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Electrocardiographic predictors of myocardial fibrosis and apical hypertrophic cardiomyopathy

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Abstract

Background: Electrocardiography (ECG) may be an efficacious diagnostic and prognostic tool in hypertrophic cardiomyopathy (HCM). This study aimed to investigate association between deep T-wave inversion (TWI) and apical HCM, and between fragmented QRS (fQRS) complex and myocardial fibrosis in patients with HCM.

Methods: Patients with documented HCM by cardiac magnetic resonance imaging (CMR) during 2005–2015 were studied. The 12-lead ECG and CMR were performed on the same day. All patients underwent CMR for the assessment of cardiac structure, function, and late gadolinium enhancement (LGE). LGE was used to detect myocardial fibrosis.

Results: One hundred forty-four HCM (mean age 66 ± 15.8 years, 60.4% male) were included. Twenty-nine (20.14%) subjects had deep TWI, and apical HCM was found in 76 (52.78%). Deep TWI was associated with apical HCM with the Odds ratio (95%CI) of 5.82 (2.07, 16.04) and $p < 0.001$ in univariate analysis model. The association was still significant in multivariate analysis with adjusted Odds ratio (95%CI) of 9.86 (3.17, 30.66), $p < 0.001$. Forty-seven (32.64%) subjects had fQRS complex, and myocardial fibrosis was detected in 101 (70.14%). fQRS complex was found to be associated with myocardial fibrosis in univariate analysis with the Odds ratio (95%CI) = 2.75 (1.16, 6.54), $p = 0.019$. However, the association cannot be demonstrated in the multivariate analysis.

Conclusion: Deep TWI is independently associated with apical HCM, but the relationship between fQRS complex and myocardial fibrosis did not survive multivariate analysis.

KEYWORDS

apical hypertrophic cardiomyopathy, ECG, electrocardiographic predictors, myocardial fibrosis

1 | INTRODUCTION

The prevalence of hypertrophic cardiomyopathy (HCM) is approximately 1:500 in the general population, and it is a leading cause of heart failure, atrial fibrillation, and sudden death—especially in population under 35 years of age (Gersh et al., 2011). The method most commonly used to diagnose HCM is echocardiography. HCM is characterized by wall thickness >15 mm. This condition can lead to cardiac arrhythmia, ischemic stroke, and myocardial infarction (Eriksson et al., 2002). Apical HCM may be difficult to detect by 12-lead electrocardiogram (ECG), with a measurement error that is reported to range from 6.9% to 17.1% (Alfonso et al., 1990). Deep T-wave inversion (TWI) from ECG may be a clue that can assist clinicians in diagnosing apical HCM (Alfonso et al., 1990). Accordingly, if

deep TWI presents on ECG, the operator would be well-advised to concentrate some added attention on the apical region to investigate for apical HCM.

Myocardial fibrosis in patients with HCM is associated with ventricular tachycardia and heart failure (Konno et al., 2015). Myocardial fibrosis is commonly identified using cardiac magnetic resonance (CMR) imaging; however, CMR has limited availability in developing countries and other low resource settings. In addition to the high cost of CMR, the images must be interpreted by a specialist. Fragmented QRS complex (fQRS) from a 12-lead ECG was shown to be associated with myocardial fibrosis with a sensitivity and specificity of 40% and 80%, respectively (Konno et al., 2015). The ability to identify myocardial fibrosis and apical HCM by 12-lead ECG would lower the cost of investigation and diagnosis and would give patients in low resource settings access to a diagnostic modality that can diagnose these conditions. Accordingly, the aims of this study were to investigate association between deep TWI and apical HCM, and between fQRS complex and myocardial fibrosis in patients with HCM.

2 | METHODS

2.1 | Population

This retrospective study included patients with a diagnosis of HCM that underwent both CMR and 12-lead ECG at the Division of Cardiology, Department of Medicine, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand during the 2005–2015 study period. Siriraj Hospital is Thailand's largest national tertiary referral center. The protocol for this study was approved by the Siriraj Institutional Review Board.

Hypertrophic cardiomyopathy by CMR was defined as any wall segment thickness >15 mm that could not be solely explained by abnormal loading condition. Patients having one or more of the following were excluded: (a) ECG patterns that could adversely influence interpretation (Das et al., 2008; Guo, Li, Xu, Tang, & Li, 2012), such as Wolff-Parkinson-White syndrome; (b) myocarditis; (c) congenital heart disease; and/or, (d) ventricular paced rhythm.

