosed with breast cancer and received AbC were included in the study. ECG and transthoracic echocardiography (TTE) of patients before and after AbC were obtained from medical records. Who had heart failure (HF), CAD and fQRS in their ECG before chemotherapy and those who received trastuzumab following anthracycline therapy were not included in the study. 89 patients without TTE and/or ECG recording after chemotherapy, 37 patients whose ECGs were not suitable for analysis, 18 patients with pre-treatment transaminase levels >3 times the normal limits, 19 patients with pre-treatment creatinine level above 1.5 mg/dl, 15 patients with left ventricular hypertrophy, 39 patients who underwent radiotherapy and 46 patients taking any medication like statin, beta blocker and/or renin-angiotensin-aldosterone system blocker were excluded from the study. So, the study population included a total of 252 patients with breast cancer who received AbC. Study population was divided into two groups according to presence or absence of fQRS after chemotherapy. The Local Ethics Committee of our institution approved the study protocol.

Baseline demographic data such as age, body surface area (BSA), anthracycline dose, and risk factors of hypertension (HT), diabetes mellitus (DM) of patients were acquired from the medical records. All patients' AbC doses were converted to doxorubicin isotoxic equivalents as described in previous studies (total idarubicin dose x 5, total mitoxantrone dose x 4, total doxorubicin dose x 1, total daunorubicin dose x 0.833, total epirubicin dose x 0.67) [8,9]. Cardiotoxicity was defined as >10% decrease in LVEF to a value below the lower limit of normality [10].

Pre-AbC LVEF and LVEF values within one year after AbC that measured by TTE were determined from the medical records. Within 1 year after chemotherapy, the lowest value of LVEF was taken as post-AbC LVEF. Pre-treatment hemoglobin, hematocrit, serum creatinine, alanine amino transferase (ALT), aspartate amino transferase (AST), albumin, uric acid (UA), total bilirubin and direct bilirubin levels were recorded.

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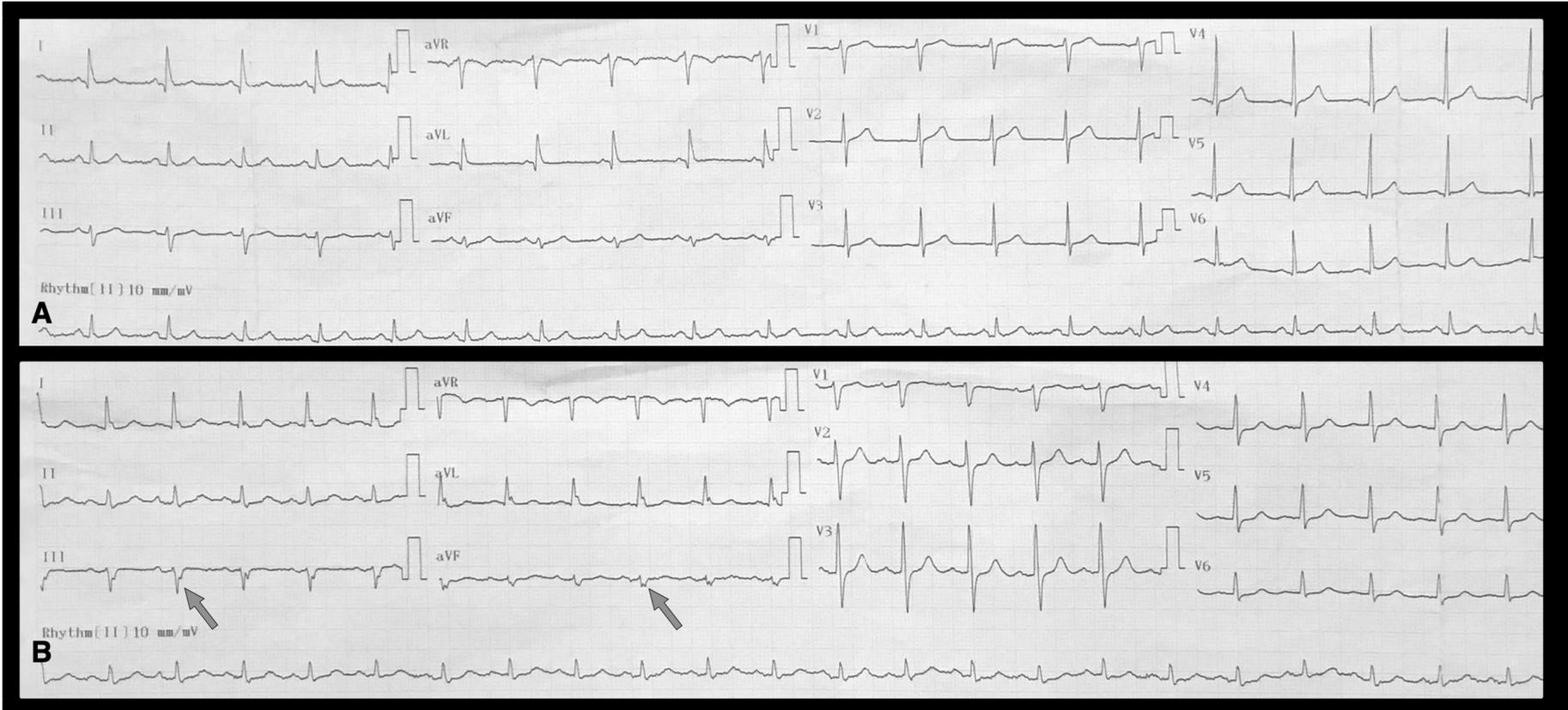


