

ORIGINAL RESEARCH

Association Between Depression and Clinical Outcomes in Patients With Hypertrophic Cardiomyopathy

Hui-Lin Hu , MD*; Hao Chen, MD*; Chun-Yan Zhu, MD*; Xin Yue, MD; Hua-Wei Wang, MD; Gang Qian, MD; Chang-Lin Zhai , PhD; Chao-Jie He , MD

BACKGROUND: Hypertrophic cardiomyopathy (HCM) is considered to be the most common cause of sudden death in young people and is associated with an elevated risk of mood disorders. Depression has emerged as a critical risk factor for development and progression of coronary artery disease; however, the association between depression and HCM outcomes is less clear. We sought to examine the impact of depression on clinical outcomes in patients with HCM.

METHODS AND RESULTS: Between January 2014 and December 2017, 820 patients with HCM were recruited and followed for an average of 4.2 years. End points were defined as sudden cardiac death (SCD) events and HCM-related heart failure events. A Chinese version of the Structured Clinical Interview followed the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* and was used to diagnose depression. During the follow-up period, SCD events occurred in 75 individuals (21.8 per 1000 person-years), and HCM-related heart failure events developed in 149 individuals (43.3 per 1000 person-years). Kaplan–Meier cumulative incidence curves showed a significant association of depression disorders with SCD events (log-rank $P=0.001$) and HCM-related heart failure events (log-rank $P=0.005$). A multivariate Cox regression analysis indicated that depression was an independent predictor of SCD events and HCM-related heart failure events (41.9 versus 21.7 per 1000 person-years; adjusted hazard ratio [HR], 1.9; 95% CI, 1.6–2.3; $P<0.001$; and 69.9 versus 38.6 per 1000 person-years; HR, 1.8; 95% CI, 1.6–2.1; $P<0.001$, respectively).

CONCLUSIONS: Depression is common among patients with HCM. The diagnosis of depression is significantly and independently associated with an increased risk of SCD events and heart failure events in patients with HCM.

Key Words: depression ■ hypertrophic cardiomyopathy ■ outcomes

Hypertrophic cardiomyopathy (HCM) is a common autosomal dominant cardiac disease (1:500) and a major cause of sudden death in young people. It is characterized by the presence of left ventricle wall hypertrophy (for adults, thickness ≥ 15 mm in 1 or more left ventricular myocardial segments) that is not explained simply by abnormal loading conditions.^{1–3} The most serious complication is HCM-related sudden death caused by ventricular arrhythmias or death after

heart failure or stroke.^{4,5} Several clinical parameters have been recognized as major risk factors of sudden cardiac death (SCD) in HCM, including unexplained syncope, family history of SCD, ventricular tachycardia (VT) during Holter monitoring, and maximum left ventricle wall thickness >30 mm.^{6,7} In most patients, HCM-related heart failure deaths occurred more frequently in middle age and beyond, as a result of a lifetime process of progressive and adverse myocardial

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CLINICAL PERSPECTIVE

What Is New?

- Depression is frequent in patients with hypertrophic cardiomyopathy.
- Depression is associated with an increased risk of sudden cardiac death events and heart failure events in patients with hypertrophic cardiomyopathy.

What Are the Clinical Implications?

- This study supports the viewpoint that depression predicts adverse clinical outcomes in patients with hypertrophic cardiomyopathy.
- Further study should be encouraged to validate whether psychological intervention for depression can improve clinical outcomes in this population.

Nonstandard Abbreviations and Acronyms

HCM	hypertrophic cardiomyopathy
LVOTO	left ventricular outflow tract obstruction
SCD	sudden cardiac death

remodeling, featured by myocardial fibrosis and wall thinning.⁸

Depression is the most common emotional disorder and currently affects an estimated 350 million people.⁹ It is characterized by significant impairment of social and occupational functioning, and the patients may experience remissions and relapses throughout their lives.¹⁰ Accumulating evidence has consistently shown that depression is a risk factor for mortality and adverse clinical outcomes in patients with coronary heart disease and heart failure.¹¹ Over the past 2 decades, numerous prospective studies have provided support for an association of depression with SCD in the elderly and patients with acute myocardial infarction or stable coronary artery disease.^{12–14} Studies on the mental health of patients with HCM showed that these individuals are under more psychological distress than is the general population, and have impaired quality of life and sociability.^{15,16} Despite the high prevalence and poor clinical prognosis, psychological intervention is frequently neglected in this population.

Thus far, no specific data on the prevalence of depressive disorder in patients with HCM exist. Furthermore, the relationship between depression and prognosis has not hitherto been examined in patients with HCM. Therefore, we sought to explore the

prevalence of depression in patients with HCM and determine the association between depression and clinical outcomes in this population.

METHODS

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Study Population and Design

We consecutively enrolled 856 patients admitted to the Jiaying First Hospital Heart Center from January 2014 to December 2017 with a diagnosis of HCM. In accordance with the European Society of Cardiology guidelines, patients who were aged >18 years and fulfilled the diagnostic criteria of HCM were eligible for inclusion if they had an unexplained hypertrophied left ventricle with either a maximum wall thickness of ≥ 15 mm on 2-dimensional echocardiography. If patients presented with a lesser degree of wall thickness (≥ 13 mm), the diagnosis of HCM required assessments of other information, including a family history of first-degree relatives, clinical symptoms, and an abnormal electrocardiogram.⁶ The major exclusion criteria were (1) patients with cognitive impairment or senile dementia, (2) patients with a malignant tumor whose expected survival time was <1 year, (3) patients with severe renal disease or chronic obstructive pulmonary disease, (4) patients whose age was ≤ 18 years old, and (5) patients who refused to participate in the study. All participants provided informed consent before recruitment. The study protocol was approved by the Ethics Committee of the Affiliated Hospital of Jiaying University based on the Helsinki declaration. The median follow-up from the depression ascertainment to the latest evaluation (clinical visit, WeChat, or telephone interview) or end point event was 3.8 years (interquartile range, 1.8–4.4 years).

