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Prognosis of patients with familial hypertrophic cardiomyopathy: A single-center cohort study with ten-year follow-up by propensity score matching analysis

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ABSTRACT

Objectives: Hypertrophic cardiomyopathy (HCM) is the most common hereditary cardiomyopathy. However, few studies have investigated the prognosis of familial HCM (FHCM) through clinical data. The purpose of this study was to compare the clinical outcomes of FHCM and non-FHCM through propensity score matching analysis.

Methods and results: The cohort study included 1243 patients with HCM between 1996 and 2013 in Fuwai Hospital, Chinese Academy of Medical Sciences, among whom 125 patients had FHCM. During a mean follow-up of 7.6 ± 3.8 years (interquartile range: (IQR) 5.0–10.0 years), 217 (16.57%) of the 1243 patients had died, including 3 patients who underwent cardiac transplantation. Using 30 demographic and clinical variables, a 4:1 propensity score matched cohort for FHCM was established. The stepwise variable selection procedure for the Cox proportional hazards model was performed to identify the factors associated with mortality and competing risk regression analysis was performed to analyze the competitive risk of cardiovascular and non-cardiovascular mortality. The results showed that FHCM patients had a higher risk of cardiovascular mortality/cardiac transplantation (log-rank $\chi^2 = 6.8$, $P = 0.0084$) and an increased tendency of sudden cardiac death (SCD) (log-rank $\chi^2 = 3.2$, $P = 0.074$) compared with non-FHCM patients, but there was no difference in all-cause mortality (log-rank $\chi^2 = 2.7$, $P = 0.1$) between the two groups. Moreover, the Cox model showed that FHCM was an independent prognostic predictor for cardiovascular mortality/cardiac transplantation in HCM patients.

Conclusion: FHCM patients had a higher risk of cardiovascular mortality/cardiac transplantation and a higher tendency of SCD than non-FHCM patients, but there was no difference in all-cause

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mortality. Moreover, FHCM was an independent prognostic predictor for cardiovascular mortality/cardiac transplantation in HCM patients.

1. Introduction

Hypertrophic cardiomyopathy (HCM) is the most common heritable cardiomyopathy and manifests as left ventricular hypertrophy (LVH) without a secondary cause and a nondilated left ventricle [1–3]. Familial HCM (FHCM) is a type of cardiomyopathy most closely associated with sarcomere gene mutations that accounts for 50–70% of all HCM cases [2,4–7], and patients with sarcomere mutations have been reported to show earlier clinical symptoms and a worse prognosis [5,8].

Genetic testing plays an important role in family screening and phenotypic identification, and thousands of mutations associated with HCM have been identified in more than 60 genes [9–11]. The most commonly affected genes identified thus far include *MYH7* (myosin heavy chain) and *MYBPC3* (myosin binding protein), which are affected in 50–80% of all genotype-positive patients with HCM [12–15]. To date, there have been some studies on the prognosis of FHCM with specific gene mutations [15–17]. Genotype-positive patients with HCM have higher cardiovascular mortality/cardiac transplantation rates, a higher prevalence of a family history of HCM and SCD (sudden cardiac death), and an increased risk of stroke, heart failure, atrial fibrillation and malignant arrhythmias compared with genotype-negative patients [8,11,18]. Therefore, current consensus guidelines recommend cardiac monitoring for first-degree relatives of patients with FHCM and genetic testing for known familial mutations [19].

However, to our best knowledge, no research has been conducted to study the prognosis of FHCM based only on clinical data. The primary aim of this study was to compare the clinical outcomes of patients with FHCM and non-FHCM and to investigate the prognostic value of FHCM in HCM patients through propensity score matching analysis based on clinical follow-up data.

2. Methods

2.1. Study population

We performed a single-center cohort study with 1243 hospitalized HCM patients in Fuwai Hospital between May 1996 and August 2013. There were 125 FHCM patients and 1118 non-FHCM patients. Thirty demographic and clinical variables were chosen, and 4:1 propensity score matching analysis was used to control for variable imbalance. After matching, there were 125 patients with FHCM and 500 patients without FHCM. The data were abstracted from the baseline characteristics, electrocardiogram (ECG), cardiac magnetic resonance (CMR), echocardiography and laboratory tests.

2.2. Diagnostic criteria and definitions

The diagnostic criteria for HCM were as follows: in adults, any imaging examination [including two-dimensional echocardiography, CMR, and computed tomography (CT)] showing unexplained asymmetrical LV hypertrophy (LVH) $\geq$15 mm, and patients with a definite family history of HCM showing $\geq$13 mm [2,6]. In children, the diagnosis of HCM requires LV wall thickness to be two standard deviations above the predicted mean [2]. FHCM is defined as having two or more HCM patients in the same family, including a first-degree relative under the age of 40 who has developed SCD [6]. Patients with cardiac or systemic disease capable of producing similar magnitudes of hypertrophy, such as Fabry disease, Noonan syndrome and amyloidosis cardiomyopathy, were excluded.