Fig. 1. Demonstration of a patient's ECGs before (A) and after (B) anthracycline-based chemotherapy from our study population (Gray arrows indicate fragmentation).

In our clinic, ECG and TTE are performed routinely before and one month after AbC. ECGs that were taken just before and one month after the treatment were obtained. Twelve-lead ECGs (filter range, 0.15–100 Hz; AC filter, 50 Hz, 25 mm/s, 10 mm/mV) were examined by two blinded independent cardiologists. ECGs were evaluated by a third independent reviewer when there was a discrepancy between the evaluations of the two readers. All ECGs were scanned and a more detailed analysis was done on the personal computer with $\times 400\%$ magnification. Fragmented QRS is characterized by the presence of an additional R wave (R'), R wave or the S wave notching, or the presence of more than one R' wave in two consecutive leads (Fig. 1) [1].

Statistical analysis

Continuous variables were summarized by median and interquartile range or mean \pm standard deviation. Categorical variables were expressed as frequencies and percentages. The variables were tested for normal distribution by normality test of Shapiro-Wilk. Mann-Whitney *U* test was used for the analysis of non-normally distributed variables. Univariate analysis was performed for continuous variables and Pearson Chi-square test was applied for categorical variables. Binary logistic regression analysis were performed for identify potential prognostic factors. IBM SPSS Statistics 21.0 (IBM Corp. Released 2012. IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp.) was used for statistical analyses. A 'p value' of <0.05 was considered significant.

Results

A total of 252 breast cancer patients who received AbC were included in the study. The study population was divided into 2 groups according to whether or not fQRS occurs after AbC. 67 (26.6%) patients had fQRS after AbC. The mean age (53.82 ± 9.37 vs 50.24 ± 10.63) of fQRS (+) patients was significantly higher than those fQRS (-). Pre-treatment serum UA level ($4.3 [3.5-5.9]$ mg/dL vs $4.0 [3.5-4.7]$ mg/dL, $p = 0.019$) was significantly higher, while total bilirubin ($0.30 [0.22-0.41]$ mg/dL vs $0.43 [0.35-0.54]$ mg/dL, $p < 0.001$) (Fig. 2A) and direct bilirubin ($0.08 [0.05-0.13]$ mg/dL vs $0.12 [0.08-0.16]$ mg/dL, $p < 0.001$) levels were significantly lower in the group with fQRS (+). LVEF after chemotherapy ($64.0 [50.0-65.0]$ % vs $65.0 [63.0-65.0]$ %, $p < 0.001$) was significantly lower in patients with fQRS (+) (Fig. 2B). The cumulative doxorubicin equivalent dose of anthracycline administered was significantly higher ($300 [240-321]$ mg/m² vs $214 [200-240]$ mg/m², $p < 0.001$) in fQRS (+) patients (Fig. 2C). Other baseline characteristics such as BSA, pre-treatment serum hemoglobin, hematocrit, creatinine, ALT, AST, albumin levels, pre-treatment LVEF, the rate of patients with HT and DM were similar between the groups. Baseline clinical and laboratory characteristics of the patients were shown in Table 1. A total of 32 (12.7%) patients had AiC. The number of patients with AiC ($25 [37.3\%]$ vs $7 [3.8\%]$, $p < 0.001$) was significantly higher in the fQRS (+) group.

