Original Article

Lead aVR is a predictor for mortality in heart failure with preserved ejection fraction

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ABSTRACT

Background: Normally, lead augmented vector right (aVR) has a negative T wave polarity (TaVR) in the electrocardiography (ECG). Positive TaVR and ST segment deviation in lead aVR (STaVR) have negative effects on mortality in heart failure with reduced ejection fraction patients.
Aim: Our aim was to investigate the relationship between lead aVR changes and mortality in heart failure with preserved ejection fraction (HFpEF) patients.
Methods: We retrospectively examined 249 patients in 2011–2015 years (mean age 70.8 ± 11.9 years and follow-up period 38.3 ± 9.6 months). ECG, echocardiographic, and laboratory findings were recorded and compared in the study. Existence of positive TaVR, STaVR, and quantitative TaVR values were recorded and the absolute numerical values of TaVR and STaVR were recorded from the 12-lead surface ECG (T/STaVR ratio or vice versa).
Results: The patients were divided into two groups: living (171) and deceased (78). Age, systolic blood pressure, left atrial diameter, QRS duration, positive TaVR frequency, STaVR, absolute value of TaVR, and ratio were significantly higher in the deceased group. Age (OR: 1.106), STaVR (OR: 2.349), TaVR (OR: 1.612), and T/STaVR ratio (OR: 5.156) were determined as independent predictors for mortality.
Conclusions: ST segment and T wave polarity changes in lead aVR closely associated with mortality in patients with HFpEF.
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1. Introduction

Heart failure (HF) frequency is 2% in the developed countries.[1] HF is categorized as preserved ejection fraction (HFpEF), mid-range ejection fraction (HFmrEF), and reduced ejection fraction (HFrEF) according to the last guideline.[2] HFpEF is defined as patients with patients with clinical evidence of HF with normal or near-normal left ventricular ejection fraction (EF). Recently, there has been an increase in the prevalence of HFpEF patients,[3,4] primarily due to greater recognition of this entity but also due to increasing comorbidites leading to HFpEF. These patients are usually women, hypertensive and elder people. In these patients, the coronary artery disease (CAD) frequency is lower than as seen in HFrEF patients.[5]

Cardiac myocyte hypertrophy, interstitial fibrosis, inflammation, and microvascular dysfunction play an important role in HFpEF patients' pathophysiology.[6–9] Many of the mortality parameters as determined for the HFrEF patients are not valid for HFpEF patient group. Although, advances in medical devices have given us new and important information about the diagnosis, treatment, and prognosis of the diseases; but, 12-lead surface electrocardiogram (ECG) is still one of the simple and unique methods and it gives important findings. Augmented vector right (aVR) lead is mostly neglected, but it is reported as a mortality predictor in many cardiovascular diseases.[10] Lead aVR is calculated using lead I and II by ECG machines. Normally, lead aVR has a negative T wave polarity (TaVR) in the ECG. It was reported that positive TaVR had negative effects on mortality in the HFrEF patient groups.[11,12] It was shown that ST deviation in lead aVR (STaVR) had also unfavorable effects in major cardiac events.[13] Increased QRS duration, QT, and QT_c intervals were related to delayed ventricular activation in HFpEF patients. Their effects on mortality have been reported in previous studies.[14–16] There is limited data about the TaVR and STaVR's role in HFpEF patients.

Our aim was to investigate whether there is a relationship between TaVR and/or STaVR changes and mortality in HFpEF patients or not.

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2. Material and methods

2.1. Patient population

The Local Ethics Committee approved the study protocol. We retrospectively examined 1345 patients who admitted to our coronary intensive care unit due to heart failure diagnosis in 2011–2016 years. Among these, we detected 311 patients who met HFpEF criteria.[2] These criteria were left ventricular ejection fraction (LVEF) ≥ 50%, N-terminal pro brain natriuretic peptide (NT-proBNP) >125 pg/m and also one of two criteria, (1) Left ventricular hypertrophy or left atrial enlargement, (2) Diastolic dysfunction (E/e' ≥13 and a mean e' septal and lateral wall <9 cm/s in Doppler echocardiography)

Patients with systemic diseases, chronic obstructive pulmonary disease were excluded. Also, patients with diuretic therapy given due to an indication other than HF were excluded (such as, excessive contrast volume after coronary angiography or intervention, or oliguria due to acute kidney disease). Our study group consisted of 249 patients (mean age 70.8 ± 11.9 years and follow-up period 38.3 ± 9.6 months).

