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Prognostic value of albumin to fibrinogen ratio for mortality in patients with hypertrophic cardiomyopathy

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Abstract

Background Albumin to fibrinogen ratio (AFR), a new inflammatory marker, has emerged as a useful indicator to predict adverse outcomes for several diseases. However, whether AFR could be a new useful indicator to predict mortality in HCM patients remains to be evaluated. The study explored the predictive value of AFR for HCM-related death in adult HCM patients.

Methods A total of 404 HCM patients were eventually enrolled in the study according to the inclusion criteria. Patients were divided into two groups based on the median of baseline AFR. The association between AFR and HCM-related death was analyzed.

Results During a median follow-up of 4.75 years, HCM-related death was observed in 45 patients (11.1%). The incidence of HCM-related death was significantly higher in the low AFR group (log-rank $p < 0.001$). With the high AFR group as reference, the unadjusted hazard ratio (HR) for HCM-related death was 2.97 (95% confidence interval [CI]: 1.53–5.75, $p = 0.001$) in the low AFR group, and after adjusting for potentially confounding variables, the adjusted HR for low AFR group was 3.15 (95% CI: 1.56–6.37, $p = 0.001$). No significant interactions between AFR and other variables were observed in subgroup analysis. Sensitivity analyses in patients with normal albumin and fibrinogen showed similar results.

Conclusion AFR is an independent prognostic factor for HCM-related death, adult HCM patients with a lower AFR have a higher risk of HCM-related death.

Keywords Albumin, Fibrinogen, Hypertrophic cardiomyopathy, Prognosis, Inflammation

Introduction

Hypertrophic cardiomyopathy (HCM) is a common inherited heart diseases in the global, mainly caused by pathogenic mutations in genes encoding proteins associated with myocardium and characterized by left ventricular hypertrophy that cannot been explained by physiological factors, heart disease, systemic disease, metabolic disease, or abnormal loading conditions [1, 2]. The prevalence of HCM in the population is approximately 1:500, and people at any age can be diagnosed with this disease [3]. The clinical symptoms of HCM patients various, some patients without any symptoms,

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while some patients have severe symptoms, such as dyspnea, syncope/pre-syncope, chest pain, and palpitation. Sudden cardiac death (SCD), heart failure, or stroke are the most common adverse outcomes in HCM patients [4]. Although significant advances have been made in the etiology, diagnosis, treatment, and management of HCM over the past few decades, and the overall prognosis of HCM patients have been improved greatly [5], HCM and its related complications remains to bring large burden for patients and healthcare [6]. Therefore, we need to explore more indicators to predict prognosis for HCM patients and to make better risk stratify for those patients who were at high risk of adverse outcomes. Accumulating evidence has found the existence of local or systemic inflammation in HCM in recent years [7–9]. The persistence of inflammatory responses and oxidative stress may result in myocardial fibrosis, which will contribute to myocardial hypertrophy and diastolic dysfunction for HCM patients [10], and then result in adverse outcomes for these patients. Recently, some researches have showed a new inflammatory marker, albumin to fibrinogen ratio (AFR), was associated with adverse outcomes in many diseases, including peritonitis-induced sepsis [11], myocardial infarction [12], ischemic stroke [13], gastric cancer [14], and knee synovitis [15]. However, whether this indicator could be a useful prognostic factor for HCM patients remains unclear. The purpose of the study was to explored the prognostic value of AFR for mortality in Chinese adult HCM patients.

Methods

Study patients

This retrospective single-center cohort study was performed at West China Hospital of Sichuan University, a tertiary center hospital located in Chengdu, China. We included all hospitalized patients in our hospital from December 2008 to November 2018 with a discharge diagnosis containing hypertrophic cardiomyopathy ($n=546$). The diagnosis of HCM is that the presence of one or more left ventricular segments with end-diastolic maximum wall thickness ≥ 15 mm which measured by any cardiac imaging, and the left ventricular outflow tract obstruction (LVOTO) was considered as a gradient ≥ 30 mmHg at rest [16]. When collect data, a researcher first extracted the data from medical records of these patients carefully and then an experienced cardiologist rechecked the data. After rechecking by experienced cardiologist according to the criteria of the European Society of Cardiology [17], 9 patients were excluded: restrictive cardiomyopathy ($n=2$), cardiac amyloidosis ($n=5$), myocarditis ($n=1$) and dilated cardiomyopathy ($n=1$). Based on the inclusion and exclusion criteria, a total of 404 adult patients were enrolled for the present analysis among the remaining 537 patients (Fig. 1).