Clinical Characteristics

All participants completed a standardized medical history questionnaire, and baseline information included demographics, primary disease, New York Heart Association (NYHA) classification, echocardiography, electrocardiography, Holter monitor data on admission, and discharge medications with β -blockers, renin-angiotensin-aldosterone system inhibitors, calcium channel blockers, amiodarone, diuretics, and antidepressant medicine. Implantable cardioverter defibrillator (ICD) implantation is recommended in patients who have had cardiac arrest because of ventricular fibrillation or with an estimated 5-year risk of SCD of $\geq 6\%$.¹⁷ Doppler ultrasound was

performed using a multifunctional echocardiography machine (ACUSON X300PE; Siemens Co., USA) in all patients and was recorded in detail (eg, maximum left ventricular wall thickness, left ventricular ejection fraction, and instantaneous peak Doppler left ventricular outflow tract pressure gradient).

Risk Factors for Sudden Death

Each patient underwent a detailed medical history, physical examination, ambulatory ECG, and echocardiography. Then, we identified risk factors for SCD as follows: (1) unexplained syncope, (2) family history of SCD, (3) nonsustained VT on Holter, (4) maximum LV wall thickness ≥ 30 mm, and (5) left ventricular outflow tract obstruction (LVOTO).⁶ An abnormal response of blood pressure during exercise was excluded as a prespecified risk factor since it has not been independently related to SCD in the majority of multivariate survival analyses.¹⁸ In addition, its prognostic significance in individuals >40 years of age is unclear.¹⁹

Assessment of Depression

All patients were assessed for depressive symptoms during their first clinic visit or hospitalization and 12 months later using the 17-item Hamilton Depression Rating Scale (HDRS), a well-validated instrument in the cardiac populations. The measure consists of 9 items. Patients describe how frequently they experienced symptoms over the past few months using a 4-point scale that ranges from “0” (not at all) to “3” (nearly every day).²⁰ The total scores range from 0 to 27. Individuals with an HDRS score of ≥ 5 were given the Chinese version of the Structured Clinical Interview, for diagnosis of depression.²¹ It follows the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (DSM-5). In other words, the HDRS is a self-report inventory designed to screen for depressive mood rather than to determine diagnosis of major depression. Also, the Structured Clinical Interview allows trained psychologists to provide reliable psychiatric diagnoses based on DSM-5. The semistructured psychiatric interview was administered by psychologists who were blinded to the study design.

Primary and Secondary End Points

The prespecified primary end point in the current study was SCD. SCD was characterized as an unexpected sudden collapse occurring within 1 hour of the onset of symptoms in patients with a stable or uneventful clinical condition. In addition, potentially lethal cardiovascular events in which patients either were revived from cardiac arrest (with documented

VT or ventricular fibrillation) or ICD discharge were treated as equivalent to SCD events in the current data analysis.²² ICD therapy was regarded as an appropriate discharge triggered by ventricular fibrillation or VT (rate, ≥ 180 bpm). Death was confirmed by the death certificate. The secondary end points were HCM-related heart failure events, defined as a composite of heart failure death, cardiac decompensation, heart failure hospitalization, and stroke. Heart failure death was defined as death in the presence of end-stage heart failure or heart transplantation. Cardiac decompensation was defined as patients with NYHA functional class I or II that progressed to class III or IV during the follow-up period.^{23,24} HCM-related stroke was judged to be a direct consequence of embolic events related to HCM in the context of atrial fibrillation in most cases.²⁵ All participants were contacted by clinic visit, WeChat, and/or telephone interview quarterly after the initial assessment. For any medical records, interview reports regarding cause of death, and death certificates were retrieved from patients' first-degree relatives. Two cardiologists who were blind to patients' depression status reviewed all pertinent clinical and death documentation and adjudicated cardiovascular events.

Statistical Analysis

Statistical analyses were carried out using SPSS 23.0 for Windows (SPSS Inc, Chicago, IL). Continuous variables were summarized as mean \pm SD or median (25th–75th percentile) and compared using the *t* test or Mann–Whitney *U* test. The difference among multiple groups was compared with ANOVA. Categorical variables were presented as frequency and percentage and compared using χ^2 test or Fisher exact test, as appropriate. Cumulative event-free survival curves comparing patients with or without depression were examined using Kaplan–Meier analysis, and differences between groups were tested by the log-rank statistic. Univariate and multiple Cox proportional hazards models were used to determine the relationship between depression and clinical outcomes. The proportional hazard assumption was examined by adding an interaction term of follow-up duration and covariates in the models for continuous variables. As for categorical variables, the proportional hazard assumption was checked graphically for Cox regression before proceeding, and no violation was found. The multivariate model was conducted to adjust for potential confounders using a stepwise selection method with an entrance and stay criteria of $P < 0.10$, forcing the number of traditional SCD factors into all models a priori. Thus variables entered into the multivariable model for SCD events include depression (first assessment), unexplained syncope, family history of SCD, nonsustained VT on Holter,

LVOTO, and maximum LV wall thickness >30 mm. After the model was completed, the remaining candidate variables (ie, β -blockers, atrial fibrillation, and rennin-angiotensin-aldosterone system inhibitors) were retested separately with a sensitivity analysis to examine their influence on effect estimates. Multivariable models were built individually for SCD and heart failure events in a similar pattern. Hazard ratios (HR) and 95% CI were calculated. We also divided HDRS scores into 4 categories: <8, 8 to 13, 14 to 18, and ≥ 19 , and assessed the HDRS predictability for SCD in patients with HCM. Two-sided $P < 0.05$ was considered a significant difference.