Age, gender, height, weight, diabetes mellitus, hypertension, hyperlipidemia, CAD, stroke history, and current medication information were recorded from the patient files. Patients' current statuses were obtained from the hospital visits or phone connections.

2.2. Evaluation of laboratory findings

Renal function, lipid parameters, high sensitive C reactive protein (hs-CRP), uric acid, NT-proBNP, thyroid functions, and complete blood count were determined from routinely taken blood samples.

2.3. Electrocardiographic and echocardiographic evaluation

Twelve lead surface ECGs of all patients were recorded by the Nihon Kohden Cardiofax V model ECG-1550 K device. Electro-cardiograms had 25 mm/sec speed and 1 mv/10 mm standard calibration. These ECGs were assessed by two independent cardiologists. QRS duration and axis, fragmentation in QRS complex, P wave duration, PR, QT, and QTc intervals, number of patients with the existence of positive TaVR, the numerical value of STaVR, the numerical value of TaVR values were recorded (Figs. 1 and 2). Total TaVR magnitude was calculated in biphasic T wave ones (Fig. 3). In a previous study, TaVR and STaVR's absolute numerical values were recorded and a ratio was obtained from the

division of bigger absolute value by lesser absolute value (|TaVR |/| STaVR| or |STaVR|/| TaVR |).[17] This ratio (T/STaVR or vice versa) was found closely related to the significance of CAD. We calculated and used this ratio as well. We recorded EF, left ventricular end diastolic and end systolic diameters (LVDD, LVSD), left atrium diameter (LaD) from echocardiographic data (Epiq 7, Philips Healthcare, DA Best, Netherlands). Pulsed wave E velocity, A velocity, S velocity, e' velocity, a' velocity, and E/e' values were measured with tissue Doppler method and systolic pulmonary artery pressures were recorded.

2.4. Statistical analysis

Variables were divided into two groups as categorical and continuous. Categorical data were expressed as numbers and percentages and compared with the chi-square test. Kolmogorov-Smirnov test was used to determine whether continuous variables had normal distribution or not. Normal distributed continuous variables were compared with the independent sample *t*-test Not normal distributed variables were compared with Mann-Whitney U test. Binominal logistic regression analysis was performed with significant variables. Independent predictors were found for mortality. All statistical analyses were calculated with SPSS 20.0 (SPSS Inc., Chicago, IL, United States). A P value <0.05 was considered to be statistically significant.

3. Results

We retrospectively screened 1345 patients with HF and exlcuded 996 of them due to HFrEF and HFmrEF. The patients were divided into two groups: living and deceased. The living group consisted of 171 patients (mean age 68.9 ± 11.8 years, mean follow-up period 37.5 ± 9.6 months) and the deceased group had 78 (31.3%) patients (mean age 75.1 ± 11.3 years, mean follow-up period 39.9 ± 9.2 months). In the demographic comparison, deceased group had significantly higher mean age (p < 0.001), lower systolic blood pressure (p = 0.04), other findings were similar (Table 1). Both groups had similar laboratory and drug treatment findings (Tables 2 and 3). LaD was higher (p = 0.021) in the deceased group (Table 4), QRS duration (p = 0.044), number of pateints with positive TaVR (p < 0.001), STaVR (p = 0.001), TaVR (p = 0.002), and T/STaVR ratio (<0.001) were significantly higher in deceased group (Table 5). Age (OR:1.106, %95 CI:1.057-1.157, p < 0.001), STaVR (OR:2.349, %95 CI:1.498-3.684, p < 0.001), TaVR (OR:1.612, %95 CI:1.183-2.196, p = 0.002), and T/STaVR ratio