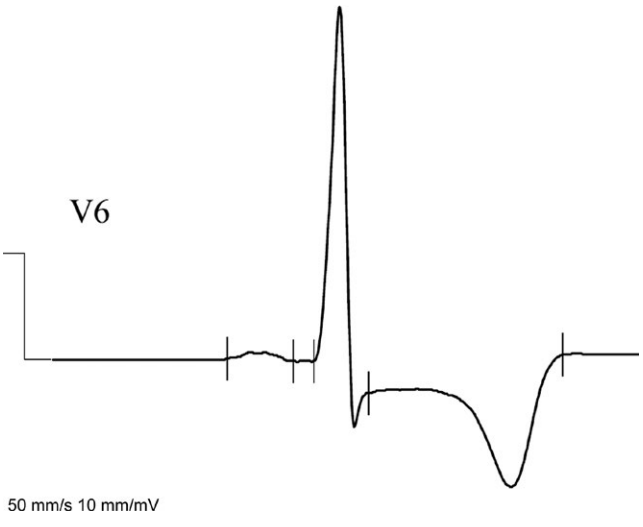

FIGURE 1 Deep T-wave inversion (TWI) in lead V_6 in patients with apical hypertrophic cardiomyopathy (HCM)

2.2 | Electrocardiography

All patients underwent 12-lead ECG (GE MAC 1200; GE Marquette Medical Systems, Milwaukee, WI, USA) at rest in the supine position with the machine adjusted to the following settings: 40 Hz, 50 Hz, 25 mm/s, and 10 mm/mV.

2.3 | Cardiac magnetic resonance protocol

All patients underwent CMR on a Philips Gyroscan NT Intera 1.5 Tesla scanner (Philips Medical Systems, Best, the Netherlands) for assessment of cardiac structure, function, and late gadolinium enhancement (LGE) images after 10 min of intravenous administration of gadolinium-DTPA (diethylenetriamine penta-acetic acid) (0.15 mmol/kg).

The CMR parameters for functional images were 8 mm slice thickness, 70 degree flip angle, repetition time/echo time/number of excitations (TR/TE/NEX) = 3.7/1.8/2, 390 × 312 mm field of view, 256 × 240 matrix, and 1.52 × 1.3 reconstruction pixel. The parameters for LGE images were 3D segmented-gradient-echo inversion-recovery sequence with 8 mm slice thickness, 15 degree flip angle, 1.5 SENSitivity Encoding (SENSE) factor, TR/TE = 4.1/1.25 ms, 303 × 384 mm field of view, 240 × 256 matrix, and 1.26 × 1.5 mm reconstruction pixel.

2.4 | Analysis of ECG

The following ECG parameters were collected: QRS voltage, QRS duration, QRS axis, T-wave axis, and QTc interval. The following criteria for left ventricular hypertrophy were assessed: Sokolow-Lyon criteria (S in V_1 + R in V_5 or V_6 >3.5 mV or R in V_5 or V_6 >2.6 mV) (Sokolow

FIGURE 2 Fragmented QRS (fQRS) complex in patients with a QRS complex duration <120 msec: (a) additional R wave; (b) notching in nadir of S wave; and, (c) equal or more than one deflection in R prime

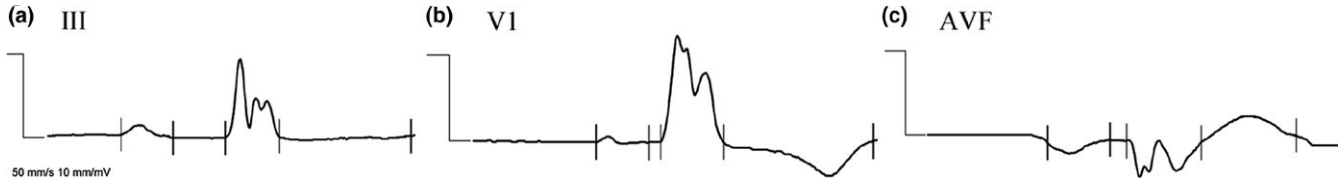

FIGURE 3 Fragmented QRS (fQRS) complexes in patients with a QRS complex duration ≥120 msec: (a) RSR' with equal or more than 2 R′; (b) equal or more than two notches in R wave; and, (c) notch in upstroke of S wave

& Lyon, 1949), Cornell voltage criteria (R in aVL + S in V_3 > 2.0 mV in female and >2.8 mV in male) (Casale et al., 1985), and Cornell product criteria (the product of QRS duration times the Cornell voltage combination with 0.6 mV added in women >244 mV × msec (Molloy, Okin, Devereux, & Kligfield, 1992).