RESULTS

Baseline Characteristics

Of 856 patients diagnosed with HCM in the Jiaying Heart Center between January 2014 and December 2017, 36 were excluded from the current study: 2 with dementia, 4 with a malignant tumor, 8 with severe

chronic obstructive pulmonary disease or renal disease, 10 who were age ≤ 18 years old, and 12 who refused to participate in the study. Therefore, the study cohort included 820 patients, of which 192 (23.4%) patients had a diagnosis of depression (Figure 1). Among the overall patients, 387 (47.2%) participants had HDRS scores ≥ 5 . The clinical and demographic characteristics of the study population are shown in Table 1. No statistically significant differences existed in the clinical and demographic characteristics between the 2 groups. The mean patient age was 48.2 ± 12.8 years (range, 18–81 years), 470 (57.3%) were male, and the initial NYHA class was 1.5 ± 0.8 . Three hundred sixty-one patients had 1 or more conventional risk factors for SCD. Only 27 patients with depression (14.1%) agreed to take antidepressants with selective serotonin reuptake inhibitors; the remaining 165 patients (85.9%) refused to take medicine or chose to go to the psychiatric hospital for confirmation. Mean HDRS score in depressed and nondepressed patients at the first assessment were 14.9 ± 7.9 and 4.7 ± 3.2 , and after 12 months were 14.4 ± 7.8 and 4.5 ± 3.1 , respectively.

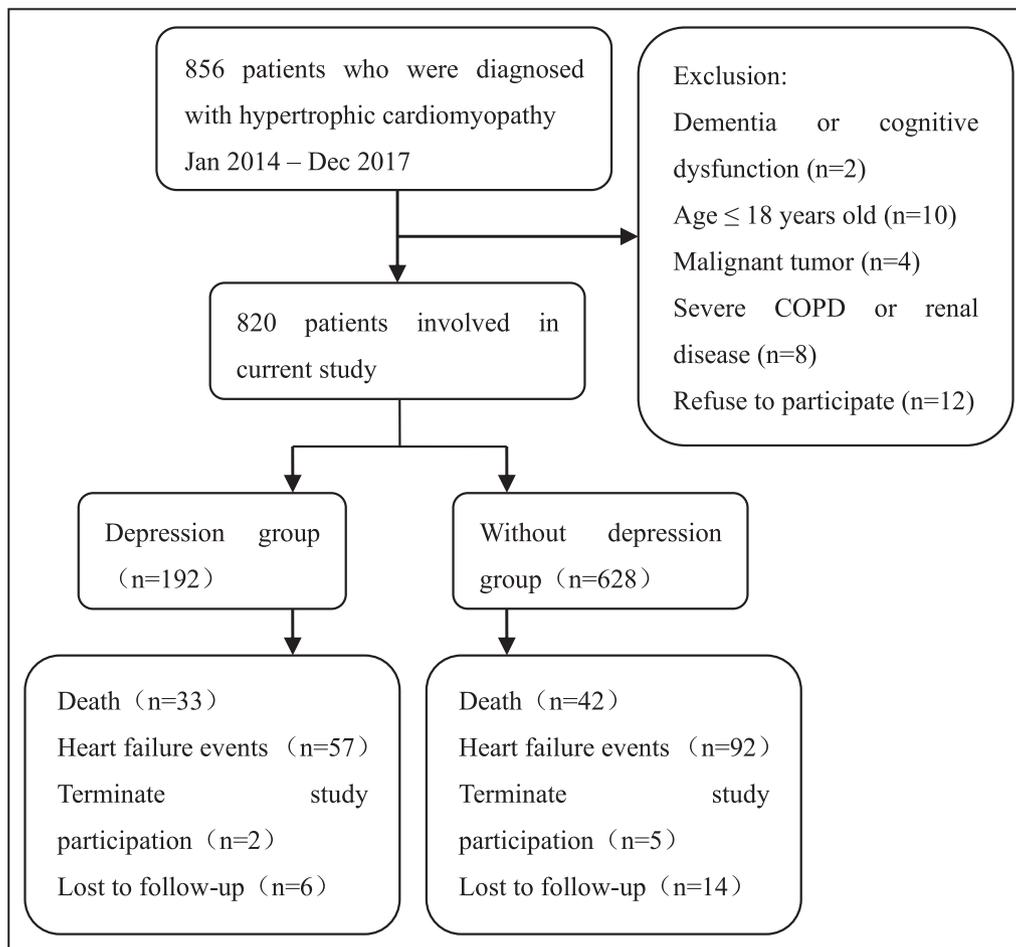


Figure 1. Flowchart of the screening process and dropouts of the current cohort study. COPD indicates chronic obstructive pulmonary disease.