Fig. 1. Demonstration of the ratio calculation. Absolute value of 'a' and 'b' were calculated. Then, bigger one was divided smaller one, ratio was abtained. In this patient, the ratio= b/a.
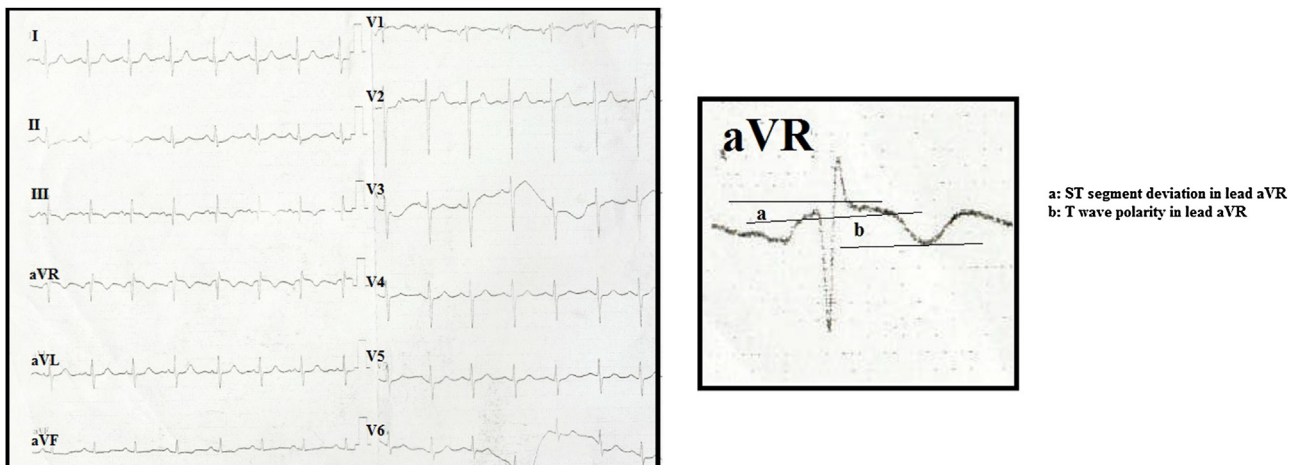
Fig. 2. Demonstration of the ratio calculation. Absolute value of 'a' and 'b' were calculated. Then, bigger one was divided smaller one, ratio was abtained. In this patient, the ratio= b/a.

Fig. 3. Demonstration of the ratio calculation. Absolute value of 'a' and 'b + c' were calculated. Then, bigger one was divided smaller one, ratio was abtained. In this patient, the ratio= a/b + c.
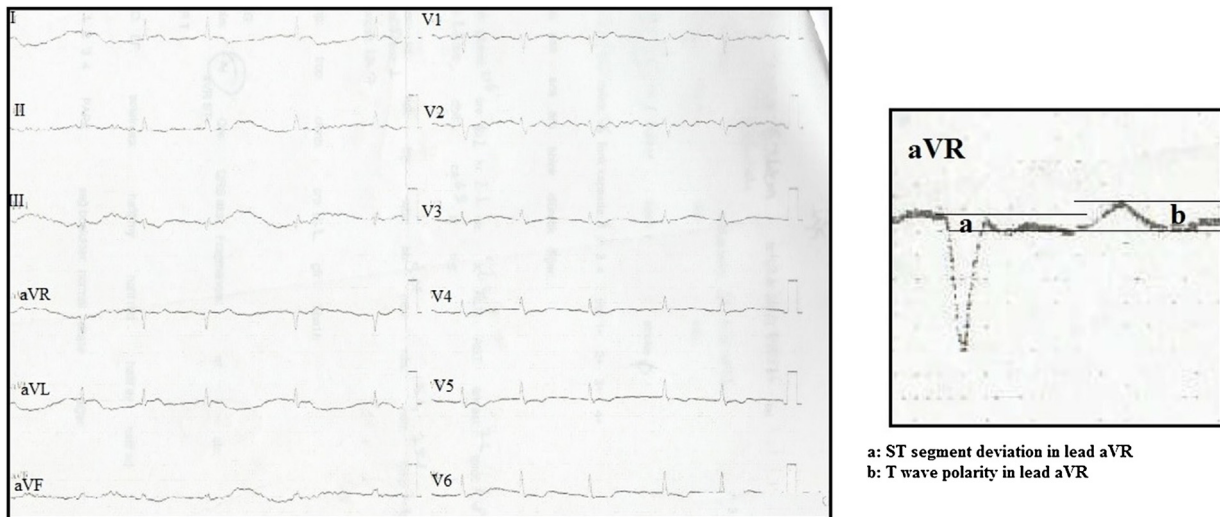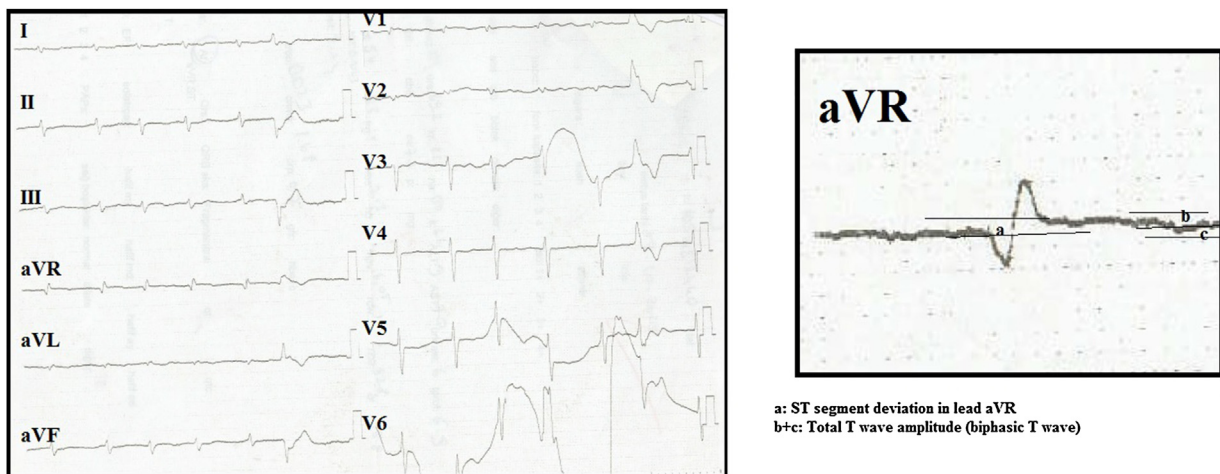
Table 1
Comparison of patients demographic findings.