2.3. Follow-up and endpoints

Follow-up was completed in August 2021. The primary endpoint of the study was all-cause mortality, and the secondary endpoints were cardiovascular mortality/cardiac transplantation and SCD. SCD, in which unexpected death occurred in the absence of or within 1 h from symptom onset in patients who had previously experienced a relatively stable or uneventful course. Data on the occurrence of all-cause mortality and cardiovascular mortality (SCD, appropriate implantable cardioverter defibrillator (ICD) shock, heart failure or stroke) or cardiac transplantation at follow-up were collected by reviewing medical records (outpatient clinic attendance and hospitalization), performing telephone interviews and reviewing survival status records status through the National Police Stations. The Institutional Review Board Committee of Fuwai Hospital approved the study protocol.

2.4. Statistical analysis

The data are presented as the means $\pm$ standard deviations for continuous variables and as counts and proportions for categorical variables. Baseline differences between the FHCM and non-FHCM groups were assessed using standardized mean differences (SMD), which defined as the difference in means, proportions or ranks divided by the mutual standard deviation. Propensity scoring was performed to control the variable imbalance between the FHCM and non-FHCM groups by matching. To estimate the propensity score, a data-driven method was proposed to select the potential confounding factors in the comparison between the FHCM and non-FHCM groups. A logit model was performed based on 30 baseline variables, and variables with a P value less than 0.15 were then entered into a propensity score matching. Variables with SMD $<$10% between the FHCM and non-FHCM groups were consider well-balanced after

propensity scoring matching [28].

Estimates for long-term outcomes were made by the Kaplan–Meier method, and significant differences were assessed by the log-rank test. A stepwise variable selection procedure for the Cox proportional hazard model was performed to identify the factors associated with mortality. Hazard ratios (HRs), 95% confidence intervals (CIs), and P values were provided, a P value < 0.05 was considered statistically significant.

Cardiovascular mortality/cardiac transplantation was the secondary endpoint, and non-cardiovascular mortality was treated as a competing event. The cumulative incidence function was used to determine the cumulative risk of the FHCM and non-FHCM groups, and the Gray test was used to examine the difference in cumulative risk across groups. Univariate and multivariate analysis were made using competing risk Fine-Gray regression to explore the influencing factors.

Statistical and visual analyses were conducted using R version 4.1.2 software, where the variable selection procedure and propensity score matching were conducted using the R packages My. stepwise and MatchIt, respectively, the survival curve and cumulative hazard curves and the competing risk regression were obtained based on the R packages survival and cmprsk, respectively.

Table 1
Baseline characteristics of the unmatched and the propensity score matched cohort under Miss Forest impute data.

