ORIGINAL RESEARCH

Prognostic Significance of Plasma High-Sensitivity C-Reactive Protein in Patients With Hypertrophic Cardiomyopathy

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***Background*—**Elevated high-sensitivity C-reactive protein (hsCRP) has been associated with increased risks of adverse outcomes of various cardiovascular diseases. The relationship between hsCRP and the prognosis of hypertrophic cardiomyopathy remains to be evaluated.

***Methods and Results*—**The study used an observational cohort methodology. A total of 490 patients were enrolled in the Fuwai Hospital from 2001 to 2011 and were followed for 3.7±2.0 years. According to the risk category of hsCRP, subjects in the high hsCRP group (>3.0 mg/L) had a higher risk of developing adverse events than the low hsCRP group (<1.0 mg/L): cardiovascular death (adjusted hazard ratios[HR] 5.41, 95% CI 1.96–14.93, *P*=0.001), all-cause mortality (adjusted HR 4.78, 95% CI 1.99–11.47, *P*<0.001), sudden cardiac death (adjusted HR 11.29, 95% CI 1.38–92.20, *P*=0.024), and heart failure–related death (adjusted HR 4.38, 95% CI 1.15–16.60, *P*=0.030). Similarly, the continuous variable of hsCRP was also an independent predictor for adverse outcomes: cardiovascular death (adjusted HR 1.15, 95% CI 1.06–1.25, *P*=0.001), all-cause mortality (adjusted HR 1.17, 95% CI 1.09–1.26, *P*<0.001), sudden cardiac death (adjusted HR 1.20, 95% CI 1.06–1.36, *P*=0.003), and heart failure–related death (adjusted HR 1.15, 95% CI 1.02–1.30, *P*=0.020).

***Conclusions*—**Our results indicate that elevated plasma hsCRP is associated with increased risk for adverse outcomes in patients with hypertrophic cardiomyopathy. **(*J Am Heart Assoc*. 2017;6:e004529. DOI: 10.1161/JAHA.116.004529.)**

Key Words: cardiovascular death • high-sensitivity C-reactive protein • hypertrophic cardiomyopathy • prognosis

Hypertrophic cardiomyopathy (HCM) is one of the most common monogenic inherited cardiovascular diseases.[1] The disease affects all age groups, with marked clinical heterogeneity, ranging from a normal lifespan without symptoms to poor outcomes such as sudden cardiac death (SCD), advanced heart failure, or stroke.[2,3] Although several factors have been proposed for risk stratification in patients with HCM, including family history of sudden death, unexplained syncope, degree of left ventricular wall thickness, resting left ventricular outflow tract obstruction, nonsustained ventricular tachycardia, and congestive symptoms, the clinical outcomes of HCM are still largely unpredictable.[1,4,5]

Inflammation is a well-established risk factor for the development of cardiovascular disease.[6] Currently, C-reactive protein level, a nonspecific inflammatory marker,[7] has been associated with adverse events in various cardiovascular diseases, including myocardial infarction,[6,8] heart failure,[9,10] ischemic stroke,[6,11] atrial fibrillation,[12,13] type 2 diabetes

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Accompanying Tables S1 through S7 and Figures S1 through S4 are available at http://jaha.ahajournals.org/content/6/2/e004529/DC1/embed/inline-supplementary-material-1.pdf

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Received August 19, 2016; accepted January 4, 2017.

mellitus,[14,15] and hypertension.[16] A previous study showed that the plasma level of high-sensitivity C-reactive protein (hsCRP) was higher in patients with HCM.[17] These findings provide evidence that the plasma levels of hsCRP are closely involved in the development of HCM clinical outcomes. However, the prognostic significance of hsCRP in the clinical outcomes of HCM remains to be evaluated.

Methods

Study Population

The study used an observational cohort methodology. In total, 543 subjects were invited to participate in the study at Fuwai Hospital from 2001 to 2011. Patients with autoimmune or inflammatory disease (6 patients), active infections (1 patient), and cancer (2 patients) were excluded. Forty-four patients (8.2%) were lost during follow-up in the study (the baseline characteristics of the 44 patients with HCM according to risk category of hsCRP are listed in Table S1. The final study subjects consisted of 490 patients (Figure S1). HCM was ascertained by an unexplained maximal left ventricle wall thickness $\geq$15 mm on echocardiography and/or cardiac magnetic resonance imaging in the absence of other cardiac or systemic diseases capable of producing that magnitude of hypertrophy.[1,3] All of the patients gave informed consent to participate in this study, which was approved by the ethics committee of Fuwai Hospital. This observational cohort study was performed in keeping with the requirements of the Declaration of Helsinki.

Clinical Data Collection

The data of baseline characteristics and clinical outcomes of patients with HCM were prospectively collected with prospectively designed data forms by experienced physicians. Finally, the data were entered into the network database (Likang Times Technology Co. Ltd, Beijing, China). The twice-entry method was used for data entry. When the values of the 2 entries were consistent, the data would enter the database. Otherwise, the system would automatically flag an error, and it could then be corrected by checking the raw data. Twice data entry of the same sample was performed by different people.

HsCRP Measurement

Baseline blood samples were obtained at enrollment. After collection, the blood samples were rapidly centrifuged at 1800 g for 10 minutes and the separated plasma samples were immediately stored at −70°C until analysis. The plasma level of hsCRP was measured using the Immunoturbidimetric Assay (Orion Diagnostica, Finland). All measurements were performed in the laboratory at Fuwai Hospital.

Clinical Outcomes

The end points of this study were cardiovascular death and all-cause mortality. The cardiovascular death included SCD, heart failure–related death, and stroke-related death. SCD was defined as witnessed, unexpected, and instantaneous collapse leading to death within 1 hour of the onset of symptoms. Death related to heart failure was defined as death preceded by symptoms of heart failure >1 hour.

Statistical Analysis

Participants were divided into 3 groups according to risk category of hsCRP (low hsCRP group <1.0 mg/L, median hsCRP group 1.0–3.0 mg/L, high hsCRP group >3.0 mg/L)[18] or according to tertiles of hsCRP level. The baseline characteristics among the 3 groups were analyzed by ANOVA for parametric variables, the Kruskal–Wallis test for nonparametric variables, and the χ^2 test for categorical variables. Survival estimates were calculated by the Kaplan–Meier method and the log-rank test was used for comparison. The association between hsCRP and development of adverse outcomes of HCM were estimated with univariate and multivariate Cox proportional hazards regression models. Model 1 was unadjusted. Model 2 was adjusted for age, sex, and New York Heart Association (NYHA) class III/IV. Model 3 adjusted for age, sex, NYHA class III/IV, family history of SCD, unexplained syncope, resting left ventricular outflow tract obstruction, maximal left ventricular wall thickness, and nonsustained ventricular tachycardia. Multivariable models were fitted using backward elimination of nonsignificant factors at a 10% level. Furthermore, we also used hsCRP as a continuous variable to examine the association between hsCRP and the risk of adverse outcomes. A receiver operating characteristic (ROC) curve was generated to evaluate the accuracy of hsCRP in the prediction of adverse outcomes.

All statistical testing was 2-sided. Results were considered statistically significant at a level of $P<0.05$. All analyses were performed with PASW Statistics 18.0 software (SPSS Inc, Chicago, IL).