	Living (n = 171)	Deceased (n = 78)	p
Age (years)	68.9 ± 11.8	75.1 ± 11.3	**<0.001**
Male gender,n,(%)	57 (33.3)	28 (35.9)	0.692
Systolic blood pressure (mmHg)	115.6 ± 16.1	105.9 ± 23.2	**0.04**
Diastolic blood pressure (mmhg)	75.5 ± 12.7	70.9 ± 12.9	0.086
Pulse (beat/minute)	82.7 ± 18.7	87.1 ± 18.4	0.097
BMI (kg/m^2)	30.4 ± 6.7	30.2 ± 6.2	0.845
Smooking, n (%)	35 (20.5)	19(24.4)	0.490
DM, n (%)	60(35.1)	27 (34.6)	0.942
HT, n (%)	34 (39.9)	16 (20.5)	0.908
HPL, n (%)	3 (1.8)	0 (0)	0.554
Stroke, n (%)	6 (3.5)	5 (6.4)	0.301
AF, n(%)	33 (19.3)	20 (25.6)	0.257
CAD, n (%)	18 (10.5)	10 (12.8)	0.595

AF:atrial fibrillation, BMI:body mass index, CAD:coronary artrey disease, DM:diabetes mellitus, HT:hypertension, HPL:hyperlipidemia.

Table 2
Comparison of patients medications.

	Living n = 171	Deceased n = 78	p
ACE (n, %)	12 (7.0)	10 (12.8)	0.135
ARB (n, %)	12 (7.0)	5 (6.4)	0.860
B blocker (n, %)	45 (26.3)	19 (24.4)	0.743
Furosemid (n, %)	169(98.8)	77 (98.7)	0.940
Spironolactone (n, %)	53 (31.0)	20 (25.6)	0.389
Anticoagulant	9 (5.9)	3 (3.8)	0.628
Digoxin (n, %)	6 (3.5)	3 (3.8)	0.291
ASA (n, %)	33(19.3)	18 (23.1)	0.493

ACE:angiotensin converting enzym, ARB:angiotensin receptor blocker, ASA:acetylsalicylic acid.

Table 3
Comparison of patients laboratory findings.