Table 1. Demographic and Clinical Characteristics of the Study Population With or Without Depression

Characteristics	Depression* (n=192)	Without Depression (n=628)	P Value
Demographics			
Age, mean±SD, y	48.4±12.9	47.9±12.7	0.65
Male, n (%)	104 (54.3)	366 (58.3)	0.31
BMI, mean±SD, kg/m ²	24.4±3.7	24.7±3.8	0.62
Maximum LV thickness, mean±SD, mm	20.1±4.7	20.1±4.6	0.87
NYHA class, n (%)			
I/II	171 (89.1)	554 (88.2)	0.75
III/IV	21 (10.9)	74 (11.8)	0.75
Comorbid condition, n (%)			
Atrial fibrillation	18 (9.4)	60 (9.6)	0.94
Stroke history	3 (1.6)	7 (1.1)	0.91
Diabetes mellitus	25 (13.0)	86 (13.7)	0.81
Hypertension	34 (17.7)	105 (16.7)	0.75
Risk factors, n (%)			
Nonsustained VT on Holter	35 (18.2)	112 (17.8)	0.90
Unexplained syncope	20 (10.4)	53 (8.4)	0.42
Family history of SCD	26 (13.5)	79 (12.6)	0.73
LVOTO	41 (21.3)	142 (22.6)	0.71
Maximum LV wall thickness ≥30 mm	10 (5.2)	29 (4.6)	0.74
Echocardiography, mean±SD			
LVEF (%)	61.2±6.2	63.2±6.0	0.31
Left atrial diameter	40.1±9.2	39.8±9.0	0.26
ICD implantation			
ICD, n (%)	20 (10.4)	65 (10.4)	0.98
Medications at discharge, n (%)			
β-blockers	117 (60.9)	401 (63.8)	0.46
Calcium channel blockers	33 (17.2)	112 (17.8)	0.84
RAAS inhibitors	31 (16.1)	99 (15.8)	0.90
Diuretic	15 (7.8)	44 (7.0)	0.71
Amiodarone	5 (2.6)	17 (2.7)	0.94
Antidepressant	27 (14.1)	0 (0)	<0.001
Laboratory parameters on admission, mean±SD			
Pro-BNP, pg/mL	582.0±482.0	625.1±494.5	0.80
Creatinine, μmol/L	74.1±13.8	75.1±14.0	0.66
HDRS score	14.9±7.9	4.7±3.2	<0.001

BMI indicates body mass index; HDRS, 17-item Hamilton Depression Rating Scale; ICD, implantable cardioverter defibrillator; LV, left ventricle; LVEF, left ventricular ejection fraction; LVOTO, left ventricular outflow tract obstruction; NYHA, New York Heart Association; Pro-BNP, pro-brain natriuretic peptide; RAAS, rennin-angiotensin-aldosterone system; SCD, sudden cardiac death; and VT, ventricular tachycardia.

*Depression is defined by the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (DSM-5).

Clinical Outcomes

Eight hundred patients were successfully followed up, and 20 (2.4%) individuals were lost to follow-up. Over an average follow-up period of 4.2 years, SCD events occurred in 75 individuals (21.8 per 1000 person-years) and HCM-related heart failure events developed in 149 individuals (43.3 per 1000 person-years): 45 sudden death (109 versus 38 per 1000 person-years; HR, 3.3; 95% CI, 1.8–5.9), 7 aborted arrests (15 versus 6 per 1000 person-years; HR, 2.4;

95% CI, 1.3–4.8), 23 ICD discharge (47 versus 22 per 1000 person-years; HR, 2.2; 95% CI, 1.2–4.7), 15 deaths from heart failure (26 versus 16 per 1000 person-years; HR, 1.7; 95% CI, 1.0–3.3), 1 heart transplantation (0 versus 2 per 1000 person-years; HR, 1.6; 95% CI, 0.2–15.2), 16 heart failure–related strokes (26 versus 18 per 1000 person-years; HR, 1.5; 95% CI, 0.5–4.3), 28 heart failure hospitalizations (47 versus 30 per 1000 person-years; HR, 1.7; 95% CI, 1.2–3.5), and 89 patients with progressive heart

failure symptoms to NYHA class III/IV (198 versus 81 per 1000 person-years; HR, 2.5; 95% CI, 1.9–4.4, Table 2 and Figure S1). Clinical features of 33 patients with depression with HCM-related SCD events are presented in Table S1. The average age was 45.9±15.3 years old (range, 21–73), and the mean NYHA class was 1.5±0.7 at initial evaluation. Of 33 individuals with depression, 10 (30.3%) had no risk factor for sudden death, and 9 (27.3%) had at least 2 risk factors. During follow-up, 21 died suddenly, 3 survived an aborted cardiac arrest, and 9 received appropriate defibrillation shocks from an ICD.

Association of Depression and Clinical Outcomes

Kaplan–Meier cumulative incidence curves showed a significant association of depression disorders with SCD events (log-rank $P=0.001$) and HCM-related heart failure events (log-rank $P=0.005$; Figure 2). In the univariate Cox regression model, depression had a significant relationship with increased risks of SCD events (HR, 2.1; 95% CI, 1.8–2.4; $P<0.001$) as well as HCM-related heart failure events (HR, 2.0; 95% CI, 1.6–2.3; $P<0.001$; Table 3), and depression was retained as an independent prognostic factor for SCD events and HCM-related heart failure events after adjustment for conventional risk factors (41.9 versus 21.7 per 1000 person-years; HR, 1.9; 95% CI, 1.6–2.3; $P<0.001$; and 69.9 versus 38.6 per 1000 person-years; HR, 1.8; 95% CI, 1.6–2.1; $P<0.001$, respectively) (Table 4). In addition, when the analysis was restricted to the SCD other than ICD discharge, the relative risk of SCD events remained essentially unchanged (26.7 versus 17.8 per 1000 person-years; HR, 1.5; 95% CI, 1.2–1.9; $P<0.001$). Notably, unexplained syncope, a family history of SCD, LVOTO, nonsustained VT on ambulatory Holter, and maximum LV wall thickness >30 mm were significantly associated with sudden cardiac death, agreeing with the findings of previous studies.

