

## Ciddi Aort Darlığı Olan Hastalarda Fragmente QRS Kompleksi ile Sol Ventrikül Kütle İndeksi Arasındaki İlişki

### The Relationship Between Fragmented QRS Complex and Left Ventricle Mass Index in Patients with Severe Aortic Stenosis

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#### ÖZ

**Giriş:** Aort darlığı (AD), Avrupa ve Kuzey Amerika'da en sık görülen primer kapak lezyonudur ve sıklıkla cerrahi veya transkateter müdahale gerektirir. Artan ard yük nedeniyle sol ventrikül hipertrofisi (LVH) meydana gelir. Elektrokardiyogramdaki (EKG) fragmente QRS (fQRS), QRS morfolojisindeki spesifik değişikliklerle tanımlanır ve miyokardiyal fibroz, iskemi ve kötü kardiyovasküler sonuçlarla ilişkilidir. Bu çalışmanın amacı semptomatik ciddi AD hastalarında fQRS ile sol ventrikül kütle indeksi (LVMI) arasındaki ilişkiyi araştırmaktır.

**Yöntem:** Bu retrospektif çalışmaya, dışlama kriterlerinden sonra Ocak 2018 ile Aralık 2023 tarihleri arasında ciddi AD tanısı konan 209 hasta dahil edilmiştir. Hastalara fQRS varlığını ve LVH parametrelerini değerlendirmek için EKG ve ekokardiyografi yapılmıştır. İstatistiksel analizler fQRS olan ve olmayan hastalar arasındaki değişkenleri karşılaştırmış ve regresyon analizleri yüksek LVMI'nin belirleyicilerini tanımlamıştır.

**Bulgular:** Hastalar fQRS varlığına göre iki gruba ayrılmıştır. fQRS grubunda interventriküler septum kalınlığı (IVS), LV arka duvar kalınlığı (LVPWT), LVMI ve pik aortik hız anlamlı olarak daha yüksekti. Regresyon analizlerine göre KOAH, düşük glomerüler filtrasyon hızı (GFR), artmış sistolik pulmoner arter basıncı (sPAP) ve fQRS varlığı yüksek LVMI'nin bağımsız belirleyicileri olarak bulunmuştur. Çalışmanın genel popülasyonunda LVMI değerinin 131.7 olmasının EKG'de fQRS varlığını %62.5 duyarlılık ve %62 özgüllük ile öngördüğü saptanmıştır.

**Sonuç:** Çalışmamızda EKG'de fQRS varlığının şiddetli AD hastalarında daha yüksek LVMI'nin önemli bir göstergesinin olduğu saptanmıştır. EKG'de fQRS'nin tanımlanması bu hastalarda LVH şiddetinin öngörülmesinde yardımcı olabilir.

**Anahtar Kelimeler:** aort darlığı, fragmente QRS kompleksi, sol ventrikül hipertrofisi, sol ventrikül kütlesi

#### ABSTRACT

**Objective:** Aortic stenosis (AS) is the most common primary valve lesion in Europe and North America, often requiring surgical or transcatheter intervention. Due to increased afterload left ventricular hypertrophy (LVH) occurs. Fragmented QRS (fQRS) on an electrocardiogram (ECG) is defined by specific alterations in the QRS morphology and is associated with myocardial fibrosis, ischemia, and poor cardiovascular outcomes. This study aimed to investigate the relationship between fQRS and left ventricular mass index (LVMI) in patients with symptomatic severe AS.

**Method:** This retrospective study included 209 patients diagnosed with severe AS between January 2018 and December 2023, after exclusion criterias. Patients underwent ECG and echocardiography to assess the presence of fQRS and LVH parameters, including LVMI. Statistical analyses compared variables between patients with and without fQRS, and logistic regression identified predictors of high LVMI.

**Results:** Patients were divided into two groups based on the presence of fQRS. The fQRS group had significantly greater interventricular septal thickness (IVST), LV posterior wall thickness (LVPWT), LVMI, and peak aortic velocity. According to regression analyses COPD, low glomerular filtration rate (GFR), increased systolic pulmonary artery pressure (sPAP), and the presence of fQRS was found as independent predictors of high LVMI. The LVMI value of 131.7 was found to predict the presence of fQRS on ECG with 62.5% sensitivity and 62% specificity in the general population of the study.