Results

Baseline Characteristics

The baseline characteristics of the 490 patients with HCM according to risk category of hsCRP are listed in Table 1. Patients were from 15 to 87 years old (mean age: 51.6±13.6 years), and consisted of 72.0% men. Plasma

Table 1. Baseline Clinical Characteristics of the Study Patients According to Risk Category of hsCRP

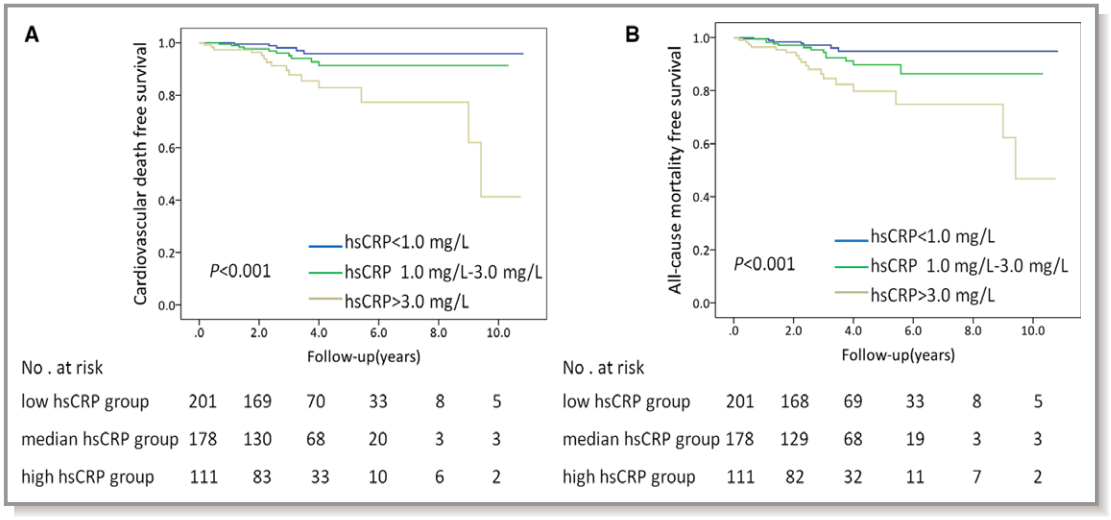
	hsCRP, mg/L				
	Total (0.01–16.70)	Low (<1.0)	Median (1.0–3.0)	High (>3.0)	
	(n=490)	(n=201)	(n=178)	(n=111)	*P* Value
Age, y	51.6±13.6	48.4±13.4	53.3±12.4	55.0±14.5	<0.001
Male, n (%)	353 (72.0)	149 (74.1)	129 (72.5)	75 (67.6)	0.460
BMI, kg/m^2	25.7±3.3	25.3±3.0	25.8±3.1	26.3±3.9	0.038
Heart rate, bpm	71.2±13.3	69.4±12.1	70.8±11.3	75.0±17.3	0.023
CHD, n (%)	89 (18.2)	33 (16.4)	29 (16.3)	27 (24.3)	0.160
Diabetes mellitus, n (%)	46 (9.4)	15 (7.5)	15 (8.4)	16 (14.4)	0.113
NYHA III–IV, n (%)	91 (18.6)	36 (17.9)	30 (16.9)	25 (22.5)	0.460
AF, n (%)	61 (12.4)	22 (10.9)	25 (14.0)	14 (12.6)	0.658
Stroke, n (%)	14 (2.9)	2 (1.0)	6 (3.4)	6 (5.4)	0.071
LV end-diastolic diameter, mm	45.3±6.9	45.1±7.3	44.8±6.3	46.3±6.9	0.208
LV ejection fraction, %	66.6±9.3	67.2±9.4	67.5±8.4	64.1±10.0	0.009
Left atrial diameter, mm	40.7±7.1	40.7±6.9	40.0±6.6	41.7±8.2	0.413
Symptoms, n (%)	395 (80.6)	162 (80.6)	142 (79.8)	91 (82.0)	0.899
Chest pain, n (%)	196 (40.0)	78 (38.8)	68 (38.2)	50 (45.0)	0.464
Palpitations, n (%)	205 (41.8)	89 (44.3)	70 (39.3)	46 (41.4)	0.619
Syncope or presyncope, n (%)	118 (24.1)	43 (21.4)	49 (27.5)	26 (23.4)	0.372
NYHA III–IV, n (%)	91 (18.6)	36 (17.9)	30 (16.9)	25 (22.5)	0.460
Unexplained syncope, n (%)	77 (15.7)	30 (14.9)	30 (16.9)	17 (15.3)	0.868
Family history of SCD, n (%)	63 (13.3)	28 (13.9)	21 (11.8)	14 (12.6)	0.822
Resting LVOT obstruction, n (%)	209 (42.7)	78 (38.8)	72 (40.4)	59 (53.2)	0.037
Maximal LV wall thickness, mm	21.0±5.0	20.9±5.3	20.9±4.9	21.3±5.0	0.724
NSVT, n (%)	15 (3.1)	6 (3.0)	4 (2.2)	5 (4.5)	0.554
Family history of HCM, n (%)	94 (19.2)	34 (16.9)	34 (19.1)	26 (23.4)	0.376
ICD implantation	3 (0.6)	1 (0.5)	0 (0)	2 (1.8)	0.156
Septal reduction therapy, n (%)	84 (17.1)	37 (18.4)	30 (16.9)	17 (15.3)	0.780
Surgical septal myectomy, n (%)	15 (3.1)	6 (3.0)	3 (1.7)	6 (5.4)	0.202
Alcohol septal ablation, n (%)	69 (14.1)	31 (15.4)	27 (15.2)	11 (9.9)	0.355
β-Blocker, n (%)	378 (77.1)	157 (78.1)	135 (75.8)	86 (77.5)	0.868
Verapamil or diltiazem, n (%)	92 (18.8)	41 (20.4)	35 (19.7)	16 (14.4)	0.402

Continuous variables are presented as mean±SD; categorical variables are presented as numbers or percentages. AF indicates atrial fibrillation; BMI, body mass index; CHD, coronary heart disease; HCM, hypertrophic cardiomyopathy; hsCRP, high-sensitivity C-reactive protein; ICD, implantable cardioverter-defibrillator; LV, left ventricular; LVOT, left ventricular outflow tract; NSVT, nonsustained ventricular tachycardia; NYHA, New York Heart Association; SCD, sudden cardiac death.

hsCRP ranged from 0.01 to 16.70 mg/L. Median hsCRP for the entire study population was 1.27 mg/L (interquartile range: 0.57–2.68 mg/L). Subjects in the higher hsCRP group showed higher age (low: 48.4±13.4, median: 53.3±12.4, high: 55.0±14.5, years, $P<0.001$), higher body mass index (low: 25.3±3.0, median: 25.8±3.1, high: 26.3±3.9, kg/m^2, $P=0.038$), higher heart rate (low: 69.4±12.1, median: 70.8±11.3, high: 75.0±17.3, bpm, $P=0.023$), higher resting left ventricular outflow tract obstruction ratio (low: 38.8%, median: 40.4%, high: 53.2%, $P=0.037$). Subjects in the high hsCRP group showed significantly lower left ventricular ejection fraction levels (low: 67.2±9.4, median: 67.5±8.4, high: 64.1±10.0, $P=0.009$). In addition, the differences among the 3 groups according to tertiles of hsCRP were similar to the risk category of hsCRP (Table S2).

Survival Analysis

During the follow-up of 3.7±2.0 years, there were 30 (6.1%) cardiovascular deaths, including SCD in 11 patients, heart



No . at risk

low hsCRP group	201	169	70	33	8	5
median hsCRP group	178	130	68	20	3	3
high hsCRP group	111	83	33	10	6	2

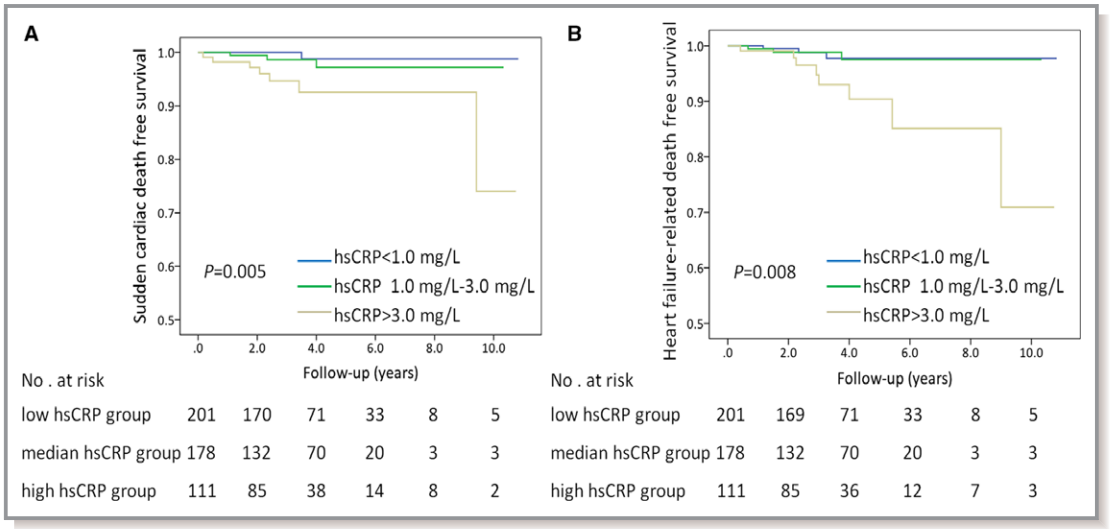
No . at risk

low hsCRP group	201	168	69	33	8	5
median hsCRP group	178	129	68	19	3	3
high hsCRP group	111	82	32	11	7	2