The study has been registered on the website of Chinese Clinical Trial Registry (https://www.chictr.org.cn/enIndex.aspx; registration number: ChiCTR2000029352). It was conducted according to the principles of the Declaration of Helsinki, and was approved by the Biomedical Research Ethics Committee, West China Hospital of Sichuan University (approval number: 2019–1147). Since this was a retrospective study, informed consent was waived. Other detailed information has been reported in the recently published article [18, 19].

Clinical evaluation

We collected these patients' current history, past medical history, the general condition on admission, the results of peripheral blood test, 12-lead electrocardiogram, doppler echocardiography, and the treatment during hospitalization and discharge medication. Cardiac magnetic resonance imaging and other imaging results were also collected as much as possible. All patients had their peripheral venous blood collected by nurses using a tube with EDTA anticoagulant at the time of hospital admission, and the blood samples were sent to the laboratory within 30–60 min. The level of serum albumin was measured by a fully automatic biochemical immunoassay (Roche Cobas 8000), and the fibrinogen measurement was performed by a fully automatic blood clotting analyzer (Sysmex CS-5100). The normal ranges of serum albumin and fibrinogen in our clinical medical laboratory center, which is accredited by the American CAP Medical Laboratory, are 40–55 g/L and 2.0–4.0 g/L, respectively. The AFR was calculated using the following formula: AFR = serum albumin (g/L) / fibrinogen (g/L).

Study outcomes and follow-up

The study endpoint was HCM-related death, including heart failure (HF)-related death [20], stroke-related death [21, 22], SCD [23], and perioperative death due to ventricular septal myectomy. Follow-up was conducted through medical records or contact with the patients themselves or their relatives by telephone. All patients were followed from the first evaluation up to the endpoint or the most recent evaluation.

Statistical analysis

Patients were divided into two groups according to the median of baseline AFR, which was evaluated by the receiver operating characteristic (ROC) analysis. ROC analysis revealed that the area under curve of AFR (cut-off = 15.94) to predict HCM-related death was 0.650, and the sensitivity and specificity were 73.3% and 52.9%, respectively (Figure S1). Kruskal–Wallis test,