**Conclusion:** The presence of fQRS on ECG is a significant marker of higher LVMI in patients with severe AS. Identifying fQRS on ECG can help predict LVH severity in these patients.

**Keywords:** aortic stenosis, fragmented QRS complex, left ventricular hypertrophy, left ventricular mass

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## INTRODUCTION

Aortic stenosis (AS) is the most common primary valve lesion requiring surgical or transcatheter intervention in Europe and North America (1). Chronic left ventricular (LV) pressure overload occurs in haemodynamically significant AS. As a result of the increased pressure, both an increase in myocardial muscle mass and changes in LV geometry occurs in order to reduce wall stress and maintain cardiac output. The inability of the myocardial microvascular system to meet the increased metabolic demands results in microvascular ischaemia. Progressive microvascular ischaemia leads to anginal symptoms, myocardial fibrosis and eventually myocardial dysfunction (2).

Fragmented QRS (fQRS) is defined as alterations in QRS morphology with distinct RSR' patterns. Various RSR' patterns include: additional R wave (R') corresponding to abnormal cardiac depolarisation, or notching in the R wave or S wave, or the presence of >1 R' in two adjacent leads (3). As a mechanism of fQRS formation, it has been reported that slow and inhomogeneous propagation of ventricular activation due to myocardial ischaemia and scar leads to fragmentation in electrocardiography (ECG) (4).

In patients with severe AS, fQRS rates were observed more frequently than in healthy subjects (5). Another study on hypertensive patients showed that hypertensive patients with fQRS had a higher left ventricular mass index (LVMI) than patients without fQRS (6). The presence of fQRS, which has been associated with myocardial fibrosis, has been shown to be an important prognostic marker of cardiovascular events and mortality in some studies (7, 8).

The aim of our study was to investigate the relationship between the presence of fQRS and LVM in patients with symptomatic severe AS.

## MATERIALS AND METHODS

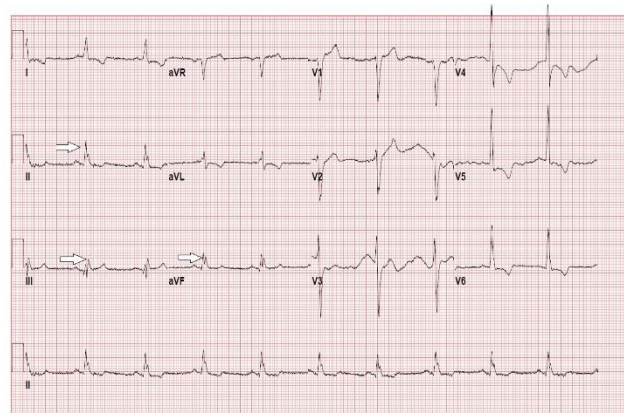
### Study Population

After exclusion criteria, this retrospective study was performed between January 2018 and December 2023 with 209 patients diagnosed with severe AS. Exclusion criteria of our study were: Patients with wall motion abnormality, coronary artery disease, concomitant severe valvular disease, presence of pulmonary hypertension, previous permanent pacemaker implantation, presence of right or left bundle branch block, past coronary artery by-pass or valvular surgery. Demographic and laboratory data were obtained from hospital medical records. The study was designed in accordance with the principles of the Declaration of Helsinki. The local ethics committee approved the study. Written informed consent was not obtained from the patients due to the retrospective nature of the study.

### Electrocardiography

All patients underwent a 12-lead ECG (filter range, 0.15-100 Hz; AC filter, 60 Hz, 25 mm/sec and 10 mm/mV) in the supine position at rest. ECGs were evaluated by a single cardiologist blinded to the patients. The presence of a fQRS was determined by using a 12-lead ECG. fQRS was defined as the presence of an additional R wave (R'), notching or >1 R' (fragmentation) at the extreme end of the R or S wave, QRS complex with >2 R' waves in a wide QRS complex including bundle branch block, paced rhythm or premature ventricular complexes, or different QRS

morphologies with varying RSR' patterns in 2 adjacent leads with notching in the R or S wave (Fig 1) (3).