Deep TWI was defined as more than 10 mV of negative T-wave amplitude in at least one lead in any wall segment (Figure 1) (Elliott et al., 2014).

fQRS complex (Konno et al., 2015) was defined, as follows:

1. If QRS duration was <120 msec and at least one of the following findings was present (Figure 2):
   1.1 Additional R wave (Figure 2a)
   1.2 Notching in nadir of the S wave (Figure 2b)
   1.3 Equal or more than one deflection in R prime in two contiguous leads (Figure 2c)
2. If QRS duration was equal to or more than 120 msec and at least one of the following findings was present (Figure 3):
   2.1 RSR′ with equal or more than 2 R′ deflection (Figure 3a)
   2.2 Equal or more than two notches in R wave (Figure 3b)
   2.3 Notch in down stroke or upstroke of S wave in two contiguous leads (Figure 3c).

fQRS complexes in more than two leads in the same wall segment (V_{1-4} = anterior wall segment; V_5, V_6, and aVL = lateral wall segment; and, II, III, and aVF = inferior wall segment) were defined as fQRS complexes.

2.5 | CMR analysis

Left ventricular ejection fraction (LVEF) was calculated from left ventricular end-systolic and end-diastolic volume data. Left ventricular (LV) mass was calculated from the summation of subtraction of left ventricular end-diastolic epicardial and endocardial area and slice thickness of each slide.

Patients having one of the following on CMR were diagnosed with apical HCM:

1. Apical LV thickness >15 mm that cannot be solely explained by abnormal loading condition or flow-limiting coronary artery disease (Helmy et al., 2011); or,
2. Ratio of maximal apical part to maximal posterior part that is >1.5 (Eriksson et al., 2002) that cannot be solely explained by abnormal loading condition or flow-limiting coronary artery disease.

Cardiac magnetic resonance LGE images were used to identify myocardial fibrosis; (Elliott et al., 2014; Konno et al., 2015). Myocardial fibrosis was diagnosed by the presence of the area with hyperintense signal which was evaluated the visual assessment of two cardiologists. Disagreements in interpretation were resolved by

TABLE 1 CMR and ECG finding

Variables	
CMR findings	
HCM patterns	
Septal	52 (36.1%)
Apical	76 (52.8%)
Concentric	16 (17.1%)
LVEDV/BSA (ml/m^2)	75.2 ± 21.9
LVESV/BSA (ml/m^2)	21.5 ± 14.9
Left ventricular mass (g)	152.3 ± 61.7
LVEF (%)	72.5 ± 9.5
Maximal wall thickness (mm)	21.3 ± 5.0
Maximal wall thickness ≥30 mm	9 (6.3%)
Presence of LGE	101 (70.1%)
ECG findings	
S in V_1 (mV)	12.6 ± 7.4
R in V_5 (mV)	24.7 ± 12.3
R in V_6 (mV)	23.0 ± 11.4
R in aVL (mV)	8.2 ± 6.6
S in V_3 (mV)	13.4 ± 9.8
QRS duration (msec)	102.6 ± 15.7
QRS product (Cornell product) (mV × msec)	2,492 ± 140
QTc interval (msec)	457.8 ± 26.2
QRS axis	28.8 ± 43.2
T-wave axis	59.7 ± 112.6
LVH by Sokolow-Lyon	65 (45.1%)
LVH by Cornell voltage	49 (34.0%)
LVH by Cornell product	60 (41.7%)

Notes. Values are shown as mean ± standard deviation or number and percentage.
A *p*-value < 0.05 indicates statistical significance.
BSA: body surface area; CMR: cardiac magnetic resonance; ECG, electrocardiography; HCM: hypertrophic cardiomyopathy; LGE: late gadolinium enhancement; LVEDV: left ventricular end-diastolic; LVEF: left ventricular ejection fraction; LVESV: left ventricular end-systolic; LVH: left ventricular hypertrophy.