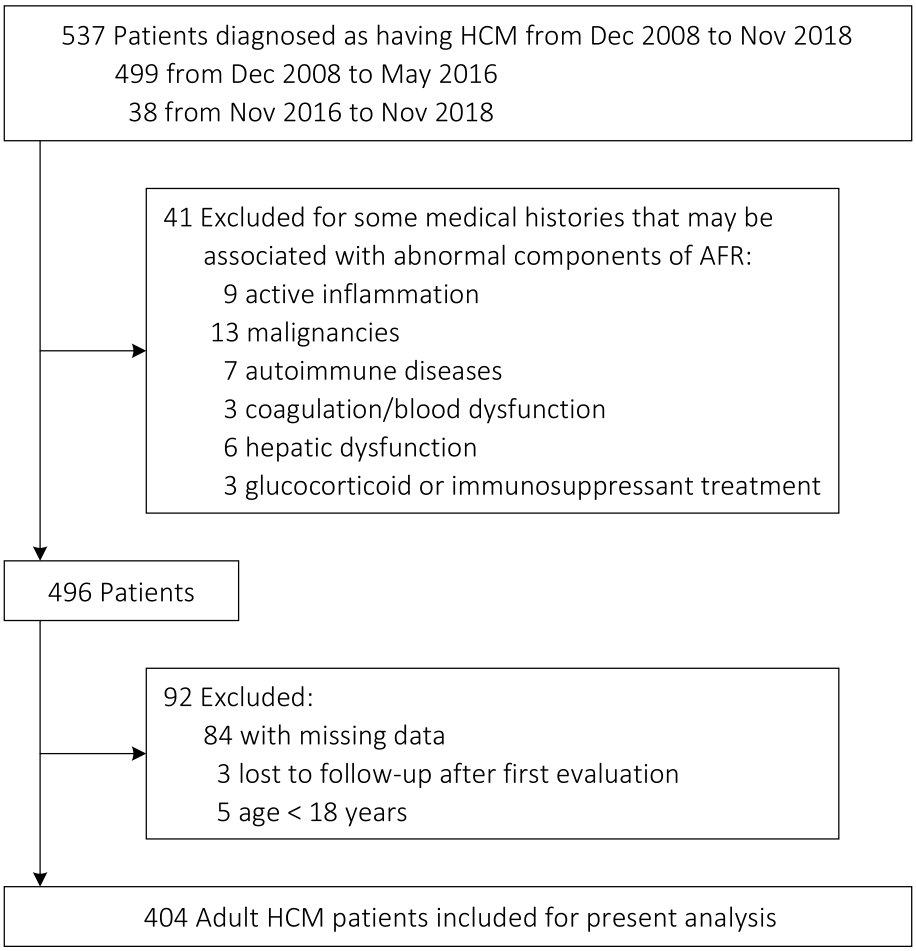

Fig. 1 Study flow diagram

Shapiro–Wilk test, Chi-square test or Fisher exact test were used for data analysis appropriately. For each group, continuous variables were presented as mean ± standard deviation (SD) or median with interquartile range (IQR) appropriately, and categorical variables as number with percentages. Survival curves were constructed using Kaplan–Meier, and the cumulative incidence of HCM-related death was compared using the log-rank test. Cox proportional hazard regression model was applied to perform prognostic analysis. We constructed two multivariate models and variables for inclusion were carefully chosen to ensure parsimony of multivariate models. Model 1, the basic model, adjusted for age and gender. For model 2, we used a backward stepwise modeling approach to select variables, including variables that showed a significant relationship with HCM-related death in univariate analysis ($p < 0.05$) and some clinically relevant variables. Additionally, stratified analysis was performed to assess whether the association between AFR and HCM-related death was consistent in different subgroups. Furthermore, in case of some unknown factors that might affect AFR was not ruled out, we also conducted sensitivity analysis in patients with normal albumin and fibrinogen to assess the relationship between AFR and HCM-related death.

All analyses were performed with R version 4.1.0 (R Project for Statistical Computing). A two-sided p value < 0.05 was considered statistically significant.

Results

Baseline characteristics

The present study comprised 404 patients (male: 54.64%) with a median age of 57.00 (IQR: 46.00–67.00) years. Patients were divided into two groups: low AFR group (AFR < 15.94) and high AFR group (AFR ≥ 15.94). Baseline characteristics of the two groups are summarized in Table 1 with detailed. Patients in the low AFR group were older and the proportion of women is higher. Patients with hypertension and New York Heart Association III/IV were more common in low AFR group. Compared

Table 1 Baseline characteristics

Variable	All ($n=404$)	Low AFR ($n=202$)	High AFR ($n=202$)	*p* value
Age (years)	57.00 (46.00, 67.00)	60.00 (49.00, 68.75)	53.00 (42.25, 65.00)	< 0.001
Gender, male	220 (54.46%)	95 (47.03%)	125 (61.88%)	0.004
Family history of HCM	36 (8.91%)	19 (9.41%)	17 (8.42%)	0.861
Family history of SCD	14 (3.47%)	6 (2.97%)	8 (3.96%)	0.786
NYHA III-IV	143 (35.40%)	84 (41.58%)	59 (29.21%)	0.013
SBP (mmHg)	120.00 (110.00, 136.00)	120.00 (108.00, 140.00)	120.00 (110.00, 132.00)	0.468
DBP (mmHg)	71.00 (65.00, 80.00)	70.00 (64.00, 80.00)	74.00 (65.25, 80.00)	0.305
Smoke	137 (33.91%)	67 (33.17%)	70 (34.65%)	0.834
Symptom				
Dyspnea	237 (58.66%)	123 (60.89%)	114 (56.44%)	0.419
Chest pain	233 (57.67%)	113 (55.94%)	120 (59.41%)	0.546
Syncope/pre-syncope	136 (33.66%)	65 (32.18%)	71 (35.15%)	0.599
Palpitation	159 (39.36%)	79 (39.11%)	80 (39.60%)	1.000
Medical history				
Prior TE	20 (4.95%)	11 (5.45%)	9 (4.46%)	0.819
Vascular diseases	34 (8.42%)	18 (8.91%)	16 (7.92%)	0.858
Hypertension	130 (32.18%)	75 (37.13%)	55 (27.23%)	0.043
Diabetes	29 (7.18%)	17 (8.42%)	12 (5.94%)	0.441
Atrial fibrillation	77 (19.06%)	35 (17.33%)	42 (20.79%)	0.447
Therapy				
Aspirin	77 (19.06%)	39 (19.31%)	38 (18.81%)	1.000
Clopidogrel	26 (6.44%)	13 (6.44%)	13 (6.44%)	1.000
Warfarin	41 (10.15%)	20 (9.90%)	21 (10.40%)	1.000
Beta blockers	305 (75.50%)	147 (72.77%)	158 (78.22%)	0.247
ACEI or ARB	86 (21.29%)	48 (23.76%)	38 (18.81%)	0.274
Intervention of obstruction				0.134
None	356 (88.12%)	184 (91.09%)	172 (85.15%)	
Alcohol septal ablation	42 (10.40%)	15 (7.43%)	27 (13.37%)	
Septal myectomy	6 (1.49%)	3 (1.49%)	3 (1.49%)	
Device				0.650
None	354 (87.62%)	179 (88.61%)	175 (86.63%)	
Pacemaker	17 (4.21%)	9 (4.46%)	8 (3.96%)	
ICD	33 (8.17%)	14 (6.93%)	19 (9.41%)	
Echocardiographic				
LVEDD (mm)	43.00 (40.00, 47.00)	43.00 (39.00, 47.00)	43.00 (40.00, 47.00)	0.729
LAD (mm)	40.00 (36.00, 45.00)	40.00 (36.00, 45.00)	41.00 (36.00, 45.75)	0.220
MWT (mm)	19.00 (17.00, 22.00)	19.00 (16.00, 21.00)	20.00 (17.00, 23.00)	0.003
LVEF (%)	68.00 (63.00, 72.00)	68.00 (63.00, 72.00)	69.00 (64.00, 72.75)	0.389
Resting LVOTG ≥ 30 mm Hg	172 (42.57%)	86 (42.57%)	86 (42.57%)	1.000
Laboratory tests				
Hgb (g/L)	138.50 (126.75, 151.00)	135.00 (123.00, 146.00)	143.00 (131.00, 154.00)	< 0.001
PLT (10^9/L)	146.00 (110.00, 186.00)	153.00 (113.00, 198.50)	141.00 (108.25, 173.75)	0.024
WBCC (10^9/L)	6.31 (5.20, 7.71)	6.46 (5.34, 8.31)	6.12 (5.10, 7.27)	0.017
Albumin (g/L)	42.40 (39.88, 45.02)	41.25 (38.45, 43.40)	43.65 (41.70, 46.30)	< 0.001
ALT (IU/L)	23.00 (16.00, 34.00)	21.00 (15.00, 33.00)	24.00 (18.00, 34.75)	0.020
AST (IU/L)	26.00 (21.00, 32.00)	26.00 (20.00, 33.00)	26.00 (21.00, 32.00)	0.814
Glucose (mmol/L)	5.44 (4.88, 6.43)	5.42 (4.88, 6.53)	5.46 (4.89, 6.33)	0.723
Creatinine (umol/L)	80.60 (67.22, 94.03)	81.00 (66.03, 96.00)	80.25 (68.40, 92.40)	0.837
TG (mmol/L)	1.26 (0.96, 1.87)	1.25 (0.93, 1.70)	1.28 (0.97, 1.98)	0.187