	Living n = 171	Deceased n = 78	p
Glucose (mg/dl)	123.2 ± 82.5	123.7 ± 67.8	0.961
WBC (uL)	9.9 ± 4.1	11.1 ± 4.8	0.056
Hb (mg/dl)	12.2 ± 1.6	11.8 ± 1.5	0.065
BUN (mg/dL)	51.2 ± 21.2	51.0 ± 20.9	0.937
Cr (mg/dL)	1.3 ± 0.7	1.4 ± 0.5	0.215
Na (mmol/L)	135.7 ± 4.5	136.9 ± 5.2	0.073
K (mmol/L)	4.2 ± 0.5	4.2 ± 0.7	0.71
Gfr (mL/min/m^2)	62.6 ± 20.4	58.1 ± 13.9	0.340
Uric acid (mg/dL)	7.3 ± 2.4	7.4 ± 2.7	0.827
Total protein (g/dL)	6.4 ± 1.2	6.3 ± 1.1	0.368
Albumin (g/dL)	3.6 ± 0.6	3.5 ± 1.0	0.378
Calcium (mg/dL)	8.8 ± 0.6	8.7 ± 0.8	0.306
Phospor (mg/dL)	4.5 ± 0.6	4.9 ± 3.5	0.817
Hs-CRP (mg/L)	2.6 ± 2.7	3.3 ± 3.1	0.109
NT-proBNP (pg/mL)	4033 ± 6937	6325 ± 9686	0.101
Hs-TnT (pg/L)	0.4 ± 1.4	1.5 ± 7.9	0.247

BUN:blood urea nitrogen, Cr:creatinin,Hs-CRP:high sensitive C reactive protein, Hs-TnT:high sensitive troponin T, NT-proBNP: N-terminal brain natiuretic peptide. WBC: white blood cells, Hb:hemoglobin.

Table 4
Comparison of patients echocardiographic findings.

	Living n = 171	Deceased n = 78	p
EF (%)	55.2 ± 5.3	54.7 ± 4.8	0.375
LVDD (mm)	46.5 ± 3.1	47.0 ± 3.2	0.292
LVDS (mm)	35.4 ± 1.8	35.5 ± 1.8	0.489
IVS (mm)	0.9 ± 0.2	0.9 ± 0.1	0.747
LaD (mm)	44.6 ± 4.1	45.9 ± 3.7	**0.021**
E velocity (cm/s)	89.3 ± 23.9	91.2 ± 20.5	0.344
A velocity (cm/s)	60.7 ± 21.0	61.8 ± 21.4	0.692
S velocity (cm/s)	7.2 ± 1.9	7.3 ± 1.9	0.804
e' velocity (cm/s)	7.1 ± 1.9	7.0 ± 2.0	0.792
a' velocity (cm/s)	4.1 ± 1.7	3.9 ± 1.7	0.217
E/e'	13.4 ± 5.1	13.9 ± 4.7	0.415
PAPs (mmhg)	33.2 ± 8.6	32.2 ± 7.9	0.379

EF:ejection fraction, LaD:left atrium diameter, PAPs:systolic pulmonary artery pressure.

(OR:5.156, %95 CI: 3.141–8.465, p < 0.001) were determined as independent predictors for mortality in the binominal logistic regression analysis (Table 6).

4. Discussion

To the best of our knowledge, this study is the first article that reports about the relationship between TaVR and/or STaVR changes in lead aVR and mortality in patients with HFpEF. The mortality rate in the study was 31.3% and this ratio was similar to as reported previously.[18] STaVR and increased TaVR were found to be significantly associated with mortality. The division of TaVR and STaVR's absolute values (T/STaVR ratio) was found closely associated with mortality when compared to TaVR and STaVR alone.

Myocardial structural changes occur with the age and hypertension in HFpEF patients. Increased arterial stiffness causes chronic pressure overload. As a consequence, left ventricular remodeling and increase in diastolic filling pressure happen. In time, diastolic pressure overload and LaD create HF symptom and findings.[19,20]

Mean age was >65 years in our groups. Deceased patients had significantly higher mean age. Hypertension frequency was similar

Table 5
Comparison of patients' electrocardiographic findings.