Variables	Unmatched Cohort (n = 1243)				Matched cohort under Miss Forest impute data (n = 625)		
	Non-FHCM (n = 1118)	FHCM (n = 125)	SMD	% missing	Non-FHCM (n = 500)	FHCM (n = 125)	SMD
Sex, female, n (%)	354 (30.9)	41 (32.8)	0.042	0	135 (27.0)	41 (32.8)	0.127
Age (mean (SD)), years	51.57 (13.97)	44.23 (14.49)	0.516	0	45.44 (14.61)	44.23 (14.49)	0.083
Course of disease (mean (SD)), (months)	70.63 (79.62)	98.78 (98.76)	0.314	0	89.93 (93.63)	98.78 (98.76)	0.092
NYHA class I-II, n (%)	482 (43.1)	57 (45.6)	0.050	0	223 (44.6)	57 (45.6)	0.020
Atrial fibrillation, n (%)	189 (16.9)	21 (16.8)	0.003	0	74 (14.8)	21 (16.8)	0.055
LBBB, n (%))	52 (4.7)	8 (6.4)	0.077	0	33 (6.6)	8 (6.4)	0.008
RBBB, n (%)	46 (4.1)	10 (8.0)	0.163	0	34 (6.8)	10 (8.0)	0.046
Ventricular arrhythmias, n (%)	184 (16.5)	25 (20.0)	0.092	0	76 (15.2)	25 (20.0)	0.126
VT, n (%)	104 (9.3)	9 (7.2)	0.076	0	36 (7.2)	9 (7.2)	<0.001
NSVT, n (%)	79 (7.5)	9 (7.4)	0.006	5.79	37 (7.4)	9 (7.2)	0.008
DBP (mean (SD)), mmHg	75.01 (11.56)	71.92 (10.81)	0.276	0.08	73.85 (11.63)	71.95 (10.77)	0.169
Syncope, n (%)	159 (14.2)	25 (20.0)	0.154	0	74 (14.8)	25 (20.0)	0.137
Family history of SCD, n (%)	0 (0.00)	18 (14.4)	0.580	0	0 (0.0)	18 (14.4)	0.580
ASA or SM, n (%)	407 (36.4)	49 (39.2)	0.058	0	225 (45.0)	49 (39.2)	0.118
ICD, n (%)	35 (3.1)	8 (6.4)	0.154	0	13 (2.6)	8 (6.4)	0.184
Electrocardiograph							
QRS (mean (SD)), ms	108.77 (30.28)	117.25 (29.42)	0.284	1.37	112.94 (32.20)	116.70 (29.30)	0.122
QT (mean (SD)), ms	427.25 (49.95)	432.44 (39.00)	0.116	1.69	427.70 (52.20)	431.93 (38.77)	0.092
QTc (mean (SD)), ms	462.51 (51.63)	472.47 (47.87)	0.200	1.69	467.76 (52.76)	471.96 (47.42)	0.084
PR (mean (SD)), ms	171.09 (36.19)	177.25 (39.43)	0.163	8.93	174.23 (36.45)	177.01 (37.56)	0.075
Echocardiography							
LV diameter (mean (SD)), mm	44.81 (6.96)	44.33 (8.12)	0.062	7.16	44.05 (7.18)	44.35 (7.77)	0.040
LA diameter (mean (SD)), mm	39.90 (7.18)	41.29 (7.96)	0.183	7.48	40.61 (7.21)	41.34 (7.65)	0.098
RA, n (%)	12 (1.2)	3 (2.7)	0.108	11.1	6 (1.2)	3 (2.4)	0.090
RV diameter (mean (SD)), mm	20.10 (3.58)	19.81 (3.25)	0.083	16.2	19.94 (3.48)	19.88 (3.03)	0.019
LVEF (mean (SD)), %	66.51 (9.53)	65.17 (11.72)	0.125	8.20	66.63 (9.51)	65.16 (11.42)	0.140
IVS thickness (mean (SD)), mm	17.96 (5.96)	19.48 (6.21)	0.249	6.92	19.41 (5.99)	19.54 (6.03)	0.023
Maximal LV wall thickness (mean (SD)), mm	20.48 (5.37)	21.39 (5.89)	0.161	4.82	21.66 (5.44)	21.50 (5.74)	0.030
AHCM, n (%)	173 (15.5)	4 (3.2)	0.432	0	16 (3.4)	4 (3.2)	<0.001
Laboratory detection							
Log (NT-pro-BNP) (mean (SD)), fmol/L	3.07 (0.34)	3.20 (0.33)	0.376	33.2	3.12 (0.30)	3.18 (0.28)	0.198
Creatinine (mean (SD)), mmol/L	80.91 (25.33)	78.21 (20.61)	0.117	8.05	78.73 (20.56)	78.00 (19.97)	0.036
Medicine at baseline							
Beta Blocker, n (%)	958 (85.6)	113 (90.4)	0.147	0.4	453 (90.6)	113 (90.4)	0.007
Ca^{2+} Antagonists, n (%)	406 (36.5)	44 (35.2)	0.027	0.4	164 (32.8)	44 (35.2)	0.051
Endpoints							
All-cause mortality, n (%)	190 (17.0)	27 (21.6)	0.117	0	71 (14.2)	27 (21.6)	0.194
Cardiovascular mortality, n (%)	112 (10.0)	22 (17.6)	0.221	0	43 (8.6)	22 (17.6)	0.269
SCD, n (%)	57 (5.1)	12 (9.6)	0.173	0	26 (5.2)	12 (9.6)	0.169

Abbreviations: SMD = standardized mean differences, NYHA=New York Heart Association, LBBB = left bundle branch block, RBBB = right bundle branch block, VT = ventricular tachycardia, NSVT = non-sustained ventricular tachycardia, ASA = alcohol septal ablation, SM= Septal myotomy, LV = left ventricular, LA = left atrial, RV = right ventricular, LVEF = left ventricular ejection fraction, IVS = interventricular septum, AHCM = apical HCM, FHCM = familial HCM; NT-pro-BNP=N-terminal fragment pro-brain natriuretic peptide.

3. Results

3.1. Baseline characteristics (Table 1)

Table 1 summarizes the baseline clinical characteristics. The unmatched cohort included 1243 HCM patients, of whom 125 (10.1%) were FHCM patients and 1118 (89.9%) were non-FHCM patients. Patients with FHCM were younger, had more family history of SCD, had a longer course of disease, QRS and QTc duration, a higher serum log (NT-pro-BNP) level, and a thicker interventricular septum (IVS) thickness, maximal LV wall thickness, and AHCM was more common in non-FHCM patients.

Ventricular tachycardia (VT), course of disease, non-sustained ventricular tachycardia (NSVT), AHCM, PR, right bundle branch block (RBBB), Beta blocker, age^2 were used for the calculation of propensity scores. After matching, sex, ventricular arrhythmias, diastolic blood pressure (DBP), syncope, family history of SCD, alcohol septal ablation (ASA) or septal myectomy (SM), ICD, QRS, left ventricular ejection fraction (LVEF), Log (NT-pro-BNP) showed significant differences between the two groups, and the other baseline characteristics were equally distributed between the two groups.

3.2. Follow-up results of the unmatched cohort

During a mean follow-up time of 7.6 ± 3.8 years (IQR: 5–10 years), there were 27 (21.6%) and 190 (17.0%) patients with all-cause mortality in the FHCM and non-FHCM groups, respectively. 22 (17.6%) and 112 (10.0%) patients experienced cardiovascular mortality/cardiac transplantation in the FHCM and non-FHCM groups, respectively, while there were 12 (9.6%) SCD patients with FHCM and 57 (5.1%) SCD patients with non-FHCM. The Kaplan–Meier curves of the unmatched cohort are shown in Fig. 1. There was no significant difference in all-cause mortality (log-rank $\chi^2 = 1.8$, $P = 0.19$), however, FHCM patients had a higher risk of cardiovascular mortality/cardiac transplantation (log-rank $\chi^2 = 6.5$, $P = 0.011$) and SCD (log-rank $\chi^2 = 4.3$, $P = 0.038$) than non-FHCM patients before matching.