Table 1 (continued)

Variable	All ($n=404$)	Low AFR ($n=202$)	High AFR ($n=202$)	p value
TC (mmol/L)	4.28 (3.56, 4.82)	4.28 (3.64, 4.82)	4.26 (3.50, 4.82)	0.652
HDL-C (mmol/L)	1.27 (1.03, 1.54)	1.29 (1.02, 1.56)	1.26 (1.03, 1.51)	0.668
LDL-C (mmol/L)	2.43 ± 0.76	2.42 ± 0.76	2.44 ± 0.76	0.841
Fibrinogen (g/L)	2.65 (2.26, 3.28)	3.28 (2.87, 3.70)	2.26 (2.02, 2.47)	< 0.001

Values are mean ± SD or median (IQR) or n (%)

Abbreviations: *HCM* Hypertrophic cardiomyopathy, *AFR* Albumin to fibrinogen ratio, *SCD* Sudden cardiac death, *NYHA* New York heart association, *SBP* Systolic blood pressure, *DBP* Diastolic blood pressure, *TE* Thrombo-embolic event, *ACEI* Angiotensin-converting enzyme inhibitor, *ARB* Angiotensin receptor blocker, *ICD* Implantable cardioverter defibrillator, *LVEDD* Left ventricular end-diastolic dimension, *LAD* Left atrial diameter, *MWT* Maximal left ventricular wall thickness, *LVEF* Left ventricular ejection fraction, *LVOTG* Left ventricular outflow tract gradient, *Hgb* Hemoglobin, *PLT* Platelet count, *WBCC* White blood cell count, *ALT* Alanine aminotransferase, *AST* Aspartate aminotransferase, *TG* Triglyceride, *TC* Cholesterol, *HDL-C* High density lipoprotein cholesterol, *LDL-C* Low density lipoprotein cholesterol

with patients in the high AFR group, hemoglobin (Hgb), albumin and alanine aminotransferase (ALT) were lower in the low AFR group, while platelet count (PLT), white blood cell count (WBCC) and fibrinogen were higher in these patients. There was no significant difference in family history of HCM, family history of SCD, vascular diseases, medical history, therapy, intervention of obstruction, AST and creatinine between the two groups.