TABLE 2 Baseline demographic and clinical characteristics of the study population

Characteristics	All	Deep TWI	No deep TWI	*p*-Value	fQRS	No fQRS	*p*-Value
Age (years)	66.0 ± 15.8	64.8 ± 13.7	66.3 ± 16.3	0.664	63.0 ± 18.2	67.4 ± 14.4	0.149
Male gender	87 (60.4%)	23 (79.3%)	64 (55.7%)	*0.02*	28 (59.6%)	59 (60.8%)	0.886
Atrial fibrillation	13 (9.0%)	1 (3.4%)	12 (10.4%)	0.467	5 (10.6%)	8 (8.8%)	0.758
CAD	17 (11.8%)	2 (6.9%)	15 (13.0%)	0.525	3 (6.4%)	14 (14.4%)	0.16
Heart failure	6 (4.2%)	1 (3.4%)	5 (4.3%)	1	3 (6.4%)	3 (3.3%)	0.392
Calcium channel blocker	35 (24.3%)	5 (17.2%)	30 (26.1%)	0.321	10 (21.3%)	25 (25.8%)	0.555
Beta blocker	75 (52.1%)	18 (62.1%)	57 (49.6%)	0.228	28 (59.6%)	47 (48.5%)	0.21
LVEF (%)	72.5 ± 9.5	74.8 ± 6.1	71.9 ± 10.6	*0.047*	69.4 ± 9.7	73.9 ± 9.0	*0.007*
LV mass (g)	152.3 ± 61.7	164.0 ± 57.8	149.3 ± 62.6	0.254	167.9 ± 62.9	144.7 ± 60.0	*0.034*

Notes. Values are shown as mean ± standard deviation or number and percentage.
A *p*-value < 0.05 indicates statistical significance (italic value).
CAD, coronary artery disease; fQRS, fragmented QRS complex; LV, left ventricular; LVEF, left ventricular ejection fraction; TWI, T-wave inversion.

consensus. Visual assessment was shown to have excellent agreement with the quantitative technique for detention of myocardial fibrosis from LGE (Kappa = 0.963 and 0.952, respectively; $p < 0.001$) (Krittayaphong et al., 2007).

2.6 | Statistical analysis

SPSS Statistics version 20 (SPSS, Inc., Chicago, IL, USA) was used to perform all data analyses. Categorical data are described as number and percentage, and continuous data are shown as mean ±standard deviation (*SD*). Comparisons of continuous variables were made using Student's *t* test for unpaired data, and comparisons of categorical variables were made using chi-square test or Fisher's exact test. Multiple logistic regression analysis was employed to evaluate association between ECG and MRI findings. Univariate and multivariate analyses were performed to evaluate for factors independently associated with HCM and with myocardial fibrosis. The results of those analyses are reported as odds ratio (OR) and 95% confidence interval (CI). A *p*-value <0.05 was considered statistically significant for all tests.

3 | RESULTS

3.1 | Population

One hundred and forty-four subjects were included in this study. The average age of patients was 66.0 ± 15.8 years, and 87 (60.4%) were male. Table 1 summarizes CMR and ECG findings. Compared to nonapical HCM, apical HCM was more common in elderly (70.8 ± 12.5 vs. 60.6 ± 17.4 years, $p < 0.001$), had less LV mass (135.7 ± 49.4 vs. 170.8 ± 68.8 g, $p = 0.001$), and less likely to have myocardial fibrosis (56.6% vs. 85.3%, $p < 0.001$). LVH by Sokolow-Lyon criteria was positive more (63.2% vs. 25.0%, $p < 0.001$)

TABLE 3 Univariate and multivariate analysis for factors independently associated with apical hypertrophic cardiomyopathy by cardiac magnetic resonance (CMR) images

	Univariate analysis		Multivariate analysis	
Variables	OR (95% CI)	*p*	OR (95% CI)	*p*
Age ≥65 years	3.000 (1.484, 6.065)	*0.002*	3.071 (1.334, 7.069)	*0.008*
Male gender	1.010 (0.517, 1.971)	0.977		
Atrial fibrillation	5.585 (1.191, 26.182)	*0.016*	5.286 (1.705, 25.996)	*0.04*
Coronary artery disease	1.320 (0.473, 3.686)	0.595		
Heart failure	0.432 (0.077, 2.439)	0.33		
Calcium channel blocker	1.083 (0.505, 2.326)	0.837		
Beta blocker	0.937 (0.487, 1.804)	0.845		
LVEF <50%	0.892 (0.122, 6.511)	0.91		
LV mass ≥144 g	0.426 (0.218, 0.833)	*0.012*	0.451 (0.207, 0.981)	*0.045*
T-wave inversion	5.815 (2.074, 16.307)	*<0.001*	9.857 (3.169, 30.656)	*<0.001*