3.3. Outcome analysis

3.3.1. Primary outcome: all-cause mortality of the matched cohort

There were 27 (21.6%) and 71 (14.2%) patients with all-cause mortality in the FHCM and non-FHCM groups after propensity score matching, respectively. The propensity scores matching analysis data were presented in Fig. 2a. FHCM patients did not have a significantly higher risk of all-cause mortality (log-rank $\chi^2 = 2.7$, $P = 0.1$). To avoid overfitting, a stepwise variable selection procedure for the Cox proportional hazards model was performed, and the results of the imputed data cohorts were shown in Table 2. FHCM was not entered into the final model, and FHCM was not an independent prognostic predictor of all-cause mortality. In addition, age [HR: 0.840; 95% CI: 0.790–0.892; P value < 0.001], age^2 [HR: 1.002; 95% CI: 1.001–1.003; P value < 0.001], LVEF [HR: 0.971; 95% CI: 0.952–0.991; P value 0.004], LV diameter [HR: 1.049; 95% CI: 1.020–1.079; P value < 0.001], Log (NT-pro-BNP) [HR: 2.249; 95% CI: 1.038–4.873; P value 0.040], and creatinine [HR: 1.010; 95% CI: 1.002–1.019; P value 0.019] were independent prognostic predictors

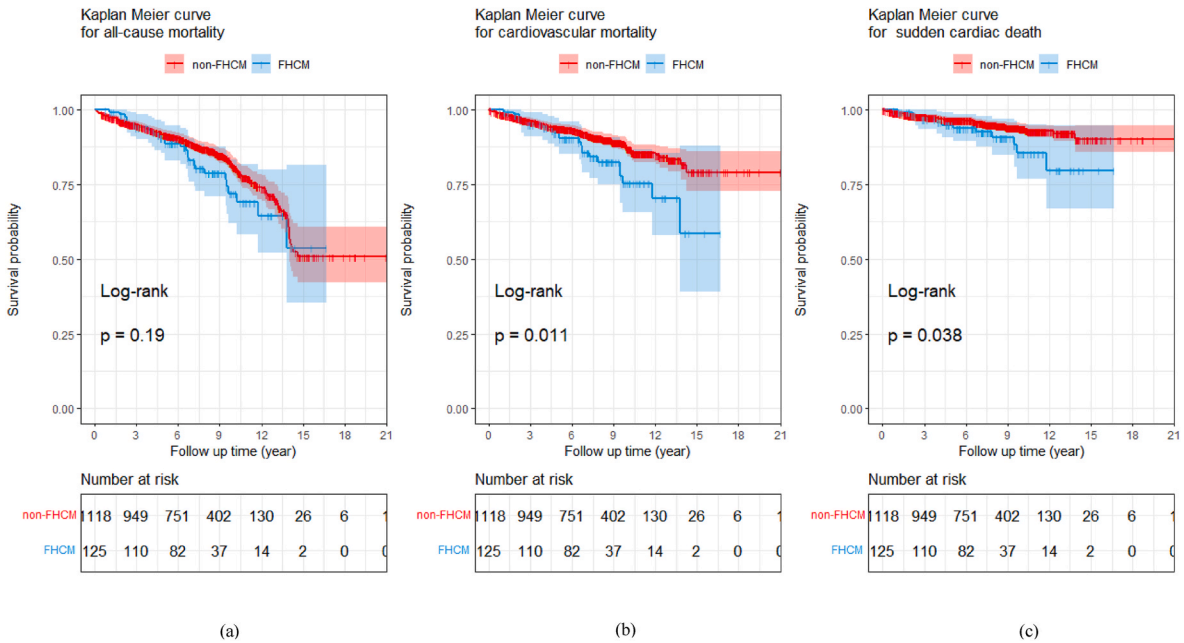

Fig. 1. Kaplan Meier curves of the unmatched cohort. (a) All-cause mortality. (b) Cardiovascular mortality/cardiac transplantation. (c) SCD.