Some 56.5% of the study sample had HDRS scores in the low normal range (<8), followed by 18.0% with scores indicative of mild depression (8–13), 14.9% with scores indicative of moderate depression (14–19), and only 10.6% who could be considered severely depressed (≥ 19). The clinical characteristics of the patients are shown in Table S2. Also, HDRS scores differ significantly for family history of SCD and LVOTO among groups. Results of the relationship of HDRS as categorical and continuous scores with SCD, both unadjusted and adjusted for risk factors, are shown in Table 5. Compared with the least-depressed participants, the adjusted HRs (95% CIs) were 1.3 (1.1–1.6) for HDRS score of 8 to 13, 1.6 (1.3–1.8) for HDRS score of 14 to 19, and 2.3 (1.9–3.0) for patients in the most depressed categories (HDRS ≥ 19), respectively. Furthermore, there was evidence of a dose–response relationship between depression symptoms classified by HDRS scores and prognosis of SCD that began below the cutoff point of ≥ 8 (Figure 3).

DISCUSSION

To our knowledge, this is the first prospective cohort study to evaluate the prevalence of depressive disorders in patients with HCM and investigate the potential association between depression and clinical outcomes in this population. One major methodological strength in the current study was that we diagnosed depression via formal psychological evaluation based on DSM-5. Our results indicated that depression is common among patients with HCM with a high prevalence of 23.4%, and, in addition to traditional risk factors, depression can also predict adverse clinical outcomes for patients with HCM. In our earlier studies concerning the relation of depression on all-cause mortality and cardiovascular events in patients with myocardial infarction

Table 2. Major Clinical Events of the Study Population During Follow-Up

Major Clinical Events, n (%)	Depression* (n=192)	Without Depression (n=628)	HR (95% CI)
HCM-related sudden death	21 (10.9)	24 (3.8)	3.3 (1.8–5.9)
Aborted arrest	3 (1.6)	4 (0.6)	2.4 (1.3–4.8)
ICD discharge (VT/VF)	9 (4.7)	14 (2.2)	2.2 (1.2–4.7)
Heart failure death	5 (2.6)	10 (1.6)	1.7 (1.0–3.3)
Heart transplantation	0 (0)	1 (0.2)	1.6 (0.2–15.2)
HCM-related stroke	5 (2.6)	11 (1.8)	1.5 (0.5–4.3)
Progression to NYHA class III/IV	38 (19.8)	51 (8.1)	2.5 (1.9–4.4)
Noncardiac death	3 (1.6)	8 (1.3)	1.2 (0.8–2.7)
Heart failure hospitalization	9 (4.7)	19 (3.0)	1.7 (1.2–3.5)

HCM indicates hypertrophic cardiomyopathy; HR, hazard ratio; ICD, implantable cardioverter defibrillator; NYHA, New York Heart Association; VF, ventricular fibrillation; and VT, ventricular tachycardia.

*Depression is defined by the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5)*.

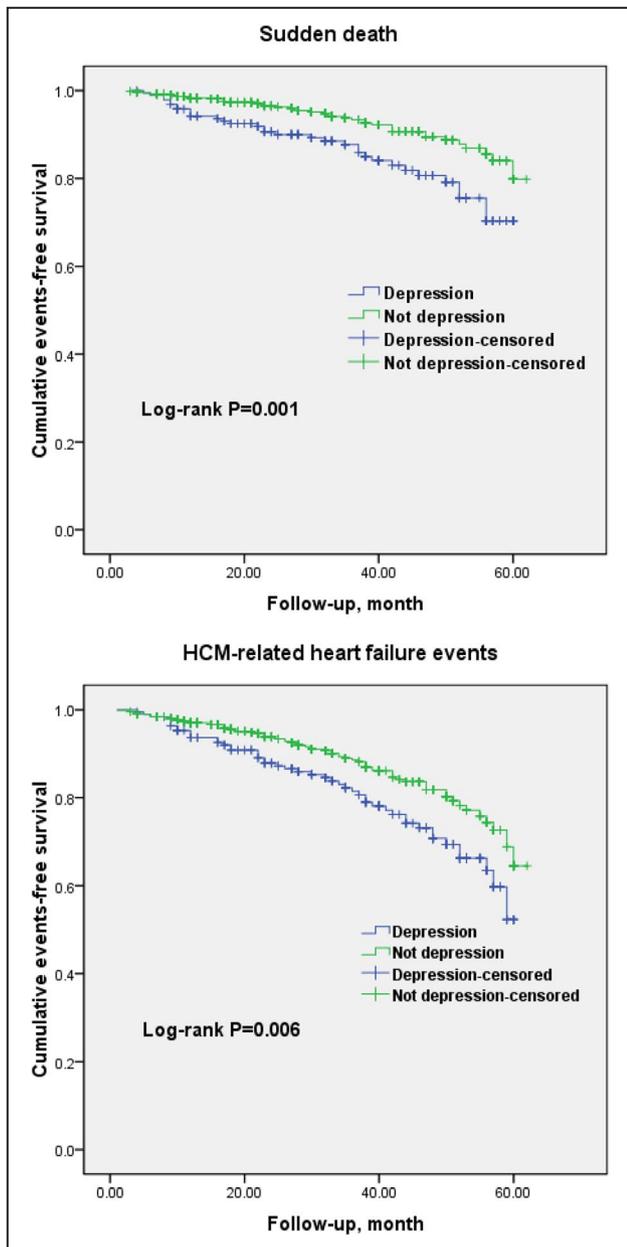


Figure 2. Kaplan-Meier curves for sudden cardiac death events and hypertrophic cardiomyopathy-related heart failure events in patients with and without depression.

and nonobstructive coronary arteries, patients with myocardial infarction and nonobstructive coronary arteries had 7.25 times the risk of mortality at a mean follow-up of 3 years.²⁶ Compared with these findings, although depression in patients with HCM did not have as strong an association with these outcomes, the diagnosis of depression still had independent prognostic significance in patients with HCM.