Study endpoints

During a median follow-up of 4.75 years (IQR: 2.2–6.8 years), HCM-related death occurred in 45 (11.1%) patients, including 22 (5.4%) HF-related death, 8 (2.0%) stroke-related death, 13 (3.2%) SCD and 2 (0.5%) HCM-related postoperative death.

Association between AFR and mortality

The cumulative incidence of HCM-related death was significantly higher in the low AFR group (log-rank p <0.001) (Fig. 2), as well as HF-related death (log-rank p = 0.006) and SCD (log-rank p = 0.036) (Figure S2). Univariate Cox regression analysis indicated that AFR and some other variables could predict HCM-related death, with AFR increased per 1 SD, the HR for HCM-related death was decrease by 36% (Table S1). With the high AFR group as reference, the unadjusted HR for HCM-related death was 2.97 (95% CI: 1.53-5.75, p = 0.001) in the low

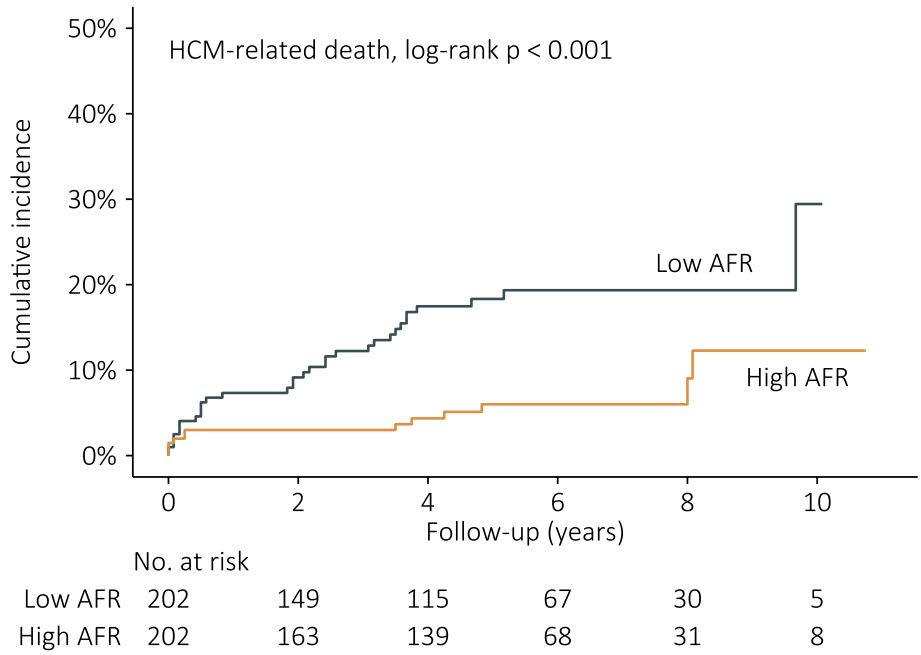

Fig. 2 Baseline AFR and HCM-related death by Kaplan–Meier curve analysis. Patients in the low AFR group (AFR < 15.94) had higher incidence of HCM-related death than in the high AFR group (AFR ≥ 15.94) (log-rank p < 0.001). HCM: hypertrophic cardiomyopathy; AFR: albumin to fibrinogen ratio

AFR group. After adjusting potential confounders, the risk of HCM-related death was approximately three times in the low AFR group than in the high AFR group (fully adjusted HR: 3.15, 95% CI: 1.56-6.37, $p = 0.001$) (Table 2). The results of stratified analysis showed that the mortality rates were consistently higher in the low AFR group in different subgroups and no interaction effect was observed between AFR and other variables for mortality prediction (Fig. 3).

Sensitivity analysis

Sensitivity analysis was performed in patients with normal albumin and fibrinogen ($n = 251$) and the results were consistent with the main analysis. There were 16 (6.3%) patients occurred in HCM-related death. Kaplan–Meier analysis demonstrated the incidence of HCM-related death was higher in the low AFR group (log-rank $p = 0.008$) (Figure S3). With the high AFR group as reference, the unadjusted HR for HCM-related death was 4.72 (95% CI:1.34–16.62, $p = 0.016$) in the low AFR group. After adjusting potential confounders, the adjusted HR for HCM-related death was 9.21 in the low AFR group (95% CI:1.97–43.10, $p = 0.005$) (Table S2).

Correlation

AFR was negatively correlated with age ($r = -0.189$, $p < 0.001$) and WBCC ($r = -0.102$, $p = 0.041$), and positively correlated with Hgb ($r = 0.140$, $p = 0.005$), ALT ($r = 0.254$, $p < 0.001$), AST ($r = 0.245$, $p < 0.001$) and maximal left ventricular wall thickness ($r = 0.121$, $p = 0.015$). In addition, AFR was no correlation with PLT, lipid, left ventricular end-diastolic dimension, left atrial diameter, and left ventricular ejection fraction (Table S3).