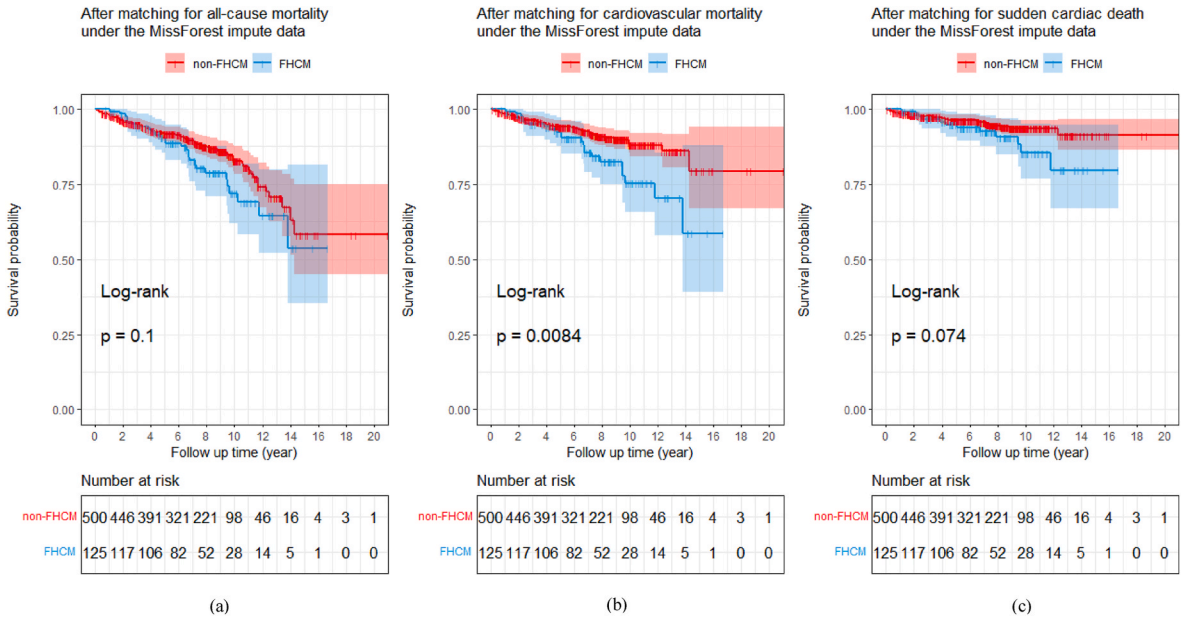

Fig. 2. Kaplan Meier curves of the matched cohort. (a) All-cause mortality. (b) Cardiovascular mortality/cardiac transplantation. (c) SCD.

Table 2
Multivariate Cox regression for matched cohort.

Variables	All-cause mortality			Cardiovascular mortality/cardiac transplantation			Sudden cardiac death		
	Hazard ratio	95% CI	*P*-value	Hazard ratio	95% CI	*P*-value	Hazard ratio	95% CI	*P*-value
FHCM	–	–	–	1.770	(1.050–2.984)	0.032*	1.929	(0.958–3.885)	0.066
Age	0.840	(0.790–0.892)	<0.001***	0.824	(0.776–0.875)	<0.001***	0.798	(0.732–0.869)	<0.001***
Age^2	1.002	(1.001–1.003)	<0.001***	1.002	(1.001–1.003)	<0.001***	1.002	(1.001–1.003)	<0.001***
LV diameter	1.049	(1.020–1.079)	<0.001***	1.061	(1.028–1.095)	<0.001***	1.077	(1.042–1.114)	<0.001***
Creatinine	1.010	(1.002–1.019)	0.019*	1.012	(1.002–1.022)	0.025*	1.016	(1.001–1.032)	0.035*
NYHA class I-II	0.684	(0.439–1.067)	0.094	–	–	–	–	–	–
Atrial fibrillation	1.619	(0.967–2.710)	0.067	2.316	(1.283–4.180)	0.005**	–	–	–
LA diameter	1.026	(0.992–1.061)	0.137	–	–	–	1.049	(1.001–1.099)	0.046*
RA diameter	0.292	(0.082–1.037)	0.057	0.120	(0.015–1.022)	0.049*	–	–	–
LVEF	0.971	(0.952–0.991)	0.004**	0.971	(0.947–0.995)	0.020*	–	–	–
Log (NT-pro-BNP)	2.249	(1.038–4.873)	0.040*	3.412	(1.297–8.975)	0.013*	–	–	–
AHCM	0.273	(0.037–2.002)	0.202	–	–	–	–	–	–
Course of disease	–	–	–	1.003	(1.000–1.005)	0.032*	–	–	–
QT	–	–	–	1.004	(1.000–1.009)	0.098	1.007	(1.000–1.013)	0.044*
PR	–	–	–	–	–	–	0.991	(0.981–1.001)	0.077
Concordance	0.777			0.792			0.786		

Note: "***" represent the significant level $p \leq 0.001$, "**" represent the significant level $p \leq 0.01$, "*" represent the significant level $p \leq 0.05$,"—"indicates that there is no value.

for all-cause mortality.

3.3.2. *Secondary outcomes: cardiovascular mortality/cardiac transplantation and SCD in the matched cohort*

There were 22 (17.6%) and 43 (8.6%) patients with cardiovascular mortality/cardiac transplantation in the FHCM and non-FHCM groups after propensity score matching, respectively. FHCM had a higher risk of cardiovascular mortality/cardiac transplantation (log-rank $\chi^2 = 6.8$, $P = 0.0084$) (Fig. 2b). A stepwise variable selection procedure for the Cox proportional hazards model was performed, and the results were shown in Table 2. FHCM was an independent prognostic predictor of cardiovascular mortality/cardiac transplantation in the imputed data cohorts [HR: 1.770; 95% CI: 1.050–2.984; P value 0.032]. In addition, age [HR: 0.824; 95% CI: 0.776–0.875; P value < 0.001], age^2 [HR: 1.002; 95% CI: 1.001–1.003; P value < 0.001], course of disease [HR: 1.003; 95% CI:

1.000–1.005; P value 0.032], atrial fibrillation [HR: 2.316; 95% CI: 1.283–4.180; P value 0.005], LV diameter [HR: 1.061; 95% CI: 1.028–1.095; P value < 0.001], RA diameter [HR: 0.120; 95% CI: 0.015–1.022; P value 0.049], LVEF [HR: 0.971; 95% CI: 0.947–0.995; P value 0.020], Log (NT-pro-BNP) [HR: 3.412; 95% CI: 1.297–8.975; P value 0.013], creatinine [HR: 1.012; 95% CI: 1.002–1.022; P value 0.025] were independent prognostic predictors for cardiovascular mortality/cardiac transplantation.

There were 12 (9.6%) and 26 (5.2%) patients with SCD in the FHCM and non-FHCM groups after propensity score matching, respectively. The risk of SCD in FHCM was not significantly higher after matching (log-rank $\chi^2 = 3.2$, $P = 0.074$), but there was a trend (Fig. 2c). A stepwise variable selection procedure for Cox proportional hazards model was performed, and the results were shown in Table 2. FHCM was not an independent prognostic predictor of SCD in the imputed data cohorts [HR: 1.929; 95% CI: 0.958–3.885; P value 0.066]. In addition, age [HR: 0.798; 95% CI: 0.732–0.869; P value < 0.001], age^2 [HR: 1.002; 95% CI: 1.001–1.003; P value < 0.001], LV diameter [HR: 1.077; 95% CI: 1.042–1.114; P value < 0.001], LA diameter [HR: 1.049; 95% CI: 1.001–1.099; P value 0.046]; QT [HR: 1.007; 95% CI: 1.000–1.013; P value 0.044] and creatinine [HR: 1.016; 95% CI: 1.001–1.032; P value 0.035] were independent prognostic predictors for SCD.

3.4. Competing risk regression analysis

Higher cumulative risks of cardiovascular mortality/cardiac transplantation were observed in patients with FHCM ($P1 = 0.008$), and there was no significant difference between the patients with non-FHCM and FHCM ($P2 = 0.291$) in terms of non-cardiovascular mortality competing event (Fig. 3). According to the results from Table 3 and Table 4, after multivariate adjustment, FHCM was an independent risk factor for cardiovascular mortality/cardiac transplantation, HR (P value) = 1.799 (0.038), age [HR : 0.817; P value < 0.001], age^2 [HR : 1.002, P value < 0.001], LV diameter [HR : 1.061, P value 0.002], LVEF [HR : 0.976; P value 0.048], AHCM [HR : 0.000, P value < 0.001] were independent prognostic predictors for cardiovascular mortality/cardiac transplantation. On the other hand, FHCM was not enter into the multivariate analysis, FHCM was not an independent risk factor for non-cardiovascular mortality. Besides that, age [HR : 1.568; P value < 0.001], age^2 [HR : 0.997 ; P value 0.005], creatinine [HR : 1.011 ; P value 0.038], QT [HR : 0.992; P value 0.018] were independent prognostic predictor for non-cardiovascular mortality.

4. Discussion

To the best of our knowledge, this is the first study on the prognosis of patients with FHCM by propensity score matching analysis of long-term follow-up clinical data. After propensity score matching analysis, FHCM had a higher risk of cardiovascular mortality/cardiac transplantation and a higher tendency of developing SCD, and FHCM was an independent prognostic predictor of cardiovascular mortality/cardiac transplantation. However, there was no difference in all-cause mortality between the two groups. In addition, multivariate Fine-Gary regression analyses revealed different cumulative risks for cardiovascular mortality/cardiac transplantation and non-cardiovascular mortality, and found that FHCM was a risk factor for cardiovascular mortality/cardiac transplantation, and FHCM was not a risk factor for non-cardiovascular mortality.