Figure 1. Survival free of cardiovascular death (A) and all-cause mortality (B) in patients with HCM. According to risk category of hsCRP, subjects in the high hsCRP group had lower cardiovascular death and all-cause mortality-free survival in the patients with HCM. *P*-values were calculated using the log-rank test. HCM indicates hypertrophic cardiomyopathy; hsCRP, high-sensitivity C-reactive protein.

failure–related deaths in 14 patients, and stroke-related deaths in 5 patients. Baseline clinical characteristics of patients with cardiovascular death are listed in Table S3. During follow-up, the rate of cardiovascular death in the high hsCRP group, median hsCRP group, and low hsCRP group were 13.5% (15/111), 5.6% (10/178), and 2.5% (5/201) ($P<0.001$), respectively. According to the risk category of hsCRP, survival free of cardiovascular death was lower in the high hsCRP group (log-rank $P<0.001$, Figure 1A). Similarly, 38 (7.8%) of the 490 patients had all-cause mortality. Subjects in the high hsCRP group had lower all-cause mortality-free survival (log-rank $P<0.001$, Figure 1B). Furthermore, survival free of SCD and heart failure–related death were lower in the high hsCRP group (log-rank $P=0.005$, Figure 2A; log-rank $P=0.008$, Figure 2B, respectively). There were 5 stroke-related deaths during the follow-up. The incidence of stroke-related deaths was low and did not allow for further analysis.

Subjects in the higher hsCRP group showed significantly lower 3-year survival rates of cardiovascular death and all-cause mortality (Table S4) and showed significantly higher



No . at risk

low hsCRP group	201	170	71	33	8	5
median hsCRP group	178	132	70	20	3	3
high hsCRP group	111	85	38	14	8	2

No . at risk

low hsCRP group	201	169	71	33	8	5
median hsCRP group	178	132	70	20	3	3
high hsCRP group	111	85	36	12	7	3

Figure 2. Survival free of sudden cardiac death (A) and heart failure–related death (B) in patients with HCM. According to the risk category of hsCRP, subjects in the high hsCRP group had lower sudden cardiac death and heart failure–related death-free survival than in the patients with HCM. *P*-values were calculated using the log-rank test. HCM indicates hypertrophic cardiomyopathy; hsCRP, high-sensitivity C-reactive protein.

event rates (per 100-patient years) of adverse outcomes in patients with HCM (Table S5).

Relation of hsCRP to Adverse Outcomes

To further evaluate the effect of hsCRP on development of adverse outcomes of HCM, we used univariate and multivariate Cox proportional hazards regression models to reveal whether the plasma hsCRP level could predict the adverse outcomes of patients with HCM.

In univariable Cox regression models (Model 1), compared with patients in the low hsCRP group, the hazard ratios (HR) for cardiovascular deaths in the median hsCRP group and high hsCRP group were 2.32 (95% CI 0.79–6.80, *P*=0.124) and 5.88 (95% CI 2.13–16.20, *P*=0.001), respectively. Similarly, the high hsCRP group had a higher risk of developing all-cause mortality than the low hsCRP group (HR 5.04, 95% CI 2.10–12.09, *P*<0.001). There was no significant difference in relative risk of all-cause mortality between the low hsCRP group and the median hsCRP group (HR 2.16, 95% CI 0.86–5.42, *P*=0.101). Furthermore, compared with patients in the low hsCRP group, the HR for SCD and heart failure–related death in the high hsCRP group were 12.57 (HR 12.57, 95% CI 1.54–102.45, *P*=0.018) and 4.98 (HR 4.98, 95% CI 1.31–18.86, *P*=0.018), respectively (Table 2).

Multivariate analysis showed that plasma hsCRP was independently and positively related to cardiovascular death (adjusted HR in the high hsCRP group: 5.41, 95% CI 1.96–14.93, *P*=0.001, compared with the low hsCRP group) after adjusting for age, sex, and NYHA class III/IV (Model 2). With further adjustment for age, sex, NYHA class III/IV, family history of SCD, unexplained syncope, resting left ventricular outflow tract obstruction, maximal left ventricular wall thickness, and nonsustained ventricular tachycardia (Model 3), the HR for cardiovascular deaths in the high hsCRP group showed no change (HR 5.41, 95% CI 1.96–14.93, *P*=0.001). Similarly, the high hsCRP group had a higher risk of developing all-cause mortality than the low hsCRP group (Model 2: HR 4.78, 95% CI 1.99–11.47, *P*<0.001; Model 3: HR 4.78, 95% CI 1.99–11.47, *P*<0.001). Furthermore, subjects in the high hsCRP group

Table 2. Univariate and Multivariate Cox Analysis According to Risk Category of hsCRP

	Cardiovascular Death		All-Cause Mortality		Sudden Cardiac Death		Heart Failure–Related Death	
	HR* (95% CI)	*P** Value	HR* (95% CI)	*P** Value	HR* (95% CI)	*P** Value	HR* (95% CI)	*P** Value
Model 1[†]								
Low hsCRP (n=201)	1.00		1.00		1.00		1.00	
Median hsCRP (n=178)	2.32 (0.79–6.80)	0.124	2.16 (0.86–5.42)	0.101	3.45 (0.36–33.21)	0.258	1.15 (0.23–5.70)	0.866
High hsCRP (n=111)	5.88 (2.13–16.20)	0.001	5.04 (2.10–12.09)	<0.001	12.57 (1.54–102.45)	0.018	4.98 (1.31–18.86)	0.018
Model 2[‡]								
Low hsCRP (n=201)	1.0		1.00		1.00		1.00	
Median hsCRP (n=178)	2.57 (0.87–7.55)	0.087	2.35 (0.93–5.91)	0.070	3.70 (0.38–35.73)	0.258	1.31 (0.26–6.52)	0.745
High hsCRP (n=111)	5.41 (1.96–14.93)	0.001	4.78 (1.99–11.47)	<0.001	11.16 (1.37–91.17)	0.024	4.38 (1.15–16.60)	0.030
Model 3[§]								
Low hsCRP (n=201)	1.00		1.00		1.00		1.00	
Median hsCRP (n=178)	2.57 (0.87–7.55)	0.087	2.35 (0.93–5.91)	0.070	3.53 (0.36–34.16)	0.276	1.31 (0.26–6.52)	0.745
High hsCRP (n=111)	5.41 (1.96–14.93)	0.001	4.78 (1.99–11.47)	<0.001	11.29 (1.38–92.20)	0.024	4.38 (1.15–16.60)	0.030

HR indicates hazard ratio; hsCRP, high-sensitivity C-reactive protein.
*Compared with the low hsCRP group.
[†]Model 1: unadjusted.
[‡]Model 2: multivariate adjustment was made for age, sex, New York Heart Association class III/IV.
[§]Model 3: multivariate adjustment was made for age, sex, New York Heart Association class III/IV, a family history of sudden cardiac death events, unexplained syncope, resting left ventricular outflow tract obstruction, maximal left ventricular wall thickness, and nonsustained ventricular tachycardia.

were associated with an increased risk of SCD (Model 2: HR 11.16, 95% CI 1.37–91.17, *P*=0.024; Model 3: HR 11.29, 95% CI 1.38–92.20, *P*=0.024; compared with the low hsCRP group) and heart failure–related death (Model 2: HR 4.38, 95% CI 1.15–16.60, *P*=0.030; Model 3: HR 4.38, 95% CI 1.15–16.60, *P*=0.030; compared with the low hsCRP group) (Table 2).