**Figure 1.** Twelve lead ECG example of a patient with fQRS

### Echocardiography

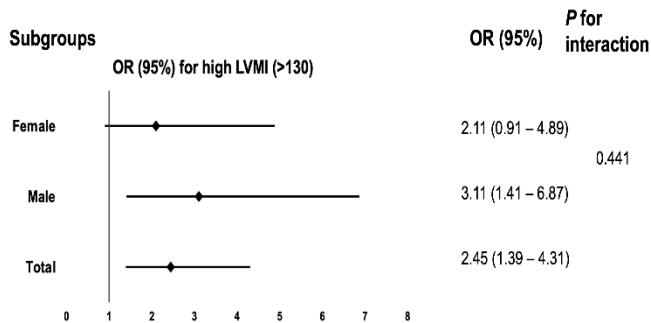
M-mode and 2D echocardiography were performed in all patients. Interventricular septal thickness (IVST), left ventricle posterior wall thickness (LVPWT), left ventricular end-systolic diameter and end-diastolic diameter (LVEDD) were measured in the parasternal long axis view by M-mode echocardiography in all patients. Left ventricle ejection fraction (LVEF) was calculated using the biplane Simpson method. LVM (g) was calculated by using the Devereux formula as  $0.8 \times 1.04 \times [(IVST + LVEDD + LVPWT)^3 - LVEDD^3] + 0.6$  and indexed according to body surface area (9). Classification of AS and aortic regurgitation, pulmonary hypertension, aortic valve area or aortic valve area index, mean and maximum transvalvular aortic gradient were defined in accordance with consensus reports and current guidelines (10).

### Statistical Analysis

The continuous variables in the dataset were first examined by Kolmogorov-Smirnov test and then histogram curves were evaluated to determine the normal distribution. Independent t-test was used to compare continuous variables with normal distribution and Mann-Whitney U test was used to evaluate continuous variables without normal distribution. Comparison of categorical variables was performed using Chi-square or Fisher's exact test. Normally distributed parameters were expressed as mean  $\pm$  standard deviation in the tables, whereas non-normally distributed parameters were expressed as median and 25-75 quartiles. Categorical variables are expressed as absolute numbers (n) and percentages (%).

A two-tailed  $p < 0.05$  value was assumed for the threshold of statistical significance. The patient population was divided into two groups,  $\leq 130$  and  $> 130$ , according to the median value of LVMI of 130. When the study population was divided according to gender, the median LVMI values were 125 and 134 in the female and male subgroups, respectively. To investigate the association of clinically relevant variables in the dataset with high LVMI ( $> 130$ , 125 and 134), univariable binary logistic regression analysis was first applied and unadjusted odds ratios (11) and 95% confidence intervals (CIs) were obtained for each variable. Then, a multivariable regression model was established with the inclusion of the variables that reached statistical significance and independent predictors

of high LVMI were investigated and adjusted ORs were found. The association of the presence of fQRS complex with higher overall median LVMI (>130) in subgroups stratified by sex is shown by Forest plot (Fig 2). In addition, the optimal cut-off values of LVMI for both overall population and subgroups for gender that can predict the presence of fQRS on electrocardiography was investigated by ROC curve analysis. IBM SPSS Statistics, version-26 (IBM Corp., NY, USA) was used for all statistical analyses.



**Figure 2.** The association of fQRS and higher LVMI (130) in subgroups stratified by sex

**RESULTS**

A total of 209 patients with severe AS were enrolled in the study. These patients were categorized into two groups based on the presence or absence of fQRS. The baseline clinical and laboratory characteristics of the patients based on the presence of baseline fQRS are presented in Table 1. Both groups were similar in terms of age, sex, hypertension, dyslipidaemia, peripheral arterial disease, chronic pulmonary disease, renal functions, previous stroke, atrial fibrillation and anaemia. Patients without fQRS have slightly higher incidence of DM (52 [43%] vs 24 [27.3%], p=0.020). Serum high-density lipoprotein cholesterol level was found lower in fQRS group (45±12.7 vs 49.2±13.5 p=0.020) while other lipid parameters were similar in both groups. Upon examining the biochemical and echocardiographic parameters, IVST (14.1 ±2.1 vs 13.1±1.8 p=0.001), LVPWT (13.2±2.1 vs 12.1±1.7 p=0.001), LVMI (147.4±37.1 vs 128.2±32.8 p= <0.001), and peak aortic velocity (4.66±0.58 vs 4.46±0.42 p=0.017) were found to be significantly greater in the fQRS group. Other echocardiographic features were not different between the groups.