We evaluated the predictors of fQRS formation by univariate and multivariate logistic regression analyses. In univariate analysis, fQRS (+) patients were likely to have increased age, pre-treatment serum UA level and cumulative doxorubicin equivalent dose and decreased pre-treatment serum total bilirubin and direct bilirubin levels. Total bilirubin level (odds ratio: 0.006, 95% CI: 0.001–0.136, $P = 0.001$) and doxorubicin equivalent dose (odds ratio: 1.042, 95% CI: 1.029–1.055, $P < 0.001$) were found to be the independent predictors of fQRS formation in multivariate logistic regression analysis (Table 2).

Discussion

Myocardial dysfunction is a serious complication that increases morbidity and mortality in cancer patients receiving chemotherapy. In order to reduce the incidence of this complication, it is required to reveal the

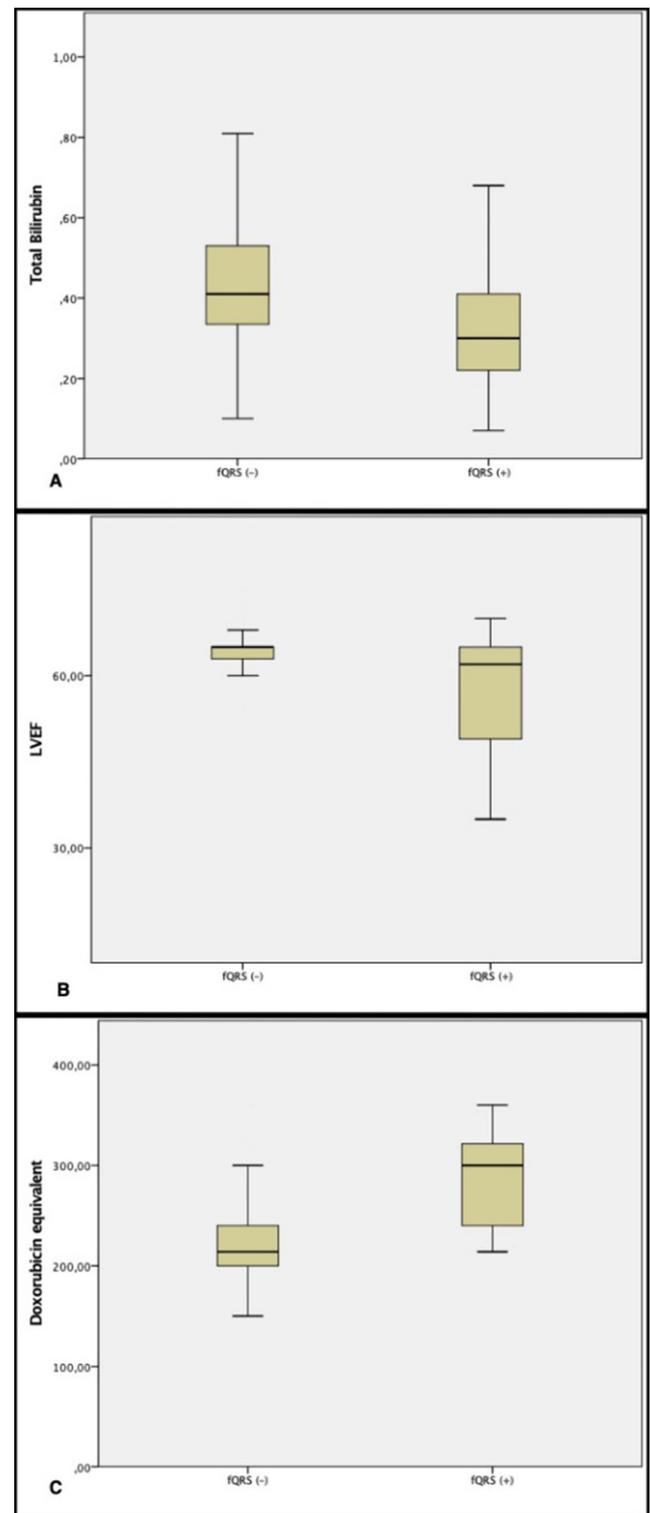


Fig. 2. Pre-treatment serum total bilirubin level and LVEF after chemotherapy were significantly lower while cumulative doxorubicin equivalent dose of anthracycline was significantly higher in fQRS (+) patients. (fQRS: fragmented QRS; LVEF: left ventricular ejection fraction).

predictors. In this retrospective cohort study, fQRS formation and its predictors were evaluated in breast cancer patients. The main findings of this study are that in breast cancer patients who received AbC, pre-treatment serum total bilirubin and doxorubicin equivalent dose of anthracycline administered were found to be the independent

Table 1
Baseline clinical and laboratory characteristics of the patients.