Table 2 Associations of AFR and HCM-related death

	High AFR	Low AFR
No. of patients (n)	202	202
Endpoints (n)	12	33
Follow-up (PYs)	995.4	904.5
Mortality rates[a] (95% CI)	1.2 (0.5–1.9)	3.6 (2.4–4.9)
Unadjusted HRs (95% CI), p	1.00 (ref)	2.97 (1.53–5.75), 0.001
Adjusted HRs (95% CI), p		
model 1	1.00 (ref)	2.80 (1.43–5.48), 0.003
model 2	1.00 (ref)	3.15 (1.56–6.37), 0.001

Model 1 with adjustment for age and gender

Model 2 with adjustment for age, gender, dyspnea, NYHA III-IV, family history of SCD, AF, AST, TG, MWT, and resting LVOTG ≥ 30 mm Hg

Abbreviations: *PYs* Person-years, *CI* Confidence interval, *HR* Hazard ratio, other abbreviations as in Table 1

[a] Per 100 PYs

Discussion

The present study showed that AFR was a significant predictor for HCM-related death in adult HCM patients. Stratified analysis in subgroups and sensitivity analysis in patients with normal albumin and fibrinogen demonstrated similar results. To our knowledge, the present study firstly illustrated the prognostic value of AFR in patients with HCM.

In recent years, more and more researches supported the association between inflammation and HCM [7, 8]. Compared with healthy patients, several inflammatory markers in peripheral blood were increased in HCM patients, such as high-sensitivity C-reactive protein (hs-CRP) [9], interleukin-6(IL-6) [24] and tumour necrosis factor-α [25]. Persistent cardiac inflammation will contribute to myocardial fibrosis and remodeling, as well as ventricular diastolic dysfunction [7, 8]. Myocardial fibrosis will cause electromechanical disturbances in the myocardium, and block the supplement of nutrients to the myocardium in some extent, resulting in a vicious cycle between inflammation, fibrosis and myocyte death [8, 26]. Meanwhile, myocardial fibrosis is one of the major determinants of SCD, heart failure and ventricular tachycardia [27–29], which are manifestations of adverse outcomes in patients with HCM. Therefore, inflammatory markers can be used as one of the indicators to assess disease severity and predict adverse outcomes of patients with HCM. In recent years, many studies have explored the relationship between inflammatory markers and the prognosis of HCM patients. Study performed by Burak et al. suggested that monocyte count to high-density lipoprotein cholesterol ratio (MHR) was an independent predictor for prognosis of patients with HCM, patients with higher MHR had higher risk of cardiovascular death and malignant arrhythmic events [30]. Zhu et al. explored the relationship between hs-CRP and the prognosis of HCM patients ($n = 490$), they found that patients with higher plasma hs-CRP have higher risk of adverse outcomes, including cardiovascular death, SCD and all-cause mortality [9]. Our team also found systemic immune-inflammation index (platelet × neutrophil/lymphocyte ratio) was a significant risk factor for all-cause mortality in HCM patients [18].

Albumin is produced primarily by the liver and usually as a negative protein in the acute-phase. Its plasma concentration is mainly influenced by several factors, including the rate of albumin synthesis, catabolism, and loss by renal [31]. Many studies have showed the level of albumin was associated with adverse outcomes of many diseases, including heart failure, atrial fibrillation, ischemic heart disease, myocardial infarction, stroke and venous thromboembolism [31–33]. In our cohort study, the level of AST and creatinine between the two groups was not