A recent large-scale meta-analysis of 92 studies with 116 295 136 participants demonstrated that depression increased the risk for cardiovascular mortality by a factor of 1.63. In their study, cardiovascular

disease was defined as a composite of coronary heart disease, congestive heart failure, and cerebrovascular disease.²⁷ Another comprehensive meta-analysis conducted 15 years ago has shown that the relationship between depression and poorer heart failure outcomes is consistent and strong. Notably, the primary causes of heart failure in their studies were ischemic heart disease, dilated cardiomyopathy, and hypertensive heart disease.²⁸

However, the existing literature on the effects of depression on HCM outcomes is scarce. Two decades ago, Cox et al conducted an interesting study using the Short Form 36 Health Survey and the Hospital Anxiety and Depression questionnaire to assess health-related quality of life and psychological well-being of patients with HCM. The conclusion was that patients with HCM were associated with substantial restrictions on health-related quality of life. In addition, their levels of anxiety and depression were also high when compared with the general population.¹⁶ In an early study, Igoumenou et al reported that patients with HCM were more depressed than the general population. In contrast, no significant association was found between depressive symptoms and the risk factors for sudden death in this population. Nevertheless, their study sample was relatively small with a short follow-up duration and the evaluation scale of depressive symptoms—the Beck Depression Inventory and the Center for Epidemiological Studies Depression Scale—was not equivalent to a diagnosis of depression.²⁹ Another study by Eva et al indicated that there was a significant reduction in psychological distress and an improvement in well-being after alcohol septal ablation in patients with HCM. Their findings emphasized the importance of psychosocial outcomes and long-term survival.³⁰ In the present study, we used the Chinese version of the Structured Clinical Interview based on the DSM-5 by psychologists for the diagnosis of depression. Our results demonstrated that depression is common in patients with HCM and had a prevalence of 23.4%. This is generally consistent with the previous study by Igoumenou et al.²⁹ We further observed that depression is significantly and independently associated with SCD events and HCM-related heart failure events in patients with HCM. Our findings indicated that, in addition to well-known risk factors, depression could be of prognostic significance in patients with HCM. In other words, the present study further outlines the importance of screening for depression disorder in the HCM population before evaluation of an ICD implantation.

Numerous studies have indicated several potential mechanisms for the relationship between depression and poor prognosis but there is no consensus yet. Biologically, depression may result in impaired heart rate variability, endothelial dysfunction, chronic systemic inflammation, and hypothalamic-pituitary-adrenal

Table 3. Univariate Cox Regression of Variables Influencing SCD Events and HCM-Related Heart Failure Events

Variables	SCD Events		HCM-Related Heart Failure Events	
	HR (95% CI)	P Value	HR (95% CI)	P Value
Age (per decade increase)	0.98 (0.88–1.09)	0.58	1.09 (0.98–1.18)	0.10
Left atrial diameter	1.1 (0.9–1.2)	0.21	1.1 (0.8–1.2)	0.12
Atrial fibrillation	1.01 (0.84–1.11)	0.49	1.3 (1.1–1.7)	0.04
β-blockers	0.8 (0.6–0.9)	0.01	0.8 (0.7–0.9)	0.03
Calcium channel blockers	0.93 (0.89–1.03)	0.25	0.97 (0.89–1.12)	0.65
RAAS inhibitors	0.97 (0.94–1.06)	0.44	0.90 (0.79–1.08)	0.07
Diuretic	1.01 (0.98–1.06)	0.70	0.96 (0.84–1.10)	0.34
NVT on ambulatory Holter	2.9 (2.4–3.6)	<0.001	1.5 (1.1–2.0)	0.01
Unexplained syncope	2.0 (1.4–2.8)	0.01	1.1 (0.9–1.2)	0.53
Family history of SCD	1.7 (1.3–2.2)	0.03	1.07 (0.95–1.12)	0.63
LVOTO	2.3 (1.6–2.9)	<0.001	2.4 (2.1–3.7)	<0.001
MLVWT ≥30 mm	1.3 (1.1–1.8)	0.04	1.5 (1.0–2.0)	0.02
Depression	2.1 (1.8–2.4)	<0.001	2.0 (1.6–2.3)	<0.001

HCM indicates hypertrophic cardiomyopathy; HR, hazard ratio; LVOTO, left ventricular outflow tract obstruction; MLVWT, maximum left ventricle wall thickness; NVT, nonsustained ventricular tachycardia; RAAS, rennin-angiotensin-aldosterone system; and SCD, sudden cardiac death.

axis dysfunction.³¹ However, the exact mechanism underlying the relationship between depression and SCD events or heart failure events is less clear. Amanda et al established a genetic mouse model of HCM by knock-in with the sarcomeric mutation gene, to investigate the influence of HCM over the development of depression and anxiety. They found that prolonged systemic stress of HCM can result in the development of mood disorders, probably by inducing structural and functional brain changes.³² Previous studies suggest that depression was associated with chronically increased catecholamine levels, high sympathetic nervous activity, easily activated platelets, and a hypercoagulable state.^{33–35} In addition, depression has also been related to symptomatic long QT syndrome and QT dispersion recorded by electrocardiography.^{36,37} Finally, patients with depression are inclined to have unhealthy lifestyles, including smoking, heavy

alcohol consumption, low physical activity, poor drug compliance, and disruptions of social relationships. However, our study found that both groups were comparable regarding smoking, body mass index, and comorbidities. Consequently, the poor prognosis in depressed patients is likely the result of biopsychosocial interactions.³⁸