Notes. A *p*-value < 0.05 indicates statistical significance (italic value).
CI, confidence interval; LVEF, left ventricular ejection fraction; LV, left ventricular; OR, odds ratio.

but Cornell voltage criteria was positive less (23.7% vs. 45.6%, $p = 0.006$) in patients with apical HCM compared to those with nonapical HCM. Patients with myocardial fibrosis had a greater LV mass compared to those without fibrosis (170.5 ± 59.8 vs. 109.6 ± 42.4 g, $p < 0.001$).

3.2 | Deep negative T-wave inversion and apical hypertrophic cardiomyopathy

The amplitude of deep negative TWI was within the range of 1.00–2.18 mV (mean 1.39 ± 0.34). Twenty-nine (20.1%) subjects had deep TWI. A comparison of baseline characteristics between patients with and without deep TWI revealed significantly more male patients in the deep TWI group than in the no deep TWI group (79.3% vs. 55.7%; $p = 0.020$) (Table 2).

Deep TWI was found to be significantly associated with apical HCM in univariate analysis [odds ratio (OR): 5.815, 95% confidence interval (CI): 2.074–16.037; $p < 0.001$], and the association between deep TWI and apical HCM remained statistically significant in multivariate analysis (OR: 9.857, 95% CI: 3.169–30.656; $p < 0.001$) (Table 3). We use LVEF 50% and median LV mass of 144 g as a cut-off for univariate and multivariate analysis. Deep TWI could detect apical HCM with a sensitivity of 31.2%, a specificity of 92.6%, a positive predictive value (PPV) of 82.8%, and a negative predictive value (NPV) of 54.8%. Figure 4 demonstrates a case of apical HCM with deep TWI.