The relation of all variables in the dataset with high LVMI (>130) was investigated by univariable binary logistic regression analysis. Thus, male gender, low body mass index, LVEF and glomerular filtration rate (GFR), presence of chronic obstructive pulmonary disease (COPD), high mean transaortic gradient, systolic pulmonary artery pressure (sPAP) ≥30 mmHg and presence of fQRS on ECG were found to be significant factors associated with high LVMI (>130). According to multivariate analysis including these covariates, presence of COPD (adjusted OR: 2.273, 95% CI: 1.047 – 4.934, p=0.038), mean transaortic gradient (adjusted OR: 1.023, 95% CI: 1.001 – 1.047, p= 0.047), GFR (adjusted OR: 0.989, 95% CI: 0.978 – 0.999, p=0.037), sPAP ≥30 mmHg (adjusted OR: 2.236, 95% CI: 1.088 – 4.595, p= 0.028) and presence of fQRS (adjusted OR: 2.255, 95% CI: 1.206 – 4.217, p=0.011) were found to be independent predictors of high LVMI (>130) (Table 2a).

**Table 1. Baseline Parameters of the Study Population in Terms of the Presence of fQRS.**

	Patients without fQRS (n=121, 57.9%)	Patients with fQRS (n=88, 42.1%)	Overall population (N=209)	P value
Age, years	63.9±12.4	65±11.6	64.4±12.1	0.653
Gender, male	65 (53.7%)	52 (59.1%)	117 (56%)	0.440
Height, meters	163.6±10.3	163.6±9.2	163.6±9.8	0.968
Weight, kgs	77.4±15.1	77.8±14.9	77.6±15	0.892
BMI, kg/m <sup>2</sup>	29.1±5.6	29.1±5.2	29±5.4	0.975
BSA, m <sup>2</sup>	1.86±0.21	1.87±0.21	1.87±0.21	0.823
NYHA class 3 or 4	47 (38.8%)	30 (34.1%)	77 (36.8%)	0.482
Angina pectoris	34 (28.1%)	27 (30.7%)	61 (29.2%)	0.685
Syncope	4 (3.3%)	7 (8%)	11 (5.3%)	0.137
Current smoker	23 (19%)	28(23.9%)	44 (21.1%)	0.395
COPD	26 (21.5%)	20 (22.7%)	46 (22%)	0.831
DM	52 (43%)	24 (27.3%)	76 (36.4%)	0.020
HT	82 (67.8%)	56 (63.6%)	138 (66%)	0.533
HPL	66 (54.5%)	56 (63.6%)	122 (58.4%)	0.188
PAD	14 (11.7%)	10 (11.4%)	24 (11.5%)	0.946
Previous stroke	7 (5.8%)	10 (11.4%)	17 (8.2%)	0.150
AF	6 (5%)	6 (6.8%)	12 (5.7%)	0.568
LVEF, %	60.4±5.7	60.4±5.6	60.4±5.7	0.729
IVS, mm	13.1±1.8	14.1±2.1	13.5±2.1	0.001
PW, mm	12.1±1.7	13.2±2.1	12.6±1.9	0.001
LVEDD, mm	47.1±5.1	48.2±5.2	47.5±5.2	0.146
LVMI	128.2±32.8	147.4±37.1	136.3±35.8	<0.001
AVA, m <sup>2</sup>	0.75±0.14	0.72±0.13	0.73±0.14	0.053
Peak aortic velocity, m/sec	4.46±0.42	4.66±0.58	4.55±0.51	0.017
Peak aortic gradient, mmHg	84.4±18.3	89.9±25.3	86.7±21.7	0.197
Mean aortic gradient, mmHg	52.1±12.1	56.6±16.1	54.1±14.1	0.069
Moderate to severe AR	35 (28.9%)	23 (26.1%)	58 (27.8%)	0.657
sPAP ≥30 mmHg	29 (24.2%)	29 (33%)	58 (27.9%)	0.163
Creatinine, mg/dL	.8 (0.7– 1)	0.8 (0.7 –1)	0.8 (0.7 – 1)	0.906
GFR, mL/min/1.73m <sup>2</sup>	92.4±31.4	93.8±34.5	93±32.7	0.997
Hemoglobin, g/dL	13.1±1.6	13.1±1.9	13.1±1.7	0.842
Total-C mg/dL	193.5±46.7	194.7±53.1	194±49.3	0.982
LDL-C, mg/dL	115.8±38.5	119.8±42.8	117.5±40.3	0.546
HDL-C, mg/dL	49.2±13.5	45±12.7	47.4±13.3	0.020
Triglyceride, mg/dL	152.3±95.7	152.8±81.7	152.5±89.9	0.548
Bicuspid AV	14 (11.7%)	8 (9.2%)	22 (10.6%)	0.569
LV concentric hypertrophy	107 (88.4%)	83 (94.3%)	190 (90.9%)	0.144