Several strengths should be noted in the present study. First, the 17-item HDRS was considered the criterion standard for assessment of depression for >50 years and defined remission of depression with a score of <7. Sawamura et al reported that a cutoff value for a 17-item HDRS score of <5 was the best candidate for the symptomatic relief if the health-related quality of life was considered.²¹ In the current study, patients with an HDRS score of ≥5 were given the Chinese version of the Structured Clinical Interview based on DSM-5 by psychologists, for diagnosis of

Table 4. Multivariate Cox Regression of Variables Influencing SCD Events and HCM-Related Heart Failure Events

Variables	SCD Events		HCM-Related Heart Failure Events	
	HR (95% CI)	P Value	HR (95% CI)	P Value
β-blockers	0.8 (0.6–1.0)	0.03	0.8 (0.7–0.9)	0.03
Atrial fibrillation	NA	NA	1.2 (1.0–1.3)	0.09
RAAS inhibitors	NA	NA	0.9 (0.8–1.1)	0.10
NVT on ambulatory Holter	2.7 (2.3–3.2)	<0.001	1.4 (1.0–1.9)	0.03
Unexplained syncope	1.9 (1.4–2.4)	0.01	1.1 (0.9–1.2)	0.72
Family history of SCD	1.7 (1.3–2.2)	0.02	1.1 (1.0–1.2)	0.86
LVOTO	2.1 (1.6–2.6)	<0.001	2.2 (1.9–2.7)	<0.001
MLVWT ≥30 mm	1.21 (1.0–1.5)	0.05	1.3 (1.1–2.0)	<0.001
Depression	1.9 (1.6–2.3)	<0.001	1.8 (1.6–2.1)	<0.001

HCM indicates hypertrophic cardiomyopathy; HR, hazard ratio; LVOTO, left ventricular outflow tract obstruction; MLVWT, maximum left ventricle wall thickness; NA, not applicable; NVT, nonsustained ventricular tachycardia; RAAS, rennin-angiotensin-aldosterone system; and SCD, sudden cardiac death.

Table 5. Relationship of HDRS Score With SCD Events During Follow-Up Period

HDRS	Unadjusted		Adjusted*	
	HR (95% CI)	P Value	HR (95% CI)	P Value
Categorical				
HDRS <7
HDRS 8–13	1.4 (1.1–1.8)	0.006	1.3 (1.1–1.6)	0.014
HDRS 14–18	1.8 (1.4–2.3)	<0.001	1.6 (1.3–1.8)	0.003
HDRS ≥19	2.4 (2.0–3.2)	<0.001	2.3 (1.9–3.0)	<0.001
Continuous	1.03 (1.02–1.05)	<0.001	1.03 (1.02–1.04)	<0.001

HDRS indicates 17-item Hamilton Depression Rating Scale; HR, hazard ratio; and SCD, sudden cardiac death.

* Adjusted for unexplained syncope, family history of SCD, nonsustained ventricular tachycardia on Holter, maximum left ventricular wall thickness ≥30 mm, and left ventricular outflow tract obstruction.

depression. Second, the well-known risk factors that have significant effects on HCM outcomes, such as unexplained syncope, family history of SCD, nonsustained VT on Holter, LVOTO, and maximum LV wall thickness >30 mm, were all used for adjustment.^{2,6} Third, the assessment of depressive symptoms was conducted at baseline and 12 months after the patients' discharge. We supposed that hospitalization might increase negative emotions at enrollment, but there was no significant difference between baseline and 1-year follow-up in HDRS score. Fourth, 1 advantage of the current observational study is that patients were contacted by instant messaging (WeChat) or telephone, which promoted the level of the quality of follow-up. In conclusion, the rate of loss to follow-up was only 2.4% in the present study.

This study has several potential limitations. First, residual confounding may coexist with depression

disorders, such as anxiety, insomnia, marital status, or economic conditions, but we did not collect relevant information on these variables. Second, an inevitable limitation is the absence of data from patients who refused to participate in this study; however, very few eligible patients were excluded from the present analysis because this was an observational study. Finally, all patients were recruited from a single Heart Center, thereby raising concerns on the generalizability of results.

CONCLUSIONS

In conclusion, the incidence of depression in Chinese patients with HCM is high. The diagnosis of depression is significantly and independently associated with an increased risk of SCD events and heart failure events in patients with HCM. Further study should be encouraged to validate whether psychological intervention for depression can improve clinical outcomes in this population.

ARTICLE INFORMATION

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Disclosures

None.

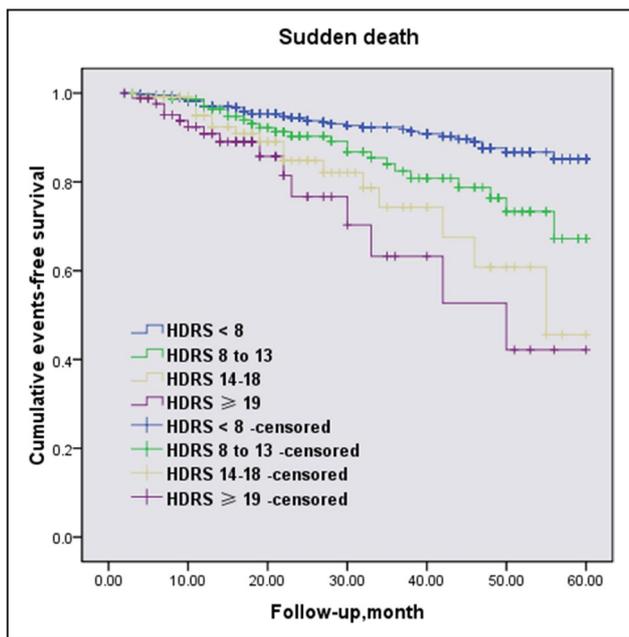


Figure 3. Kaplan-Meier curves for sudden cardiac death events in patients classified by HDRS scores. HDRS indicates Hamilton Depression Rating Scale.