	Living n = 171	Deceased n = 78	p
QRS (msn)	87.9 ± 18.4	93.8 ± 25.9	**0.044**
QRS axis (°)	20 ± 45.9	60.1 ± 86.5	0.066
Fragmentation, n (%)	30 (17.5)	18 (20.5)	0.576
P duration (ms)	91.2 ± 7.4	87.9 ± 6.3	0.013
PR interval	160.7 ± 20.2	159.8 ± 30.5	0.846
QT (ms)	386.2 ± 52.7	383.2 ± 60.0	0.699
QT$_C$ (ms)	440.4 ± 37.8	447.5 ± 47.5	0.219
Patients with positive TaVR, n (%)	39 (22.8)	36 (46.2)	**<0.001**
STaVR (mm)	0.5 ± 1.0	1.1 ± 1.1	**0.001**
TPaVR (mV)	−0.6 ± 1.3	0.1 ± 1.5	**0.002**
T/STaVR Ratio (n)	2.1 ± 1.2	4.3 ± 0.4	**<0.001**

STaVR:ST deviation in lead aVR, TaVR:T wave in lead aVR.
*T/STaVR Ratio: It was obtained from division of bigger absolute value by lesser absolute value (|TPaVR|/|STaVR| or |STaVR|/|TPaVR|).

Table 6
Independent predictors for mortality in patient wiht HfpEF.

	Odds ratio	95% Confidence Interval	p
Age	1.106	1.057-1.157	**<0.001**
QRS duration	0.997	0.977-1.017	0.748
LaD	1.088	0.992-1.193	0.075
STaVR	2.349	1.498-3.684	**<0.001**
TaVR polarity	1.612	1.183-2.196	**0.002**
T/STaVR ratio	5.156	3.141-8.465	**<0.001**

LaD: left atrium diameter, HFpEF: heart failure preserved ejection fraction, STaVR:ST deviation in lead aVR, TaVR: T wave in lead aVR.
*T/STaVR Ratio: It was obtained from division of bigger absolute value by lesser absolute value (|TPaVR|/|STaVR| or |STaVR|/|TPaVR|).

in both groups and lower than expected. Mean systolic and diastolic blood pressures were also normal. Both groups had >4 cm LaD and the deceased group had significantly higher values.

ST segment elevation or depression or T wave positivity in lead aVR reflects global ischemia in the left ventricle. Apex is the thinnest part of left ventricle.[21] In previous studies, the authors reported that T wave positivity in lead aVR was closely related to mortality in HFrEF, ST elevation myocardial infarction (STEMI) and non-ST elevation myocardial infarction (NSTEMI).[11,12,22–24] T/STaVR ratio was significantly correlated with CAD severity in a retrospective study conducted with NSTEMI patients.[17] It was also found more closely related to mortality when compared to other parameters in our study. Each one unit increase of this ratio increased the mortality about five times. Approximately, 10% of our patients had known CAD history. It is possible that correct CAD history information of patients may not be achieved due to retrospective study design. If our study had a prospective design and coronary angiography performed to all patients, maybe we could find a higher CAD frequency.

Cardiac myocyte fibrosis is seen in the HFpEF patients with aging.[19] This makes a dysfunctional diastolic relaxation in the myocardium. We thought that there may be an imbalance in tissue oxygen supply because coronary blood flow mostly happens in the diastolic phase. We also thought that tissue oxygen supply imbalance may represent itself as ischemia in lead aVR, and it may be related to mortality independent from severe CAD.

Some studies reported that there was a significant relation between QRS prolongation and poor prognosis in HFpEF patients.[25,26] As a pathophysiological mechanism, fibrosis in left ventricle could result in prolonged QRS and poor prognosis. Mean QRS duration of our patients was in normal range. Deceased

patients had significantly higher QRS duration compared to the living group, but there was no significant relation in multivariate regression analysis.

Atrial fibrillation (AF) can be seen in HFpEF patients and can lead to worsened HF symptoms. Thus, the diagnostic cut-off value of the BNP was set to a higher value in the presence of AF according to guideline.[2] Gigliotti JN et al[27] inspected the relation between QRS prolongation and AF in HFpEF patients. They reported that there was no significant correlation. Atrial fibrillation frequency was similar in our groups.

5. Limitations

The main limitation of our study is its retrospective design. We only investigated coronary intensive care unit patient files because we had no access to other unit's registries. We do not have sufficient information about coronary anatomies of all patients. No examination was done in terms of arrhythmic complications.

6. Conclusion

Changes in lead aVR of surface ECG may supply some important information about mortality in HFpEF patients. T wave polarity and ST segment changes in lead aVR should be closely monitored in these patients.

Authorship contributions

YKİ conceived the idea for the study. YKİ and ÖDU contributed to design. YKİ, YD, ÖDU, AOD, and MK were involved in data

collection. YKİ analyzed the data. YKİ coordinated funding for the project.

All authors edited and approved the final version of the manuscript.

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Conflict of interest

None declared.

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