In addition, when divided into 3 groups according to tertiles of hsCRP, the survival analysis and multivariate Cox regression analysis were similar to the risk category of hsCRP, which shows that elevated levels of hsCRP predict high risk of adverse outcomes in patients with HCM (Figures S2 and S3; Table S6).

When analyzed as a continuous variable, elevated hsCRP predicted increased risk for cardiovascular death (Model 1: HR 1.16, 95% CI 1.08–1.26, *P*<0.001; Model 2: HR 1.15, 95% CI 1.06–1.25, *P*=0.001; Model 3: HR 1.15, 95% CI 1.06–1.25, *P*=0.001) and all-cause mortality (Model 1: HR 1.18, 95% CI 1.10–1.26, *P*<0.001; Model 2: HR 1.17, 95% CI 1.09–1.26, *P*<0.001; Model 3: HR 1.17, 95% CI 1.09–1.26, *P*<0.001). The continuous variable of hsCRP was also independently and positively related to SCD (Model 1: HR 1.21, 95% CI 1.07–1.36, *P*=0.002; Model 2: HR 1.21, 95% CI 1.06–1.37, *P*=0.004; Model 3: HR 1.20, 95% CI 1.06–1.36, *P*=0.003) and heart failure–related death (Model 1: HR 1.16, 95% CI 1.04–1.31, *P*=0.009; Model 2: HR 1.15, 95% CI 1.02–1.30, *P*=0.020; Model 3: HR 1.15, 95% CI 1.02–1.30, *P*=0.020) (Table 3).

Prognostic Value of hsCRP for Adverse Outcomes

The ROC analysis indicated that hsCRP had reasonable accuracy for prediction of adverse outcomes. The area under the ROC curve was 0.71 (95% CI 0.62–0.80, *P*<0.001) for cardiovascular death (Figure 3). A cutoff of hsCRP >3.0 mg/L had a 96.0% negative predictive value for predicting cardiovascular death (Table S7). The area under the ROC curve was 0.70 for all-cause mortality (95% CI 0.62–0.79, *P*<0.001), 0.77 for SCD (95% CI 0.64–0.89, *P*=0.002), and 0.69 for heart failure–related death (95% CI 0.54–0.84, *P*=0.017) (Figure S4).

Discussion

In this study, we found that elevated hsCRP was associated with adverse outcomes in patients with HCM. Patients in the high hsCRP group had higher risk for cardiovascular death, as well as all-cause mortality, SCD, and heart failure–related death. Furthermore, when analyzed as a continuous variable, elevated hsCRP predicted increased risk for adverse outcomes in patients with HCM. The ROC analysis indicated that hsCRP had reasonable predictive accuracy for the development of adverse outcomes.

CRP measured by a highly sensitive assay (hsCRP) has considerable chemical stability, requires no special precautions for sampling, and has a relatively long half-life.[19] Therefore, it has emerged as a leading biomarker of inflammation for clinical application. HsCRP has been regarded as a traditional risk factor in cardiovascular diseases.[20] A previous study found that obstructive HCM was associated with increased CRP levels, compared with nonobstructive HCM.[21] Similarly, the plasma level of hsCRP was significantly higher in patients with obstructive HCM than nonobstructive HCM in this study. However, the prognostic value of hsCRP in HCM has not yet been reported. To our knowledge, this is the first study to demonstrate that hsCRP was an independent predictor of adverse prognosis in patients with HCM.

Histological studies support a possible association between inflammation and HCM, and infiltration of chronic inflammatory cells is found in the myocardium of patients with HCM.[22,23] Recently, the study has demonstrated that a low-grade inflammatory response may play a significant role in the phenotypic expression of myocardial fibrosis in HCM.[17] Previous studies found that CRP may have a pathogenic role

Table 3. Univariate and Multivariate Cox Analysis as a Continuous Variable of hsCRP

	Model 1*		Model 2†		Model 3‡	
Events	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
Cardiovascular deaths	1.16 (1.08–1.26)	<0.001	1.15 (1.06–1.25)	0.001	1.15 (1.06–1.25)	0.001
All-cause mortality	1.18 (1.10–1.26)	<0.001	1.17 (1.09–1.26)	<0.001	1.17 (1.09–1.26)	<0.001
Sudden cardiac death	1.21 (1.07–1.36)	0.002	1.21 (1.06–1.37)	0.004	1.20 (1.06–1.36)	0.003
Heart failure–related death	1.16 (1.04–1.31)	0.009	1.15 (1.02–1.30)	0.020	1.15 (1.02–1.30)	0.020

HR indicates hazard ratio; hsCRP, high-sensitivity C-reactive protein.
*Model 1: unadjusted.
†Model 2: multivariate adjustment was made for age, sex, New York Heart Association class III/IV.
‡Model 3: multivariate adjustment was made for age, sex, New York Heart Association class III/IV, a family history of sudden cardiac death events, unexplained syncope, resting left ventricular outflow tract obstruction, maximal left ventricular wall thickness, and nonsustained ventricular tachycardia.

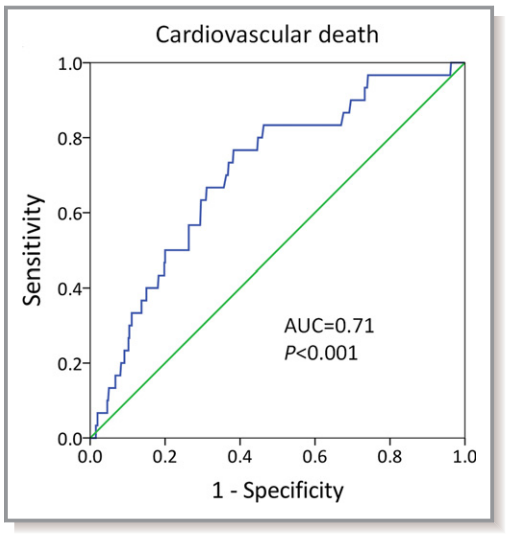


Figure 3. A ROC curve of hsCRP to predict cardiovascular death in patients with HCM. The AUC was 0.71 (95% CI 0.62–0.80, $P<0.001$). AUC indicates area under curves; HCM, hypertrophic cardiomyopathy; hsCRP, high-sensitivity C-reactive protein; ROC, receiver operating characteristic.

in the development of cardiac hypertrophy and fibrosis, possibly through the nuclear factor kappa B signaling pathways.[24] Zhang et al also found that activation of the nuclear factor kappa B signaling pathways may be the mechanisms by which CRP promotes cardiac fibrosis.[25] Myocardial fibrosis is a hallmark of hypertrophic cardiomyopathy. It is an early manifestation of HCM even before hypertrophic remodeling.[26] Meanwhile, myocardial fibrosis is a major determinant of SCD, ventricular tachyarrhythmia, left ventricular dysfunction, and heart failure.[26–28] Our results showed that elevated hsCRP predicted an increased risk for adverse outcomes in patients with HCM. These studies suggest that prolonged and low-grade myocardial inflammation induces nuclear factor kappa B upregulation and activates inflammatory cell invasion and fibroblasts, and finally leads to myocardial fibrosis.[17,25,29,30] Myocardial fibrosis is thought to play a significant role in clinical progression.