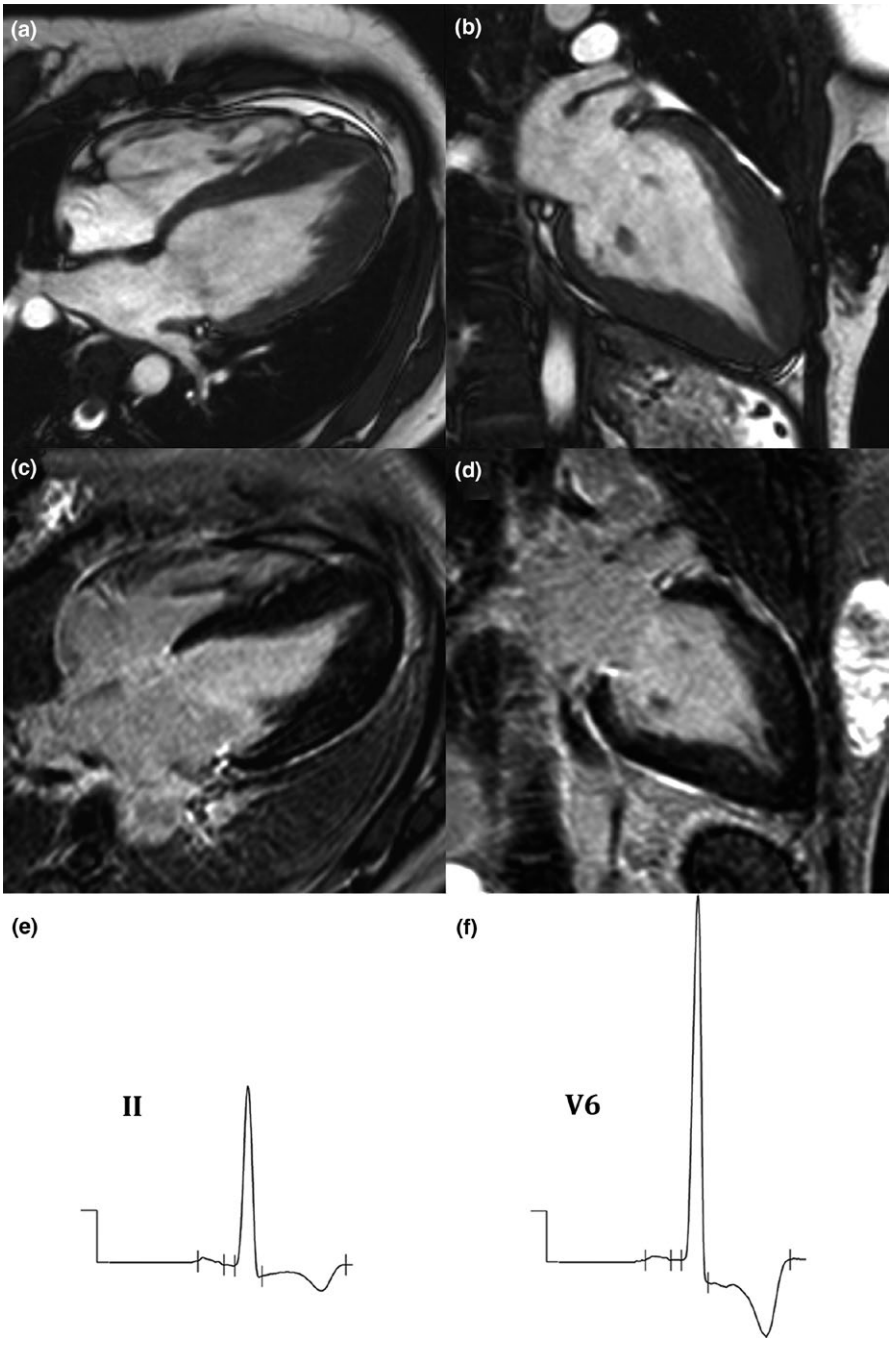

FIGURE 4 (a–d): Cardiac magnetic resonance (CMR) imaging of apical hypertrophic cardiomyopathy (HCM) shows apical hypertrophy in cine images in four-chamber (a) and long-axis (b) views, and late gadolinium enhancement (LGE) images in four-chamber (c) and long-axis (d) views. (e,f): Electrocardiogram (ECG) of apical HCM shows deep T-wave inversion (TWI) in leads II (e) and V_6 (f)

TABLE 4 Univariate and multivariate analysis for factors independently associated with myocardial fibrosis by cardiac magnetic resonance (CMR) late gadolinium enhancement (LGE) images

	Univariate analysis		Multivariate analysis	
Variables	**OR (95% CI)**	***p***	**OR (95% CI)**	***p***
Age ≥65 years	0.284 (0.120, 0.674)	*0.003*		
Male gender	3.454 (1.642, 7.262)	*0.001*	4.515 (1.852, 11.010)	*0.001*
Atrial fibrillation	0.459 (0.145, 1.457)	0.178		
Coronary artery disease	2.146 (0.584, 7.888)	0.241		
Heart failure	2.188 (0.248, 19.302)	0.471		
Calcium channel blocker	0.762 (0.338, 1.717)	0.511		
Beta blocker	0.616 (0.298, 1.272)	0.189		
LVEF < 50%	0.693 (0.621, 0.774)	0.186		
LV mass ≥ 144 g	12.152 (4.670, 31.618)	*<0.001*	14.446 (5.207, 40.081)	*<0.001*
Q wave	1.112 (0.541, 2.285)	0.619		
fQRS	2.752 (1.157, 6.544)	*0.019*		

Notes. A *p*-value < 0.05 indicates statistical significance (italic value).
CI, confidence interval; fQRS, fragmented QRS complex; LVEF, left ventricular ejection fraction; LV, left ventricular; OR, odds ratio.

3.3 | Fragmented QRS complex and cardiac fibrosis

Forty-seven (32.64%) subjects had fQRS complex, and myocardial fibrosis was detected in 101 (70.14%). Patient characteristics were similar between groups (all $p > 0.05$) (Table 2). fQRS complex was found to be associated with myocardial fibrosis in univariate analysis (OR: 2.752, 95% CI: 1.157–6.544; $p = 0.019$). fQRS could detect myocardial fibrosis with a sensitivity of 38.6%, a specificity of 81.4%, a PPV of 83.6%, and, an NPV of 36.1%. However, fQRS complex failed to achieve statistical significance in multivariate analysis (Table 4). Figure 5 demonstrates a case of HCM with myocardial fibrosis and fQRS complexes.