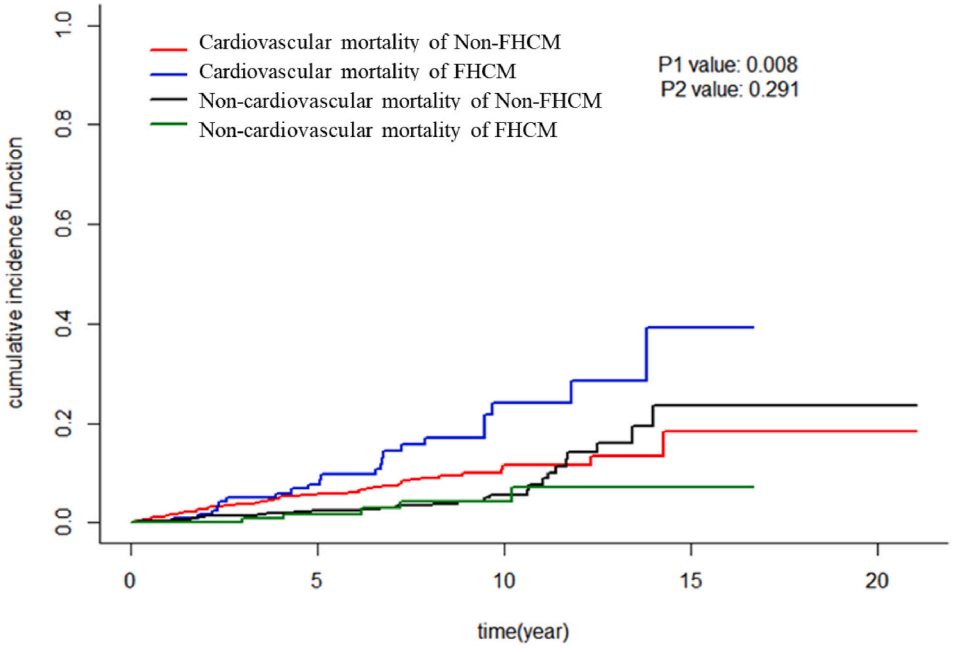

Fig. 3. Cumulative risk curve of FHCM.

Table 3
Univariate and multivariate Fine-Gray models for cardiovascular mortality/cardiac transplantation.

	Univariate analysis		Multivariate analysis	
	Hazard ratio	*P*-value	Hazard ratio	*P*-value
FHCM	1.996	0.007**	1.799	0.038*
Age	0.900	<0.001***	0.817	<0.001***
Age^2	1.000	<0.001***	1.002	<0.001***
Course of disease	1.004	<0.001***	1.001	0.220
Atrial fibrillation	2.412	0.002**	1.667	0.140
ASA or SM	0.611	0.066	0.979	0.950
LV diameter	1.073	<0.001***	1.061	0.002**
LA diameter	1.052	0.005**	1.028	0.210
LVEF	0.937	<0.001***	0.976	0.048*
Maximal LV wall thickness	0.947	0.029	0.991	0.690
AHCM	0.000	<0.001***	0.000	<0.001***
Log (NT-pro-BNP)	5.176	<0.001***	2.024	0.230
Creatinine	1.013	0.005**	1.006	0.130
Sex	1.236	0.430	–	–
NYHA class I-II	0.758	0.280	–	–
DBP	0.977	0.801	–	–
Syncope	0.771	0.490	–	–
VT	1.852	0.110	–	–
NSVT	1.493	0.320	–	–
Ventricular arrhythmias	1.713	0.064	–	–
LBBB	1.030	0.960	–	–
RBBB	1.177	0.710	–	–
Family history of SCD	1.754	0.370	–	–
QRS	1.005	0.200	–	–
QT	1.003	0.160	–	–
QTc	1.001	0.510	–	–
PR	1.001	0.850	–	–
RV diameter	1.050	0.310	–	–
RA diameter	1.015	0.990	–	–
IVS thickness	0.981	0.340	–	–
Beta Blocker	0.595	0.150	–	–
Ca^{2+} Antagonists	0.785	0.360	–	–

Note: "***" represent the significant level $p \leq 0.001$, "**" represent the significant level $p \leq 0.01$, "*" represent the significant level $p \leq 0.05$.

At present, a large number of studies have reported disease-causing genes related to FHCM [4,5,13–19]. The two most common disease genes are *MYBPC3* and *MYH7*, and several other core sarcomere genes have been found to cause HCM, including *TNNI3*, *TNNT2*, *TPM1*, *ACTC1*, *MYL2*, and *MYL3* [19–21]. Overall, a genetic cause of common sarcomere-associated genes was found in 30–50% of patients with HCM, and patients with FHCM had a higher percentage of 50–60% [22].

In general, patients with sarcomere protein mutations present earlier clinical symptoms, a younger age, worse cardiovascular mortality, a higher prevalence of family history of HCM and SCD, and an increased risk of heart failure, atrial fibrillation and malignant arrhythmias compared to those without these mutations [4,19,22–25]. Consistent with previous studies, a family history of SCD in FHCM was more common in our study. FHCM patients were younger and had higher cardiovascular mortality/cardiac transplantation rates in both the matched and unmatched cohorts. Meanwhile, FHCM was a risk factor for cardiovascular mortality/cardiac transplantation.

In the present study, we merely compared the clinical characteristics of FHCM and non-FHCM, which were diagnosed by clinical data, while using propensity score matching analysis to adjust for potential confounding factors to make the results more reliable. After matching, FHCM had higher cardiovascular mortality/cardiac transplant rates, and the SCD rate also tended to be higher, which was largely consistent with the pre-matching results. Meanwhile, the results of our clinical data are mostly consistent with the conclusion that FHCM has a poor prognosis in previous genetic testing studies [3–5,16,17,22–25]. Based on our clinical data, we suggest that for patients with FHCM and a positive family history of SCD, clinical cascade screening should be recommended with a focus on management, regardless of whether positive mutations are found.