AF: Atrial fibrillation, AR: Aortic regurgitation, AVA: Aortic valve area, BMI: Body mass index, BSA: Body surface area, COPD: Chronic obstructive pulmonary disease, DM: Diabetes mellitus, fQRS: fragmented QRS, GFR: glomerular filtration rate, HDL-C: High-density lipoprotein cholesterol, HPL: Hyperlipidemia, HT: Hypertension, IVS: Interventricular septum LDL-C: Low-density lipoprotein cholesterol, LVEDD: Left ventricular end-diastolic diameter, LVEF: Left ventricular ejection fraction, LVMI: Left ventricular mass index, NYHA: New York Heart Association functional capacity, PAD: Peripheral artery disease, PW: Posterior wall sPAP: systolic pulmonary artery pressure, Total-C: Total cholesterol

**Table 2a. Binary Logistic Regression Analyses for Investigating the Predictors of High LVMI (>130).**

Variable	High LVMI (>130)			
	Univariate		Multivariate	
	Unadjusted OR (95%CI)	P value	Adjusted OR (95% CI)	P value
Gender, male	1.839 (1.058 – 3.197)	0.031	1.632 (0.828 – 3.217)	0.157
BMI, kg/m <sup>2</sup>	0.925 (0.876 – 0.976)	0.004	0.954 (0.892 – 1.021)	0.176
COPD	2.548 (1.279 – 5.077)	0.008	2.273 (1.047 – 4.934)	0.038
LVEF, %	0.923 (0.868 – 0.981)	0.010	0.954 (0.890 – 1.022)	0.181
Mean transaortic gradient, mmHg	1.023 (1.002 – 1.044)	0.031	1.023 (1.001 – 1.047)	0.047
sPAP ≥30 mmHg	1.973 (1.061 – 3.669)	0.032	2.236 (1.088 – 4.595)	0.028
GFR, mL/min/1.73 m <sup>2</sup>	0.984 (0.975 – 0.993)	<0.001	0.989 (0.978 – 0.999)	0.037
fQRS	2.449 (1.393 – 4.304)	0.002	2.255 (1.206 – 4.217)	0.011

BMI: Body mass index, COPD: Chronic obstructive pulmonary disease, fQRS: fragmented QRS, GFR: glomerular filtration rate, sPAP: systolic pulmonary artery pressure, LVEF: Left ventricular ejection fraction, LVMI: Left ventricular mass index

After the subgroups were dichotomized based on separate median LVMI values for the female and male subgroups (125 for female and 134 for male), the association of the variables employed in the study with high LVMI was investigated separately in the two subgroups by univariate and multivariate binary logistic regression (Table 2 b and c). In the female population COPD, mean transaortic gradient, GFR and presence of fQRS were associated with high LVMI (>125), whereas LVEF, sPAP ≥30 mmHg, GFR and presence of fQRS were associated with high LVMI (>134) in male patients .