4 | DISCUSSION

The results of this study revealed deep TWI to be independently associated with apical HCM. In contrast, fQRS was found to be associated with myocardial fibrosis in univariate analysis, but that association did not remain significant in multivariate analysis.

4.1 | Deep negative T-wave inversion and apical hypertrophic cardiomyopathy

Sakamoto, Tei, Murayama, Ichiyasu, and Hada (1976 initially described the association between deep TWI and apical HCM. They reported that three of nine cases with deep TWI had apical HCM. A study of this association by Yamaguchi et al. (1979) in Western population found that 47% of patients with deep TWI had apical HCM, while only 15% of patients without deep TWI had apical HCM.

A study by Flett et al. (2015) reported that 22 of 48 (45.83%) HCM patients had apical HCM, and that 16 (73%) of those 22 patients had deep TWI. In the present study, 76 (52.78%) subjects had apical HCM, but only 24 (31.58%) of those had deep TWI. Even though our prevalence was lower than that observed in the Western population, the association still remained significant. This indicates a strong association between deep TWI and apical HCM. LVEF was not significantly different between groups with and without apical HCM. The test sensitivity was relatively low (31.16%), but the specificity was high (92.6%). This finding suggests that the investigator should pay closer attention to the apical part if deep TWI presents on the patient's ECG.

4.2 | Fragmented QRS complex and cardiac fibrosis

Fragmented QRS complex was found to be significantly associated with myocardial fibrosis in univariate analysis, but that significant association did not hold up in multivariate analysis. This finding indicates that fQRS could indicate the presence of myocardial fibrosis, but dilution by other factors or a lack of statistical power caused by the small size of our study population could have rendered fQRS nonsignificant in multivariate analysis.

In the Konno et al. (2015) study, fQRS complex was most sensitive for detecting inferior segment fibrosis (sensitivity 51%), but it was not sensitive for detecting myocardial fibrosis in other segments (sensitivity for detecting anterior segment myocardial fibrosis: 38%; sensitivity for detecting lateral segment myocardial fibrosis: 30%). In our study, most patients had anterior segment fibrosis (55 subjects, 38.20%), compare to lateral segment fibrosis (26 subjects, 18.06%) and inferior segment fibrosis (29 subjects, 20.1%). This may explain the weaker association between fQRS complex and myocardial fibrosis in our study.