Parameters	fQRS (+) (n:67, 26.6%)	fQRS (–) (n:185, 73.4%)	P
Age (years)	53.82 ± 9.37	50.24 ± 10.63	0.016
Body surface area, m ²	1.70 (1.60–1.87)	1.70 (1.60–1.80)	0.687
Hemoglobin, g/dL	13.2 (11.8–13.9)	13.0 (12.3–13.8)	0.833
Hematocrit, (%)	38.75 ± 4.34	38.31 ± 3.46	0.463
Serum creatinine, mg/dL	0.74 (0.65–0.81)	0.72(0.64–0.79)	0.249
Alanine amino transferase, u/L	15.0 (12.0–21.0)	15.0 (11.5–22.0)	0.880
Aspartate amino transferase, u/L	20.0 (17.0–24.0)	20.0 (17.0–25.0)	0.392
Albumin, g/dL	4.40 (4.20–4.50)	4.46 (4.30–4.60)	0.078
Uric acid, mg/dL	4.3 (3.5–5.9)	4.0 (3.5–4.7)	0.019
Left ventricular ejection fraction, before chemotherapy, %	65.0 (63.0–66.0)	65.0 (63.0–66.0)	0.661
Left ventricular ejection fraction, after chemotherapy, %	64.0 (50.0–65.0)	65.0 (63.0–65.0)	<0.001
Total bilirubin, mg/dL	0.30 (0.22–0.41)	0.43 (0.35–0.54)	<0.001
Direct Bilirubin, mg/dL	0.08 (0.05–0.13)	0.12 (0.08–0.16)	<0.001
Diabetes mellitus, n (%)	9 (13.4%)	18 (9.7%)	0.542
Hypertension, n (%)	15 (22.4%)	28 (15.1%)	0.245
Doxorubicin equivalent (mg/m ²)	300 (240–321)	214 (200–240)	<0.001
Cardiotoxicity, n (%)	25 (37.3%)	7 (3.8%)	<0.001

predictors of fQRS formation and AiC was significantly higher in patients with fQRS (+).

Anthracyclines, which have an important role in the treatment of patients with breast cancer, adversely may affect the prognosis of cancer patients due to its cardiotoxic effect. They cause formation of ROS and lipid peroxidation leading damage to the membranes of cardiomyocytes [11,12]. It is important to reveal the factors that play a role in the pathophysiology of this serious complication. In a recent study, 23 non-metastatic breast cancer patients who received AbC were followed-up prospectively and significant increase in the corrected QT interval and serum troponin levels after chemotherapy was found [13]. This result supports that anthracyclines lead to myocardial damage and alterations in ventricular repolarization. It has been shown that fQRS which can be easily detected from 12-lead ECG is strongly associated with myocardial scar tissue [1,14]. Chew et al. [15] assessed the relationship between fQRS and left ventricular remodeling in 705 acute myocardial infarction patients. They found that fQRS complexes were independently associated with higher risk of no LVEF recovery and stated that early post-myocardial infarction fQRS formation may be an important predictor of unfavorable LV remodeling [15]. Adar et al. [16] assessed development of fQRS in 52 breast cancer patients receiving locoregional

radiotherapy at 1-year follow-up. They found that prevalence of fQRS was significantly higher in the irradiated group (37% vs 12%; $p < 0.002$) than the control group. We planned this study considering that fQRS, which has been shown to be associated with myocardial scar tissue and dysfunction, may have a role in the pathophysiology of AiC. There isn't any study that evaluates the fQRS formation and its predictors in breast cancer patients received AbC in the literature. In our study, fQRS was developed in 26.6% of breast cancer patients after AbC. We found that AiC is significantly higher in fQRS (+) patients (<0.001). Anthracyclines can trigger apoptosis or cause necrotic myocyte death [17]. It is expected that these adverse effects of anthracyclines in patients with fQRS, which has been shown to be associated with scar tissue and negative ventricular remodeling, must be higher. This result of our study supports previous studies showing that fQRS is associated with adverse cardiovascular outcomes. We suggest that increased incidence of AiC in fQRS (+) breast cancer patients receiving AbC has increased the importance of ECG in follow-up. At this point the following question comes to mind; is fQRS a marker that occurs before cardiotoxicity develops? Large prospective studies are needed to determine this.