**Table 2b. Binary Logistic Regression Analyses for Investigating the Predictors of High LVMI in Female population (>125).**

Variable	High LVMI (>125)			
	Univariate		Multivariate	
	Unadjusted OR (95%CI)	P value	Adjusted OR (95% CI)	P value
COPD	4.063 (1.051 -5.700)	0.042	5.620 (1.191 – 6.520)	0.029
Mean transaortic gradient, mmHg	1.043 (1.007 – .080)	0.018	1.041 (1.002 – 1.082)	0.039
GFR, mL/min/1.73 m <sup>2</sup>	0.983 (0.970 – .997)	0.015	0.983 (0.970 – 0.998)	0.022
fQRS	2.755 (1.174 – .465)	0.020	2.769 (1.067 – 7.188)	0.036

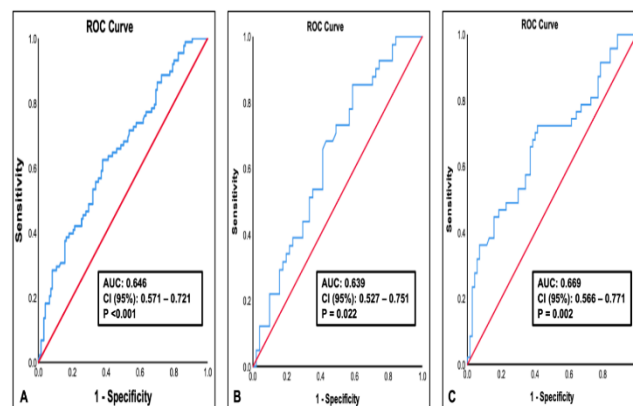
COPD: Chronic obstructive pulmonary disease, fQRS: fragmented QRS, GFR: glomerular filtration rate, LVMI: Left ventricular mass index

**Table 2c. Binary Logistic Regression Analyses for Investigating the Predictors of High LVMI in Male Population (>134).**

Variable	High LVMI (>134)			
	Univariate		Multivariate	
	Unadjusted OR (95%CI)	P value	Adjusted OR (95% CI)	P value
LVEF, %	0.908 (0.838 – 0.983)	0.018	0.928 (0.852 – 1.011)	0.086
sPAP ≥30 mmHg	3.571 (1.300 – 9.815)	0.014	2.936 (1.002 – 8.601)	0.049
GFR, mL/min/1.73 m <sup>2</sup>	0.984 (0.972 – 0.996)	0.011	0.989 (0.976 – 1.003)	0.117
fQRS	3.200 (1.470 – 6.965)	0.003	3.152 (1.368 – 7.262)	0.007

fQRS: fragmented QRS, GFR: glomerular filtration rate, sPAP: systolic pulmonary artery pressure, LVEF: Left ventricular ejection fraction, LVMI: Left ventricular mass index

Following the confirmation of the relationship between the presence of fQRS on ECG and high LVMI, the optimal predictive value of LVMI for the presence of fQRS was investigated using the ROC curve analysis (AUC: 0.646, 95% CI: 0.571 - 0.721, p<0.001). Accordingly, the LVMI value of 131.7 was found to predict the presence of fQRS on ECG with 62.5% sensitivity and 62% specificity for general population (Fig 3a). When the patient population was established according to different genders, ROC curve analysis has shown different optimal cut-off values. LVMI value of 125.3 was found to predict the presence of fQRS on ECG with 61% sensitivity and 58.8% specificity for female population (Fig 3b), while in male population LVMI value of 133 was found to predict presence of fQRS with 70.2% sensitivity and 60% specificity, as well (Fig 3c).



**Figure 3 (a,b,c).** ROC curve analysis of high LVMI for predicting fQRS in subgroups (Panel A: general population, Panel B: female population, Panel C: male population)

## DISCUSSION

In the present study, we evaluated the relationship between left ventricle hypertrophy (LVH) parameters, one of the main presentations of AS, and fQRS, one of the important signs of myocardial scar tissue. The main findings of this study were: (i) LVH parameters of patients with severe AS with fQRS on ECG were significantly higher than the patients without fQRS on ECG, (ii) peak aortic velocity was greater in patients with fQRS than without, (iii) fQRS, COPD, lower GFR, increased sPAP and mean transaortic gradient were independent predictors of high LVMI.