In the present study, the event rates were 7.8% (2.12 per 100 person-year) for all-cause mortality and 6.1% (1.67 per 100 person-year) for cardiovascular deaths. Recently, Maron et al have shown that the event rate was 8.2% (1.16 per 100 person-year) for all-cause mortality and 4.0% (0.53 per 100 person-year) for HCM-related death (7.2±5.2 years of follow-up).[31] Another study shows that the event rate of all-cause mortality was 13.1% and HCM-related death was 3.7% (6.6±5.3 years of follow-up).[32] Compared with these studies, the event rates of cardiovascular deaths in our study were somewhat higher. In other studies, Coats et al showed an event rate of all-cause mortality of 8% (68/847) (a median duration of 3.5 years of follow-up),[33] and Geske et al showed that the incidence per 100 person-year of all-cause mortality was 2.29.[34] The event rates of our study were comparable to these reports. The discrepancy of event rates among different studies may be due to the collection bias of patients, or ethnic differences. In our study, all included patients were of the Chinese Han ethnic group, and their disease may be more severe because the Fuwai Hospital is the National Center for Cardiovascular Diseases. In spite of the above, our results are still able to clearly indicate that hsCRP is a risk factor of adverse outcomes in patients with HCM.

In this study, we found that patients with higher hsCRP levels had a higher risk for adverse outcomes of HCM. Although a causal relationship between hsCRP and the prognosis of HCM had not yet been established, our findings suggest a possible association of an inflammatory state and the clinical progression of HCM.

The patients enrolled in this study come from a single center and were limited to the native Chinese population. There were 8.2% of patients lost during follow-up in the present study, which might introduce biases. In addition, the values of hsCRP were measured at enrollment. We did not have serial measurements of hsCRP in this study. These facts limit the generalizability of our findings.

Conclusions

Our results indicate that elevated plasma hsCRP is associated with increased risk for adverse outcomes in the patients with HCM. Although a causal relationship between hsCRP and the prognosis of HCM had not yet been established, our findings suggest a possible association of an inflammatory state and the clinical progression of HCM.

Sources of Funding

This study was supported by CAMS Innovation Fund for Medical Sciences (CIFMS, 2016-I2M-1-015), the National Natural Science Foundation of China (grant No. 81470380) and the Ministry of Science and Technology of China (grant No. 2015AA020407, 2011BAI11B04 and 2011CB503901).

Disclosures

None.

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Supplemental Material

Table S1. Baseline clinical characteristics of the patients lost to follow-up

	hsCRP (mg/L)				
	Total (0.05-17.31) (n=44)	First tertile (<1.0) (n=17)	Second tertile (1.0-3.0) (n=17)	Third tertile (>3.0) (n=10)	*P* value
Age ,year	49.5±15.3	47.8±14.4	47.5±16.4	56.0±14.4	0.319
Male, n %	31(70.5)	13(76.5)	11(64.7)	7(70.0)	0.753
BMI ,kg/m^2	25.3±3.5	24.8±3.8	25.9±3.8	24.9±2.4	0.352
Heart rate bpm	68.3±12.5	69.7±13.8	67.8±11.6	67.0±12.9	0.679
CHD, n %	5(11.4)	2(11.8)	1(5.9)	2(20.0)	0.535
Diabetes, n %	5(11.4)	2(11.8)	3(17.6)	0(0)	0.377
AF, n %	5(11.4)	3(17.6)	2 (11.8)	0(0)	0.377
Stroke, n %	1(2.3)	0(0)	1(5.9)	0(0)	0.444
LV end-diastolic diameter, mm	45.6±6.1	46.4±5.9	46.0±5.7	43.6±7.1	0.501
LV ejection fraction, %	67.6±8.9	67.4±7.7	65.8±10.9	71.2±6.4	0.313
Left atrial diameter, mm	38.3±6.9	36.1±7.1	39.7±7.3	39.7±5.1	0.238
Symptoms, n %	30(68.2)	10(58.8)	12(70.6)	8(80.0)	0.503
Chest pain, n %	19(43.2)	5(29.4)	8(47.1)	6(60.0)	0.277
Palpitations, n %	13(29.5)	4(23.5)	6(35.3)	3(30.0)	0.753
Syncope or pre-syncope, n %	11(25.0)	4(23.5)	6(35.3)	1(10.0)	0.336
NYHA III-IV, n %	2(4.5)	0(0)	2(11.8)	0(0)	0.189
Unexplained syncope, n %	6(13.6)	4(23.5)	2(11.8)	0(0)	0.218
Family history of SCD, n %	1(2.3)	1(5.9)	0(0)	0(0)	0.444
Rest LVOT obstruction, n %	20(45.5)	6(35.3)	9(52.9)	5(50.0)	0.556
Maximal LV wall thickness, mm	20.5±6.4	19.1±6.1	23.2±6.5	18.3±5.7	0.073
NSVT, n %	1(2.3)	0(0)	1(5.9)	0(0)	0.444
Family history of HCM, n %	4(9.1)	1(5.9)	1(5.9)	2(20.0)	0.394
ICD implantation	1(2.3)	0(0)	1(5.9)	0(0)	0.444
Septal reduction therapy, n (%)	7(15.9)	2(11.8)	4(23.5)	1(10.0)	0.544
Surgical septal myectomy, n %	2(4.5)	0(0)	1(5.9)	1(10.0)	0.457
Alcohol septal ablation, n %	5(11.4)	2 (11.8)	3(17.6)	0(0)	0.377
Beta-blocker, n %	31(70.5)	13(76.5)	11(64.7)	7(70.0)	0.753
Verapamil or diltiazem, n %	13(29.5)	4(23.5)	5(29.4)	4(40.0)	0.663

Continuous variables are presented as mean±SD; categorical variables are presented as numbers or percentages;

Abbreviations: AF= atrial fibrillation; BMI= body mass index; CHD= coronary heart disease; HCM= hypertrophic cardiomyopathy; hsCRP= high-sensitivity C-reactive protein; ICD= implantable cardioverter-defibrillator; LV= left ventricular; LVOT= left ventricular outflow tract; NSVT= non-sustained ventricular tachycardia; NYHA= New York Heart Association; SCD= sudden cardiac death.

Table S2. Baseline clinical characteristics of the study patients according to tertiles of hsCRP

	hsCRP (mg/L)			
	Total (0.01-16.70) (n=490)	First tertile (<0.76) (n=164)	Second tertile (0.76-1.94) (n=163)	Third tertile (>1.94) (n=163)	*P* value
Age ,year	51.6±13.6	47.2±13.1	53.8±12.7	53.9±13.9	<0.001
Male, n %	353(72.0)	119(72.6)	126(77.3)	108(66.3)	0.083
BMI ,kg/m^2	25.7±3.3	25.0±3.1	25.9±3.0	26.1±3.7	0.006
Heart rate bpm	71.2±13.3	69.2±12.1	70.3±11.7	74.0±15.5	0.018
CHD, n %	89(18.2)	25(15.2)	32(19.6)	32(19.6)	0.493
Diabetes, n %	46(9.4)	14(8.5)	13(8.0)	19(11.7)	0.470
AF, n %	61(12.4)	15(9.1)	26(16.0)	20(12.3)	0.176
Stroke, n %	14(2.9)	2(1.2)	5(3.1)	7(4.3)	0.244
LV end-diastolic diameter, mm	45.3±6.9	45.2±7.6	44.9±6.2	45.7±6.7	0.520
LV ejection fraction, %	66.6±9.3	67.7±9.5	66.9±8.9	65.2±9.3	0.039
Left atrial diameter, mm	40.7±7.1	40.6±7.2	40.0±6.1	41.4±7.8	0.636
Symptoms, n %	395(80.6)	131(79.9)	131(80.4)	133(81.6)	0.921
Chest pain, n %	196(40.0)	59(36.0)	68(41.7)	69(42.3)	0.433
Palpitations, n %	205(41.8)	74(45.1)	66(40.5)	65(39.9)	0.575
Syncope or pre-syncope, n %	118(24.1)	37(22.6)	39(23.9)	42(25.8)	0.793
NYHA III-IV, n %	91(18.6)	33(20.1)	21(12.9)	37(22.7)	0.061
Unexplained syncope, n %	77(15.7)	27(16.5)	23(14.1)	27(16.6)	0.789
Family history of SCD, n %	63(13.3)	24(14.6)	21(12.9)	18(11.0)	0.625
Rest LVOT obstruction, n %	209(42.7)	66(31.6)	69(33.0)	74(35.4)	0.638
Maximal LV wall thickness, mm	21.0±5.0	21.0±5.3	20.6±4.9	21.3±4.9	0.486
NSVT, n %	15(3.1)	6(3.7)	4(2.5)	5(3.1)	0.819
Family history of HCM, n %	94(19.2)	28(17.1)	32(19.6)	34(20.9)	0.675
ICD implantation	3(0.6)	1(0.6)	0(0)	2(1.2)	0.365
Septal reduction therapy, n (%)	84(17.1)	30(18.3)	33(20.2)	21(12.9)	0.188
Surgical septal myectomy, n %	15(3.1)	5(3.0)	3(1.8)	7(4.3)	0.437
Alcohol septal ablation, n %	69(14.1)	25(15.2)	30(18.4)	14(8.6)	0.034
Beta-blocker, n %	378(77.1)	125(76.2)	129(79.1)	124(76.1)	0.758
Verapamil or diltiazem, n %	92(18.8)	34(20.7)	29(17.8)	29(17.8)	0.734