Subgroups	Low AFR group *Events/patients (%)*	High AFR group *Events/patients (%)*	Adjusted HR (95% CI)	p	p for interaction
Gender					
Male	16/95 (16.80%)	5/125 (4.00%)	4.96 (1.62-15.18)	0.005	0.678
Female	17 /107 (15.90%)	7/77 (9.09%)	3.70 (1.37-9.97)	0.010	
Age (years)					
<57	11/77 (14.30%)	7/116 (6.03%)	3.07 (1.11-8.48)	0.030	0.616
≥57	22/125 (17.60%)	5/86 (5.81%)	4.13 (1.39-12.21)	0.011	
NYHA III-IV					
No	15/118 (12.70%)	7/143 (4.90%)	3.96 (1.43-10.99)	0.008	0.881
Yes	18/84 (21.40%)	5/59 (8.47%)	3.14 (1.07-9.21)	0.037	
Hypertension					
No	23/127 (18.10%)	10/147 (6.80%)	3.19 (1.42-7.51)	0.005	0.669
Yes	10/75 (13.30%)	2/55 (3.64%)	4.54 (0.81-25.65)	0.086	
Atrial fibrillation					
No	21/167 (12.60%)	3/160 (1.88%)	6.51 (1.89-22.48)	0.003	0.127
Yes	12/35 (34.30%)	9/42 (21.40%)	2.72 (0.94-7.88)	0.065	
Warfarin					
No	26/182 (14.30%)	7/181 (3.87%)	3.76 (1.56-9.02)	0.003	0.621
Yes	7/20 (35.00%)	5/21 (23.80%)	3.47 (0.26-45.61)	0.344	
Beta blockers					
No	9/55 (16.40%)	4/44 (9.09%)	2.10 (0.54-8.19)	0.288	0.488
Yes	24/147 (16.30%)	8/158 (5.06%)	4.99 (1.97-12.62)	<0.001	
Hgb (g/L)					
<138	23/114 (20.20%)	6/74 (8.11%)	4.12 (1.47-11.56)	0.007	0.530
≥138	10/88 (11.40%)	6/128 (4.69%)	2.72 (0.88-8.39)	0.081	
AST (IU/L)					
<26	9/100 (9.00%)	3/96 (3.12%)	3.24 (0.70-14.90)	0.131	0.159
≥26	24/102 (23.50%)	9/106 (8.49%)	3.26 (1.45-7.31)	0.004	
TG (mmol/L)					
<1.26	20/104 (19.20%)	8/96 (8.33%)	3.01 (1.18-7.67)	0.021	0.101
≥1.26	13/98 (13.30%)	4/106 (3.77%)	7.17 (1.70-30.14)	0.007	
LVEDD (mm)					
<43	20/97 (20.60%)	9/96 (9.38%)	2.51 (1.08-5.79)	0.032	0.170
≥43	13/105 (12.40%)	3/106 (2.83%)	4.82 (1.11-20.94)	0.036	
LVEF (%)					
<68	15/93 (16.10%)	9/90 (10.00%)	2.02 (0.79-5.16)	0.141	0.474
≥68	18/109 (16.50%)	3/112 (2.68%)	5.56 (1.51-20.46)	0.010	

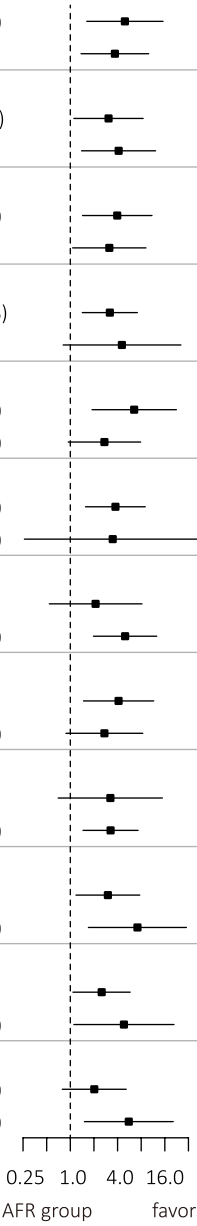

Fig. 3 Stratified analyses of HCM-related death. Each stratification adjusted for age, gender, dyspnea, NYHA class, AF, AST, TG, LVEDD, LVEF, resting LVOTG ≥ 30 mm Hg, except the stratification factor itself. The p value for interaction represents the likelihood of interaction between variable and AFR. Abbreviations as in Tables 1 and 2

significantly difference, which indicated there were no significant difference about the liver function and renal function between the two groups patients. Therefore, the main factors affecting serum albumin are inflammation and malnutrition in these patients. In addition, some studies have supported that malnutrition and inflammation play a major role in low level of serum albumin [32, 34] and the influence of inflammation on serum albumin level seems to be stronger [35, 36]. Fibrinogen, a positive acute-phase protein, produced in the liver on the stimulation of IL-6 and some other inflammatory markers, and its levels in plasma will increase with the presence of infection and inflammation [37, 38]. Several studies have demonstrated that plasma fibrinogen is a predictor for

cardiovascular disease [39, 40]. AFR, a novel inflammatory biomarker, has been widely proposed as a prognostic marker in various diseases [11–15]. AFR takes serum albumin (a negative acute-phase protein) and fibrinogen (a positive acute-phase protein) into account, it could better reflect the status of inflammation than alone. Gabay et al. [41] found anemia and hypoalbuminemia due to inflammation are common among hospitalized patients. In our study, patients with lower AFR value had lower levels of Hgb and albumin, which also demonstrating the presence of inflammation in these patients indirectly. Despite the lack of diagnostic specificity, AFR is still a useful indicator which reflect the presence of inflammatory process of patients, it could be regarded as a predictor for many diseases which associated with inflammation. Controlling the inflammatory response as much as possible may improve myocardial fibrosis in patients with HCM and reduce the incidence of adverse outcomes.