Moreover, the clinical characteristics of FHCM depend on the genetic mutation [25,26], while some mutations are associated with a poor prognosis or late-onset HCM [24,27]. The gene-to-gene phenotype varies, with some mutations being more likely to cause heart failure, some being related to more severe cardiac hypertrophy, and some being even directly associated with SCD [4,9]. Consequently, FHCM patients with a higher percentage of gene mutations are more likely to experience adverse events. Additionally, due to the complexity of the clinical phenotype of HCM, with current knowledge, we fail to identify mutations of sarcomere genes in more than half of HCM patients, and some genotype-negative patients have a severe phenotype and a strong family history of SCD or FHCM [27]. This subtype may be related to the environment and gene modification, and the inheritance pattern may be more complex [11]. Ingles J et al. also emphasized that all probands should undergo genetic testing for established HCM genes, and the designation of non-FHCM should only apply to those probands with a negative family history and negative genetic testing [24].

Table 4
Univariate and multivariate Fine-Gray models for non-cardiovascular mortality.

	Univariate analysis		Multivariate analysis	
	Hazard ratio	*P*-value	Hazard ratio	*P*-value
FHCM	0.618	0.330	–	–
Age	1.616	<0.001***	1.568	<0.001***
Age^2	0.996	0.002**	0.997	0.005**
NYHA class I-II	0.371	0.013*	0.470	0.062
QT	0.993	0.041*	0.992	0.018*
Creatinine	1.018	0.001***	1.011	0.038*
RA diameter	3.947	0.067	1.035	0.510
Sex	0.971	0.940	–	–
Course of disease	1002	0.230	–	–
DBP	1.012	0.320	–	–
Syncope	1.428	0.410	–	–
Atrial fibrillation	1.994	0.087	–	–
VT	2.227	0.098	–	–
NSVT	1.704	0.310	–	–
Ventricular arrhythmias	1.205	0.650	–	–
LBBB	2.409	0.110	–	–
RBBB	1.046	0.940	–	–
Family history of SCD	2.489	0.220	–	–
ASA or SM	0.502	0.082	–	–
QRS	0.998	0.780	–	–
QTcc	0.995	0.260	–	–
PR	0.999	0.820	–	–
LV diameter	1.024	0.250	–	–
LA diameter	1.004	0.038*	–	–
RV diameter	1.095	0.045*	–	–
LVEF	0.973	0.100	–	–
IVS thickness	0.982	0.550	–	–
Maximal LV wall thickness	0.972	0.360	–	–
AHCM	1.045	0.970	–	–
Log (NT-pro-BNP)	1.911	0.280	–	–
Beta Blocker	0.652	0.380	–	–
Ca^{2+} Antagonists	1.190	0.620	–	–

Note: "***" represent the significant level $p \leq 0.001$, "**" represent the significant level $p \leq 0.01$, "*" represent the significant level $p \leq 0.05$.

4.1. Study limitations

There are some limitations to this study. First, this was a retrospective study. Additionally, all the patients included in the study were from tertiary centers; thus, the sample selection was biased and the sample size was limited. Second, genetic testing for FHCM was not performed in our study. Thus, unfortunately, it is impossible to determine the distribution of gene mutations in the population compared with other FHCM cohorts and its possible relationship with prognosis. Third, in the present study, the medication was only inpatient, so we didn't do extensive analysis.

5. Conclusion

In the present propensity score matching analysis study, we found that FHCM patients have higher cardiovascular mortality/cardiac transplantation rates than non-FHCM patients, while a higher tendency of SCD and FHCM was an independent risk predictor for cardiovascular mortality/cardiac transplantation of HCM. Nevertheless, there was no significant difference in all-cause mortality between the two groups. And using competing risk Fine-Gray regression model to consider cardiovascular mortality and non-cardiovascular mortality as competing events, we found that FHCM was a risk factor for cardiovascular mortality/cardiac transplantation but not for non-cardiovascular mortality.

Authors contributions

Xiaoping Li, Tianhu Liu, Wei Hua and Jianhong Tao: conceived and designed the experiments; Ye He, Chaoping Yu, Hongmei Zhang and Huihui Ma: performed the experiments; Ye He, Chaoping Yu, Ling Zhou and Mingjiang Liu: analyzed and interpreted the data; Xiaoping Li, Tianhu Liu and Wei Hua: contributed reagents, materials, analysis tools or data; Ye He and Chaoping Yu: wrote the paper.

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Conflict of interest

Prof. Xiaoping Li has received one research grant from Zhong Nanshan Medical Foundation of Guangdong Province, China (No. ZNSA-2020017). Prof. Rong Luo has received one research grant from the National Natural Science Foundation of China (No. 32171182). Prof. Yan Shu has received one research grant from Sichuan Provincial Natural Science Foundation (No. 2022NSFSC0538). Prof. Xiaoping Li, Rong Luo and Yan Shu declare that he/she has no conflict of interest.

Author contribution statement

Ye He and Chaoping Yu: Performed the experiments; Analyzed and interpreted the data; Wrote the paper.
Ling Zhou and Mingjiang Liu: analyzed and interpreted the data.
Hongmei Zhang and Huihui Ma: Performed the experiments.
Jianhong Tao and Tianhu Liu: Conceived and designed the experiments.
Wei Hua and Xiaoping Li: Conceived and designed the experiments; Contributed reagents, materials, analysis tools or data.

Data availability statement

The data will be published other paper in the future, so we are not making our data public at the moment, and will open the data in the future if necessary.

Additional information

No additional information is available for this paper.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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