Continuous variables are presented as mean±SD; categorical variables are presented as numbers or percentages;

Abbreviations: AF= atrial fibrillation; BMI= body mass index; CHD= coronary heart disease; HCM= hypertrophic cardiomyopathy; hsCRP= high-sensitivity C-reactive protein; ICD= implantable cardioverter-defibrillator; LV= left ventricular; LVOT= left ventricular outflow tract; NSVT= non-sustained ventricular tachycardia; NYHA= New York Heart Association; SCD= sudden cardiac death.

Table S3. Baseline clinical characteristics of patients with cardiovascular death

	Cardiovascular death				
	Total	SCD	Heart failure related deaths	stroke-related deaths	*P* value
	(n=30)	(n=11)	(n=14)	(n=5)	
Age ,year	53.5±16.9	49.7±15.2	56.4±17.7	53.4±19.9	0.530
Male, n %	19(63.3)	7(63.6)	9(64.3)	3(60.0)	0.985
BMI ,kg/m^2	25.5±4.7	25.9±5.6	24.9±4.0	26.6±5.3	0.837
Heart rate, bpm	74.3±16.8	73.8±14.4	76.1±21.4	70.6±3.5	0.826
CHD, n %	5(16.7)	2(18.2)	3(21.4)	0(0)	0.536
Diabetes, n %	3(10.0)	0(0)	2(14.3)	1(20.0)	0.356
AF, n %	2(6.7)	0(0)	1(7.1)	1(20.0)	0.330
Stroke, n %	2(6.7)	1(9.1)	1(7.1)	0(0)	0.792
LV end-diastolic diameter, mm	49.0±9.0	49.0±8.6	48.6±8.8	50.2±11.9	0.990
LV ejection fraction, %	57.0±13.7	59.4±13.3	55.2±14.5	56.6±14.6	0.706
Left atrial diameter, mm	46.7±9.8	44.4±10.1	47.6±10.2	49.2±9.1	0.555
Symptoms, n %	24(80.0)	8(72.7)	13(92.9)	3(60.0)	0.217
Chest pain, n %	7(23.3)	1(9.1)	5(35.7)	1(20.0)	0.290
Palpitations, n %	13(43.3)	3(27.3)	8(61.5)	2(40.0)	0.322
Syncope or pre-syncope, n %	10(33.3)	4(36.4)	5(35.7)	1(20.0)	0.786
NYHA III-IV, n %	15(50.0)	6(54.5)	8(57.1)	1(20.0)	0.337
Unexplained syncope, n %	6(20.0)	4(36.4)	1(7.1)	1(20.0)	0.193
Family history of SCD, n %	6(20.0)	3(27.3)	3 (21.4)	0(0)	0.442
Rest LVOT obstruction, n %	12(40.0)	7 (63.6)	4(28.6)	1(20.0)	0.125
Maximal LV wall thickness, mm	21.4±5.7	21.4±6.6	21.4±5.9	21.4±3.4	0.975
NSVT, n %	3(10.0)	2(18.2)	1(7.1)	0(0)	0.472
Family history of HCM, n %	9(30.0)	5(45.5)	3 (21.4)	1(20.0)	0.372
ICD implantation	0(0)	0(0)	0(0)	0(0)	NA
Septal reduction therapy, n (%)	4(13.3)	2(18.2)	2(14.3)	0(0)	0.605
Surgical septal myectomy, n %	1(3.3)	0(0)	1(7.1)	0(0)	0.554
Alcohol septal ablation, n %	3(14.1)	2(18.2)	1(7.1)	0(0)	0.472
Beta-blocker, n %	21(70.0)	9(81.8)	9(64.3)	3(60.0)	0.552
Verapamil or diltiazem, n %	5(16.7)	1(9.1)	4(28.6)	0(0)	0.237

Continuous variables are presented as mean±SD; categorical variables are presented as numbers or percentages;

Abbreviations: AF= atrial fibrillation; BMI= body mass index; CHD= coronary heart disease; HCM= hypertrophic cardiomyopathy; hsCRP= high-sensitivity C-reactive protein; ICD= implantable cardioverter-defibrillator; LV= left ventricular; LVOT= left ventricular outflow tract; NSVT= non-sustained ventricular tachycardia; NYHA= New York Heart Association; SCD= sudden cardiac death.

Table S4. Three-year survival rate of cardiovascular death and all-cause mortality according to risk category of hsCRP

	Three-year survival rate(%)	95% CI(%)
Cardiovascular death		
low hsCRP (n=201)	95.8	92.0-99.5
median hsCRP (n=178)	92.4	87.4-97.3
high hsCRP (n=111)	85.2	76.6-93.7
All-cause mortality		
low hsCRP (n=201)	94.7	90.7-98.7
median hsCRP (n=178)	90.6	85.1-96.1
high hsCRP (n=111)	82.0	73.0-91.0

Abbreviations: CI =confidence interval; hsCRP= high-sensitivity C-reactive protein.

Table S5. Event rates of adverse outcomes according to risk category of hsCRP

		hsCRP(mg/L)		
	Total	Low (<1.0)	Median (1.0-3.0)	High (>3.0)
	(n=490)	(n=201)	(n=178)	(n=111)
Follow up, person years	1792.3	740.9	632.6	418.8
Cardiovascular death				
Events (per 100 patient-years)	30(1.67)	5(0.67)	10(1.58)	15(3.58)
All-cause mortality				
Events (per 100 patient-years)	38(2.12)	7(0.94)	13(2.06)	18(4.30)
Sudden cardiac death				
Events (per 100 patient-years)	11(0.61)	1(0.13)	3(0.47)	7(1.67)
Heart failure-related death				
Events (per 100 patient-years)	14(0.78)	3(0.40)	3(0.47)	8(1.91)

Abbreviations: hsCRP= high-sensitivity C-reactive protein.

Table S6. Univariate and multivariate COX analysis according to tertiles of hsCRP*

	Cardiovascular death		All-cause mortality		Sudden cardiac death		Heart failure-related death	
	HR* (95% CI)	*P** value	HR* (95% CI)	*P** value	HR* (95% CI)	*P** value	HR* (95% CI)	*P** value
Model 1†								
T1(n=164)	1.00		1.00		1.00		1.00	
T2(n=163)	0.97(0.28-3.34)	0.955	1.32(0.46-3.80)	0.609	1.94(0.18-21.39)	0.589	0.32(0.03-3.11)	0.328
T3(n=163)	4.25(1.59-11.33)	0.004	4.29(1.75-10.50)	0.001	7.88(0.98-63.10)	0.052	3.41(0.93-12.42)	0.063
Model 2‡								
T1(n=164)	1.00		1.00		1.00		1.00	
T2(n=163)	1.07(0.31-3.70)	0.916	1.45(0.50-4.18)	0.495	2.15(0.19-23.82)	0.532	0.37(0.04-3.57)	0.390
T3(n=163)	4.08(1.53-10.88)	0.005	4.20(1.72-10.29)	0.002	7.24(0.90-58.08)	0.062	3.19(0.87-11.63)	0.079
Model 3§								
T1(n=164)	1.00		1.00		1.00		1.00	
T2(n=163)	1.14(0.33-3.95)	0.842	1.45(0.50-4.18)	0.495	2.31(0.21-25.89)	0.499	0.37(0.04-3.57)	0.390
T3(n=163)	4.25(1.59-11.40)	0.004	4.20(1.72-10.29)	0.002	6.75(0.83-54.90)	0.074	3.19(0.87-11.63)	0.079

† Model 1: unadjusted.