Bilirubin is known to have antioxidant and antiinflammatory effects. It has been shown that bilirubin reduces oxidative damage in myocytes after myocardial ischemic reperfusion by decreasing ROS formation and thus reduces infarct size [18,19]. There is only limited data on the relationship between serum bilirubin level and AiC. Vera et al. [8] assessed relation of pre-treatment serum bilirubin levels to LVEF after AbC in 751 patients with different types of cancer in their retrospective cohort study. They found that pre-treatment serum bilirubin levels inversely correlate with subsequent deterioration in post-cancer treatment LVEF [8]. In our study, baseline total bilirubin and direct bilirubin levels were significantly lower in patients who developed fQRS after treatment. Also, we revealed that, baseline total bilirubin level is an independent predictor of fQRS formation after AbC. These results of our study show that; myocardial injury may be more likely because of lower antioxidant and antiinflammatory effect in those with lower bilirubin levels. Therefore, bilirubin level was significantly lower as expected in the group with fQRS after chemotherapy. This relationship increases the potential role of bilirubin in patients receiving AbC and suggests that the importance of treatment modalities affecting the bilirubin metabolism in reducing AiC may gradually increase. Hence, prospective studies involving long-term follow-up results are needed to clarify the role of bilirubin in AiC pathophysiology.

AiC is associated with the cumulative dose received. When the cumulative lifetime doxorubicin dose reaches 400 mg/m², the incidence of congestive HF has been shown to be 5% [20]. At higher doses such as 700 mg/m², the incidence is reported to be up to 48% [20]. In our study, patients who developed fQRS received higher doses of

Table 2
Predictors of fQRS in univariate and multivariate logistic regression analysis.

	Odds ratio	95% Confidence interval	P
Univariate analysis (variables)			
Age	1.03	1.006–1.064	0.017
Hypertension	1.62	0.802–3.261	0.179
Diabetes mellitus	1.44	0.613–3.382	0.403
Body surface area, m ²	1.46	0.255–8.385	0.670
Hemoglobin, g/dL	1.00	0.802–1.238	0.973
Hematocrit, (%)	1.03	0.957–1.114	0.412
Total bilirubin, mg/dL	0.22	0.003–0.174	<0.001
Direct Bilirubin, mg/dL	0.355	0.205–0.616	<0.001
Albumin, g/dL	0.48	0.197–1.149	0.099
Uric acid, g/dL	1.36	1.095–1.689	0.005
Doxorubicin equivalent (mg/m ²)	1.046	1.034–1.058	<0.001
Multivariate logistic regression analysis (variables)			
Age	1.02	0.974–1.069	0.388
Hypertension	1.72	0.506–5.815	0.386
Diabetes mellitus	1.14	0.316–4.140	0.838
Body surface area, m ²	0.77	0.077–7.62	0.820
Hemoglobin, g/dL	0.561	0.203–1.555	0.267
Hematocrit, (%)	1.17	0.831–1.644	0.369
Total bilirubin, mg/dL	0.006	0.001–0.136	0.001
Direct Bilirubin, mg/dL	0.72	0.292–1.766	0.471
Albumin, g/dL	0.76	0.179–3.214	0.708
Uric acid, g/dL	1.15	0.835–1.593	0.387
Doxorubicin equivalent (mg/m ²)	1.042	1.029–1.055	<0.001

anthracycline. Also we found that doxorubicin equivalent dose is an independent predictor of fQRS formation. Exposure to higher doses of anthracycline is expected to increase the incidence of fQRS, as it may lead to more myocardial damage and scar tissue.

Study limitations

Although our study is the first study examining the relationship between AbC and fQRS in the literature, it has some limitations. The study do not have long-term follow-up in order to assess the clinical significance because of retrospective design and the number of patients in the study is relatively small. However, only patients with breast cancer were included in the study, and those who received treatment that could reduce LVEF, such as radiotherapy and trastuzumab, were excluded from the study. Also, the rate of cardiotoxicity was found to be 12.7%. This rate is higher compared to previous studies. Our study is a retrospective study and hence the number of patients who underwent TTE due to heart failure associated complaints (e.g., dyspnea or edema) may be high. In addition, there may also be patients without decreased LVEF but with impaired systolic functions. These patients could not be evaluated in our study, because speckle tracking echocardiography and cardiac magnetic resonance imaging techniques were not used. The appropriate cut-off point for assessing QRS fragmentations is 150 Hz because the cut-off point below this value may influence high-frequency signals [21]. Therefore, another limitation of our study is that ECGs were taken using the filter range 0.15–100 Hz. To clarify the clinical outcomes and pathophysiological mechanism of fQRS formation in patients receiving AbC, prospective long-term studies are needed.

Conclusion

This study shows that in patients with breast cancer receiving AbC, pre-treatment serum total bilirubin and doxorubicin equivalent dose of anthracycline administered are the independent predictors of fQRS formation and AiC is significantly higher in patients with fQRS (+). Our study has increased the importance of fQRS formation in the follow-up of patients receiving AbC.

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