In this study, the rate of HCM-related death was about 11.1%, and the event rates of SCD, HF-related death, stroke-related death, and HCM-related postoperative death were 3.2%, 5.4%, 2.0%, 0.5%, respectively. In a large longitudinally cohort, which from two American HCM centers ($n=1000$), Maron et al. found the rate of HCM-related death was 4.0%, and the mortality rates of HF, SCD, embolic stroke, and HCM-related postoperative were 1.7%, 1.7%, 0.2%, 0.4%, respectively [42]. Zhu et al. used database from Fuwai Hospital of China to study the relationship between hs-CRP and the prognosis of HCM patients, they showed the rate of cardiovascular death was 6.1%, including 2.2% SCD, 2.9% HF-related death and 1.0% stroke-related death. The mortality rates between these studies are different, and the likely reasons are the differences in ethnicity and baseline characteristics of the study population. The HCM-related death rate in our study was higher than other studies, which may due to these patients were relatively serious and many patients were referred from local hospitals.

The study has several limitations. Firstly, this was a single center, retrospective study, and those patients were from China, lack of region diversification and race comparison. Secondly, the most widely used inflammatory indicators including the plasma CRP, procalcitonin, erythrocyte sedimentation rate, or IL-6 were not determined, thus the associations between AFR and some well-established inflammation indicators are missing. Thirdly, some important data, including non-sustained ventricular tachycardia and cardiac magnetic resonance (CMR) imaging, were lacking for some patients, which resulting in the association between AFR and HCM Risk-SCD score and the sequences of CMR cannot be explored. Finally, AFR was evaluated only initial evaluation, whether the dynamic changes of AFR could still predict HCM-related death is unclear. However, AFR is a simple and inexpensive routine laboratory test, and it can provide relevant prognostic information for patients with HCM. It could help physician with the risk stratification, facilitate follow-up. Therefore, AFR should serve as a potential screening tool for HCM patients to identify patients at higher risk for adverse outcomes.

Conclusion

The present study indicated that AFR is an independent prognostic factor for HCM-related death, a lower AFR is associated with increased risk of HCM-related death in adult HCM patients. It is unknown whether prevention and correction of low AFR could improve outcome of patients with HCM, further prospective studies are needed to assess the relationship between AFR and the prognosis of HCM.

Abbreviations

HCM	Hypertrophic cardiomyopathy
AFR	Albumin to fibrinogen ratio
SCD	Sudden cardiac death
TE	Thrombo-embolic event
LVEDD	Left ventricular end-diastolic dimension
LAD	Left atrial diameter
MWT	Maximal left ventricular wall thickness
LVEF	Left ventricular ejection fraction
LVOTG	Left ventricular outflow tract gradient
Hgb	Hemoglobin
PLT	Platelet count
WBCC	White blood cell count
HDL-C	High density lipoprotein cholesterol
LDL-C	Low density lipoprotein cholesterol

Supplementary Information

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Additional file 1: Figure S1. ROC analysis revealed that the AUC of AFR (cut-off = 15.94) to predict HCM-related death was 0.650, and the sensitivity was 73.3%, specificity = 52.9%. ROC: Receiver operating characteristic; AUC: Area Under Curve; AFR: albumin to fibrinogen ratio; HCM: hypertrophic cardiomyopathy.

Additional file 2: Figure S2. Kaplan–Meier survival curve analysis for HF-related death (A) and SCD (B) by baseline AFR.

Additional file 3: Figure S3. Kaplan–Meier survival curve analysis in HCM patients with normal albumin and fibrinogen.

Additional file 4: Table S1. Univariate Cox regression analyses for HCM-related death.

Additional file 5: Table S2. Associations of AFR and HCM-related death in patients with normal albumin and fibrinogen.

Additional file 6: Table S3. Relationships between AFR and other clinical parameters.

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Authors' contributions
SH conceived and supervised the study and performed statistical analysis of the data. LY was involved in the procedure and wrote the main body of the manuscript. CB participated in the discussion on the interpretation of the research content and took part in the procedure. YZ revised this paper. HY, MX, ZQ and MM participated in data collection. All authors critically revised and approved the final version of the manuscript. All authors read and approved the final manuscript.

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Availability of data and materials
The datasets used during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
This study was approved by the Biomedical Research Ethics Committee, West China Hospital of Sichuan University (approval number: 2019–1147), and the informed consent was waived by the Biomedical Research Ethics Committee, West China Hospital of Sichuan University, because of the retrospective nature of the study.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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