‡ Model 2: Multivariate adjustment was made for age, sex, New York Heart Association class III/IV.

§ Model 3: Multivariate adjustment was made for age, sex, New York Heart Association class III/IV, a family history for sudden cardiac death events, unexplained syncope,

rest LVOT obstruction, maximal LV wall thickness, and non-sustained ventricular tachycardia.

***** compared with the first tertile.

Abbreviations: CI = confidence interval; HR= hazard ratio; hsCRP= high-sensitivity C-reactive protein; T1= first tertile; T2= second tertile; T3= third tertile.

Table S7. Operating characteristics of hsCRP > 3.0mg/L thresholds to predict adverse outcomes of HCM

HsCRP > 3.0mg/L	Sensitivity(%)	Specificity(%)	PPV(%)	NPV(%)
Cardiovascular deaths	50.0	79.1	13.5	96.0
All-cause mortality	47.4	79.4	16.2	94.7
Sudden cardiac death	63.6	78.3	6.3	98.9
Heart failure-related death	57.1	78.4	7.2	98.4

Abbreviations: hsCRP= high-sensitivity C-reactive protein; NPV= negative predictive value; PPV= positive predictive value.

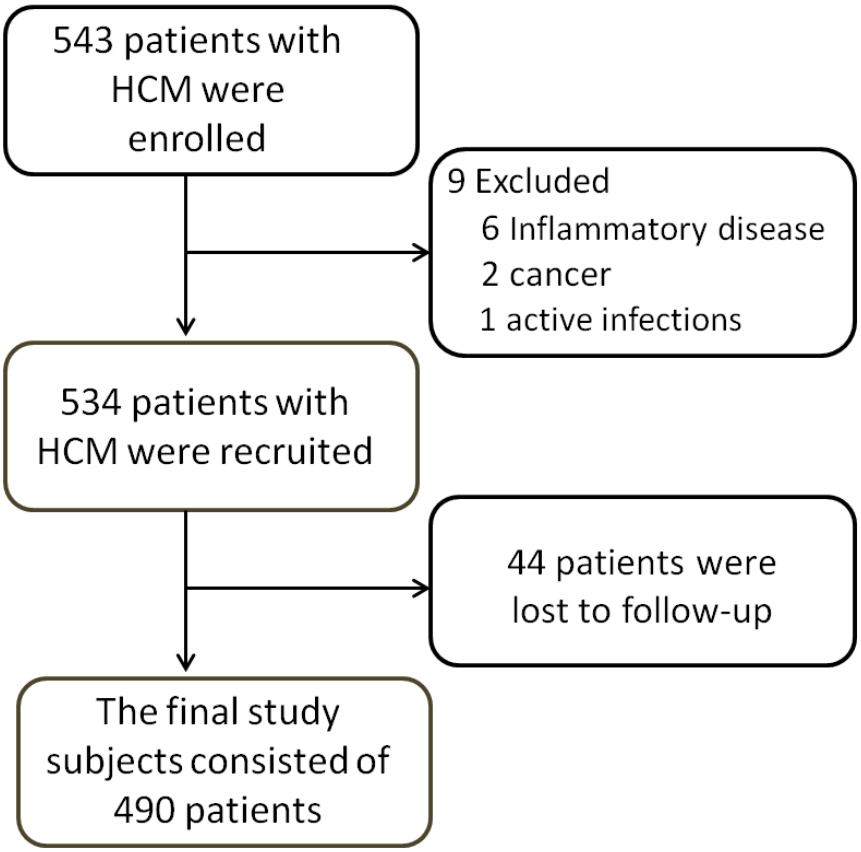

Figure S1: Patient flowchart

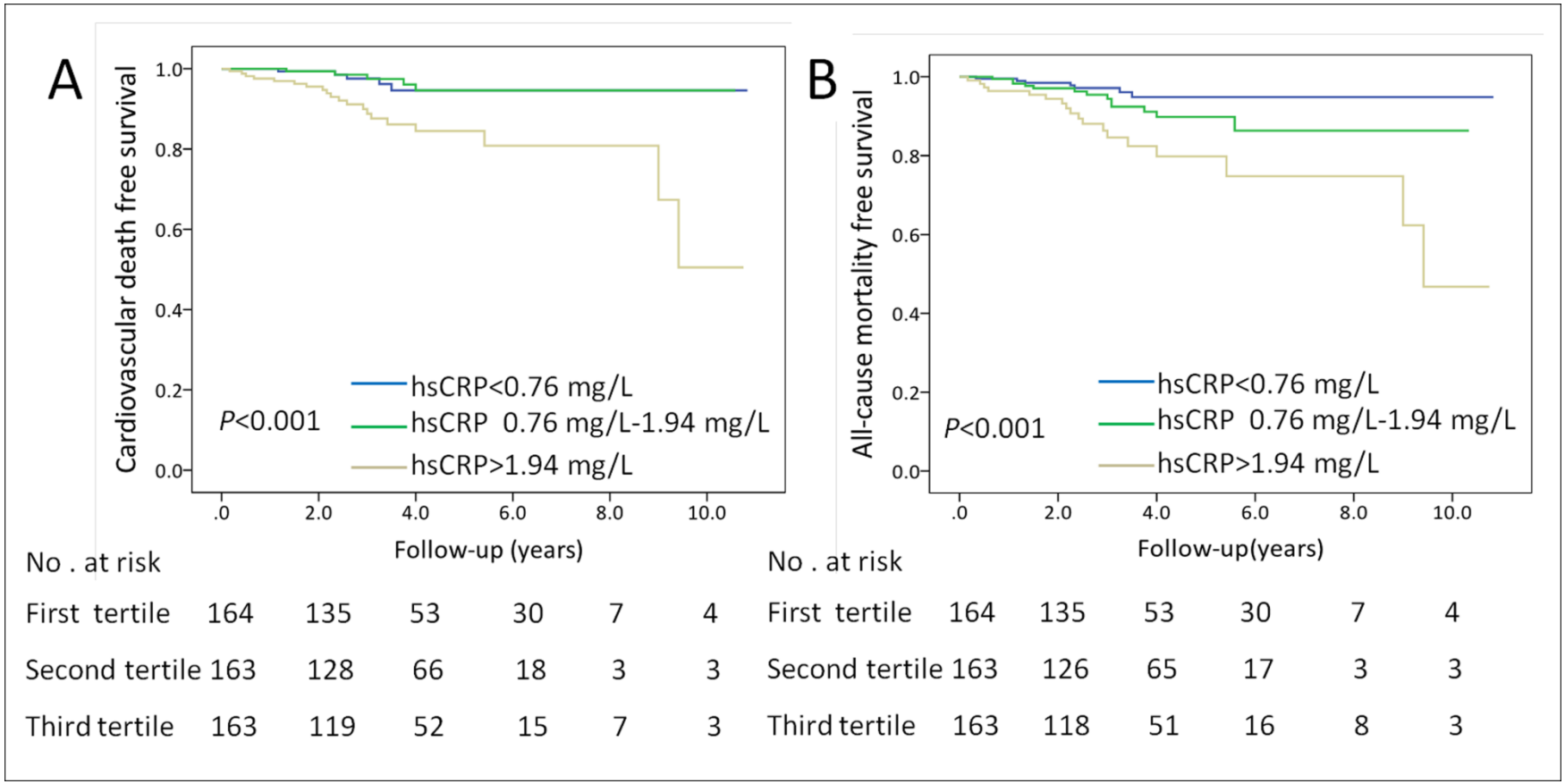

Figure S2: Survival free of cardiovascular death (A) and all-cause mortality (B) in patients with HCM. According to tertiles of hsCRP, subjects in the highest tertile of hsCRP had lower cardiovascular death and all-cause mortality free survival in the patients with HCM. p-values were calculated using the log-rank test. Abbreviations: HCM= hypertrophic cardiomyopathy; hsCRP= high-sensitivity C-reactive protein