Chronic LV pressure load resulting from haemodynamically significant AS leads to both an increase in myocardial muscle mass and changes in LV geometry as a compensatory mechanism to reduce wall stress and maintain cardiac output (12-15). However it has been shown that increased LVM is associated with decreased LV systolic function and existence of heart failure in patients with severe AS (16). In fact, the term  $\square\square$ inappropriately increased LVM $\square\square$  defines higher than expected increases in myocardial mass that exceed the estimated mechanical demands to maintain a certain afterload (12). Cioffi et al. has demonstrated that inappropriately LVM increase, especially in asymptomatic severe AS patients, is associated with an increased rate of cardiovascular events regardless of other prognostic covariates (17). In addition, in several studies it has been shown that LVH is associated with poor immediate and late adverse outcomes among patients undergoing surgical aortic valve replacement (18-20).

LVH, which occurs in AS on long term, causes myocardial degeneration and fibrosis as a consequence of excessive wall stress and relative ischaemia. These alterations occur primarily in the subendocardial layer, causing interstitial fibrosis and, in advanced stages, transformation of myocardial tissue into fibrous tissue (21-23). Furthermore, microvascular ischaemia occurs due to the inability of the myocardial microvasculature to keep pace with the increased metabolic demands. The microvascular ischaemia responsible for the anginal symptoms contributes to progressive myocardial fibrosis and ultimately to myocardial dysfunction(2, 24, 25). Myocardial fibrosis is the main cause of LV decompensation in AS (regardless of the presence or absence of CAD) (1). In line with this, some studies have demonstrated that myocardial fibrosis contribute to reduced survival rates after surgical aortic valve replacement in patients with severe AS(26, 27).

fQRS is a mark of myocardial scar, fibrosis and inhomogenous ventricular activity. The depolarisation problem in tissues that do not function electrically properly because of fibrosis is considered to be the main mechanism in fQRS formation (28). Previously, Zhang et al. reported that the presence of fQRS on ECG has a poor sensitivity of 51% for the detection of LVH. However they also have found that the fQRS was associated with LVM independently and related to a significantly higher risk for worsened LVH (29). In another study, Kadi et al found that the existence of fQRS on ECG was an important marker of LVH in hypertensive individuals (6). In addition, Dural et al. reported that LVH parameters were higher in acromegalic patients with fQRS (30).

In our study, we have used LVMI to evaluate the severity of LVH in patients with severe AS.

We divided the patients into two groups based on LVMI median value of 130. Our study has demonstrated that the existence of fQRS on ECG was independently correlated with higher LVMI.

### Limitations

This present study has some limitations that should be taken into account when interpreting the results.

First, the sample size is relatively small, and second, due to the character of retrospective studies, selection bias and unmeasured confounding factors may affect the findings. Third, cardiac MRI, which could provide better fibrosis and mass evaluation, was not performed in these patients. Nevertheless, our results are consistent with prior investigations.

## CONCLUSION

The existence of fQRS on ECG is a significant marker of higher LVMI in patients with severe AS. We suggest that fQRS on ECG may be a consequence of interstitial fibrosis occurring in these patients.

**Ethics Committee Approval:** The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Non-Interventional Clinical Research Ethics Committee of Istanbul Medipol University (decision date: 4 June 2024, decision number: 575).

**Author Contributions:** All authors contributed to the manuscript.(I) Concept: E Dervis, A Hakgör; (II) Design: All authors ; (III) Supervision: E Dervis, I Yakut ; (IV) Resources: E Dervis, A Hakgör, I Yakut; (V) Materials: E Dervis, A Hakgör; (VI) Data collection and/or processing: E Dervis, A Hakgör, I Yakut; (VII) Analysis and/or interpretation: E Dervis I Yakut ; (VIII) Literature search: All authors; (IX) Writing manuscript and critical review: All authors.

**Conflict of Interest:** The authors declare that they have no conflict of interest.

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**Informed Consent:** Written informed consent was not obtained from the patients due to the retrospective nature of the study.

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