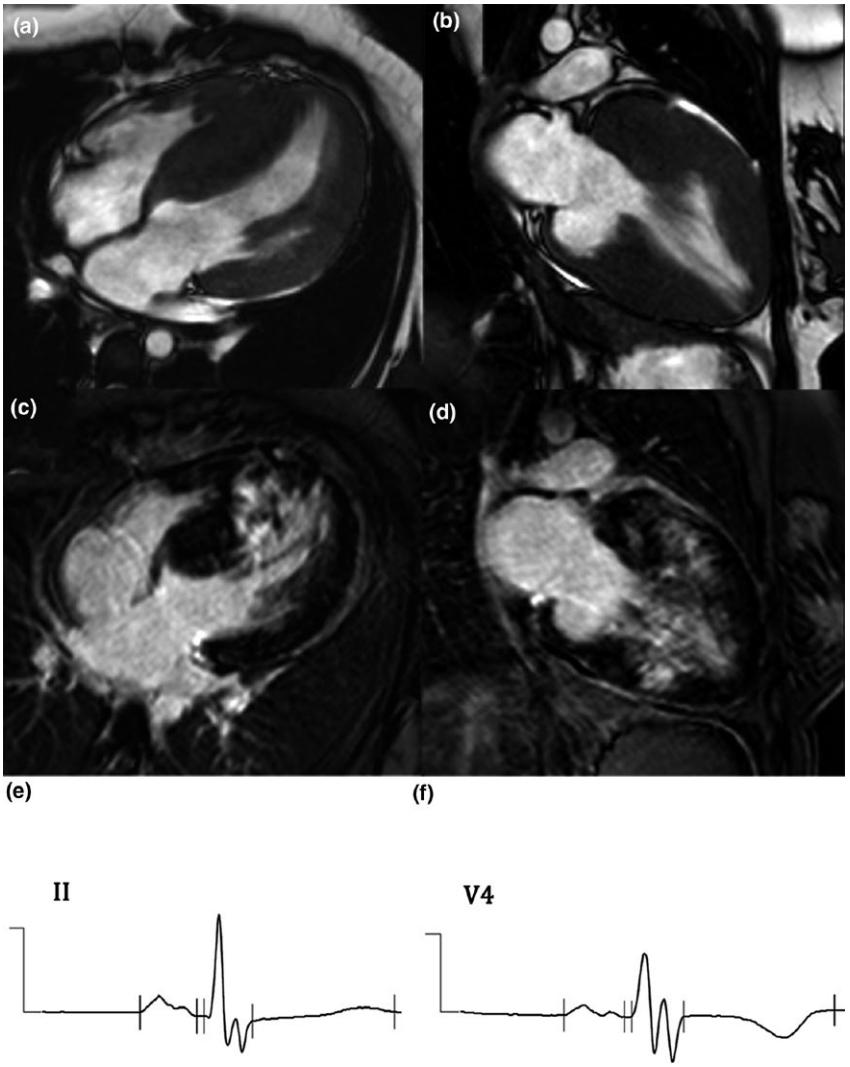

FIGURE 5 (a–d): Cardiac magnetic resonance (CMR) of hypertrophic cardiomyopathy (HCM) shows interventricular thickening in cine images in four-chamber (a) and long-axis (b) views, and myocardial fibrosis from late gadolinium enhancement (LGE) images in four-chamber (c) and long-axis (d) views. (e,f): Electrocardiogram (ECG) shows fragmented QRS (fQRS) complex in leads II (e) and V_6 (f) in HCM with myocardial fibrosis

Konno et al. (2015 also found the association between fQRS and myocardial fibrosis to vary according to the degree of LGE. Myocardial fibrosis has to be presented at a certain minimum amount in order to be reflected on a 12-lead ECG as fQRS complex. This factor may influence and explain the disparity among study findings relative to the association between fQRS complex and myocardial fibrosis.

In our study, the pathologic Q wave did not associate with myocardial fibrosis (OR: 1.112, 95% CI: 0.541–2.285; $p = 0.619$). This finding indicates the higher sensitivity of fQRS for detecting myocardial fibrosis compared to pathologic Q waves. Konno *et al.* also reported the pathologic Q wave to be significantly associated with cardiac fibrosis in univariate analysis (OR: 0.23, 95% CI: 0.145–0.315; $p = 0.015$), but there was no association in multivariate analysis (OR: 0.11, 95% CI: 0.02–0.2; $p = 0.22$).

Male gender (OR: 5.060, 95% CI: 2.001–12.798; $p = 0.001$), use of beta blocker (OR: 5.060, 95% CI: 2.001–12.798; $p = 0.025$), and LV mass above median (OR: 17.634, 95% CI: 6.025–51.613); $p < 0.001$) were also significantly associated with higher rate of myocardial fibrosis.

The sensitivity of fQRS complex for detecting myocardial fibrosis was found to be modest (38.6%), but the specificity was relatively high (81.4%). Thus, more careful interpretation of CMR should be combined with increased suspicion of the presence of myocardial fibrosis if fQRS complex is presented on 12-lead ECG.

4.3 | Limitations

This study has some mentionable limitations. First, this was a retrospective study with a study population that was recruited from a single center. Second, the size of our study population was relatively small, which means that this study may have lacked the statistical power necessary to identify all significant differences and associations. Third, some ECG tracings had a shifting isoelectric line, which may have adversely affected our ability to identify deep TWI since we

used the isoelectric line as a reference line. Fourth, fQRS complex and myocardial fibrosis may be caused by etiologies other than HCM, such as coronary artery disease and other cardiomyopathies. Although the imaging patterns of myocardial fibrosis may be different among different etiologies, it may be difficult in some cases to determine which etiology is responsible for the observed myocardial fibrosis.

5 | CONCLUSION

Deep TWI is independently associated with apical HCM, but the relationship between fQRS complex and myocardial fibrosis, which was significant in univariate analysis, did not remain significant in multivariate analysis. These findings will enhance the ability of clinicians to diagnose and treat HCM in low resource settings that do not have access to more sophisticated diagnostic methods.

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CONFLICT OF INTEREST

Both authors declare no personal or professional conflict of interests, and no financial support from the companies that produce and/or distribute the drugs, devices, or materials described in this report.

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