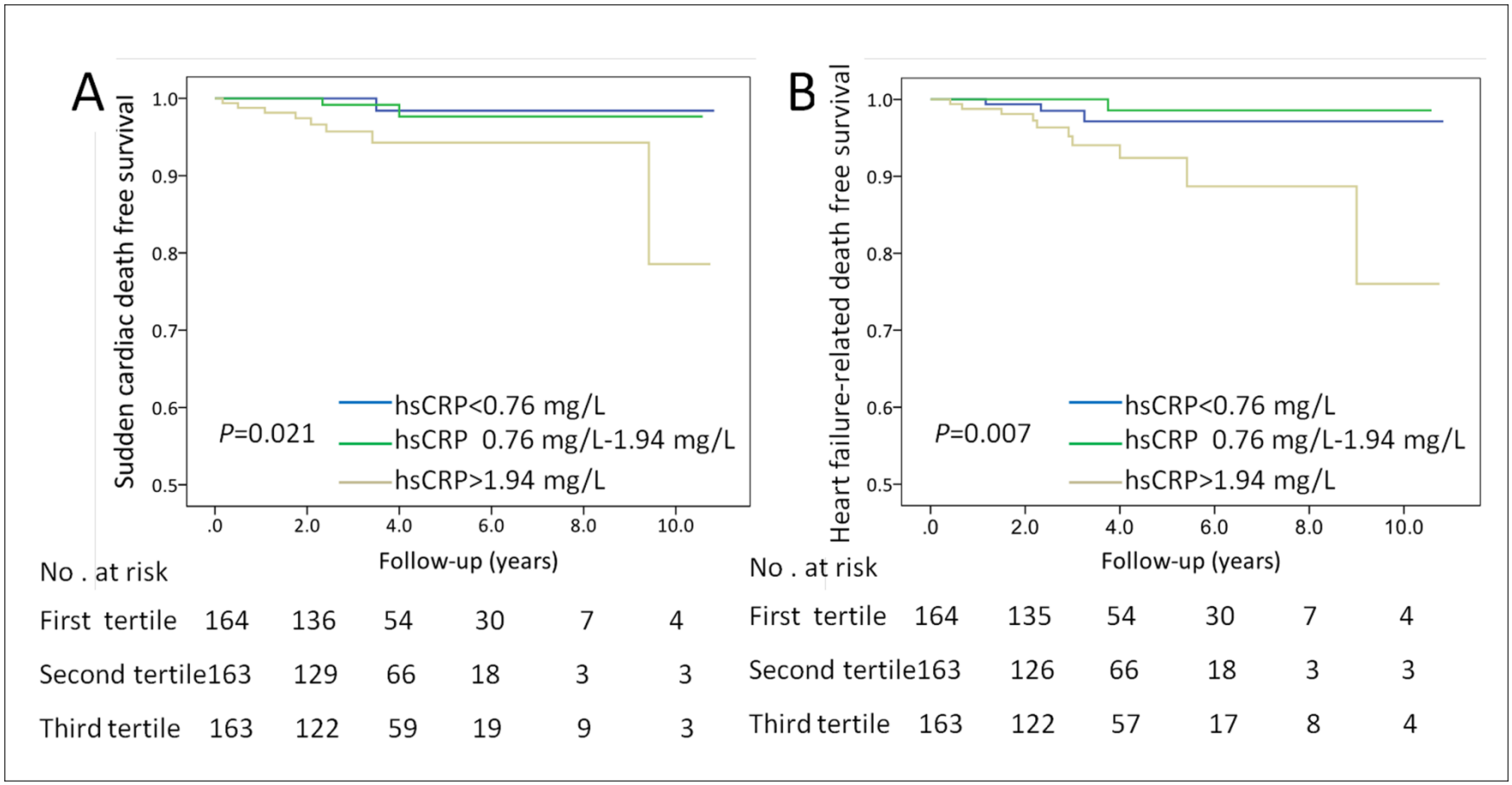

Figure S3: Survival free of sudden cardiac death (A) and heart failure-related death (B) in patients with HCM. According to relative risk category of hsCRP, subjects in the highest tertile of hsCRP had lower sudden cardiac death and heart failure-related death free

survival in the patients with HCM. p-values were calculated using the log-rank test. Abbreviations: HCM= hypertrophic cardiomyopathy; hsCRP= high-sensitivity C-reactive protein.

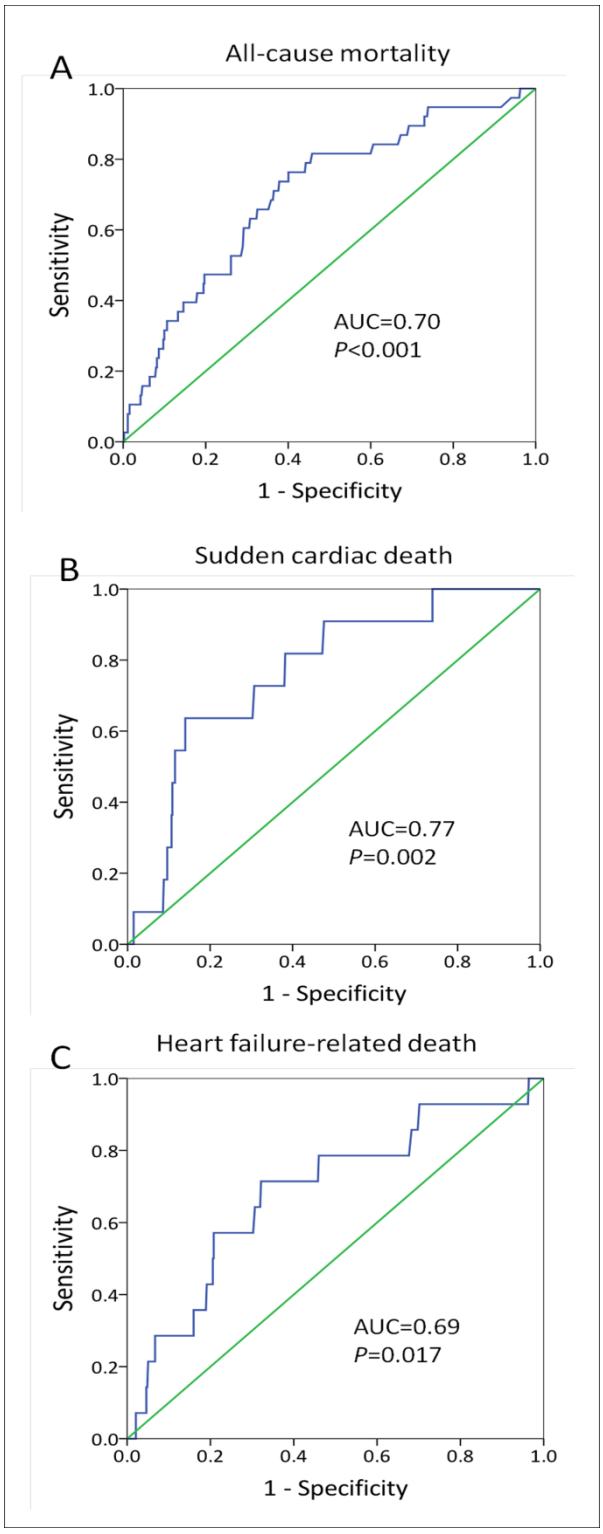

Figure S4: A ROC curve of hsCRP to predict all-cause mortality (A), sudden cardiac death (B), and heart failure-related death (C) in patients with HCM. The AUC was 0.70 for all-cause mortality (95% CI 0.62–0.79, *P*<0.001), 0.77 for sudden cardiac death (95% CI 0.64–0.89, *P* =0.002) and 0.69 for heart failure-related death (95% CI 0.54–0.84, *P* =0.017). Abbreviations: AUC= area under curves; CI= confidence interval; HCM= hypertrophic cardiomyopathy; hsCRP= high-sensitivity C-reactive protein; ROC= receiver operating characteristic.