Supplementary Material

Tables S1–S2

Figure S1

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SUPPLEMENTAL MATERIAL

Table S1. Clinical features of 33 patients with depression experiencing HCM-related SCD events.

Patients	Age, y	Sex	NYHA Class	LVEF, %	MLVT, mm	Risk Factors	Events	Time to events, month
1	21	M	I	70	16	VT	Death	38
2	22	F	I	67	18	US	Death	42
3	24	F	I	64	16	FH-SCD	Aborted arrest	28
4	24	M	II	66	22	LVOTO	Death	17
5	29	M	II	58	31	MLVT, VT, US	ICD discharge	56
6	32	F	I	66	24	US	Death	50
7	33	M	I	72	21	VT	ICD discharge	33
8	33	M	II	67	24	LVOTO	ICD discharge	16
9	35	F	III	54	29	None	Death	52
10	36	F	I	60	16	US	ICD discharge	10
11	37	M	I	66	32	MLVT	Aborted arrest	6
12	37	F	II	67	18	US	ICD discharge	16
13	39	F	I	71	25	None	Death	35
14	40	M	II	65	25	FH-SCD	Death	42
15	41	M	I	60	24	None	Death	30
16	42	F	I	62	19	None	Death	56
17	44	M	I	65	32	MLVT, LVOTO, US	ICD discharge	12
18	44	M	I	54	27	None	Death	15
19	47	M	I	65	25	US, VT	ICD discharge	5
20	48	F	III	35	16	VT	Death	23
21	51	M	I	56	15	None	Death	50
22	53	F	II	45	19	FH-SCD, VT	ICD discharge	47
23	53	F	II	67	22	LVOTO, FH-SCD	Death	25
24	55	M	I	66	23	LVOTO	Death	9
25	60	F	II	53	29	FH-SCD, VT	ICD discharge	47
26	60	F	I	67	22	LVOTO, VT	Death	33
27	64	M	I	60	20	None	Aborted arrest	8
28	64	M	I	56	19	US	Death	28
29	67	F	II	65	18	LVOTO, FH-SCD	Death	38
30	68	M	II	48	15	None	Death	52
31	68	F	I	56	22	None	Death	18
32	71	M	III	56	27	LVOTO	Death	44
33	73	M	I	70	21	None	Death	39

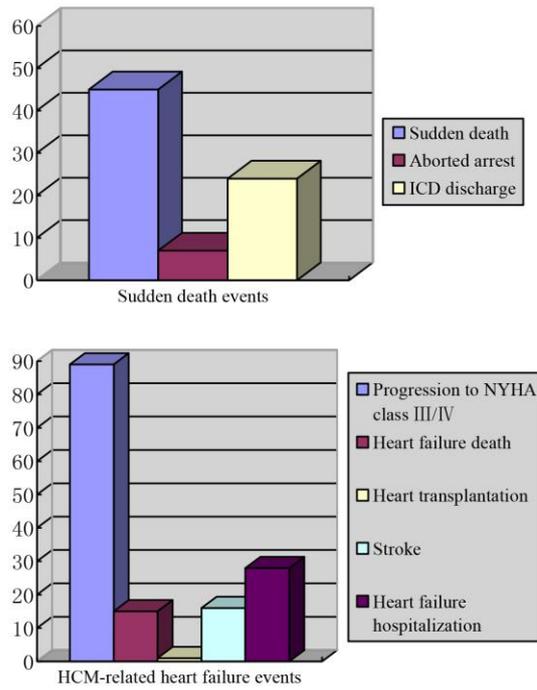
HCM indicates hypertrophic cardiomyopathy; SCD, sudden cardiac death; NYHA, New York Heart Association; LVEF, left ventricle ejection fraction; MLVT, Maximum left ventricle thickness; VT, ventricular tachycardia on ambulatory Holter; US, Unexplained syncope; FH-SCD, Family history of sudden cardiac death; LVOTO, left ventricular outflow tract obstruction; MLVT, Maximum LV wall thickness ≥ 30 mm; ICD, implantable cardioverter defibrillator.

Table S2. Clinical characteristics of the patients classified by level of depression symptoms.

Characteristics	Percent of patients with events (n)				P value
	HDRS <8 (n=463)	HDRS 8-13 (n=148)	HDRS 14-18 (n=122)	HDRS ≥19 (n=87)	
Demographics					
Age, mean±SD, y	48.2±12.9	48.1±12.8	47.9±12.6	48.5±12.6	0.62
Male, n (%)	266 (57.5)	88 (59.5)	66 (54.1)	50 (57.5)	0.23
BMI, mean±SD, kg/m ²	24.7±3.9	24.8±3.6	24.3±3.7	24.4±3.7	0.58
Maximum LV thickness, mean±SD, mm	20.2±4.8	20.0±4.7	20.1±4.6	20.2±4.5	0.87
NYHA class, n (%)					
I/II	413 (89.2)	130 (87.8)	106 (86.9)	76 (87.4)	0.44
III/IV	50 (10.8)	18(12.2)	16 (13.1)	11 (12.6)	0.19
Comorbid condition, n (%)					
Atrial fibrillation	43 (9.3)	15 (10.1)	11 (9.0)	9 (10.3)	0.53
Stroke history	3 (0.6)	3 (2.0)	2 (1.6)	2 (2.3)	0.77
Diabetes	63 (13.6)	18 (12.2)	17 (13.9)	13 (14.9)	0.63
Hypertension	77 (16.6)	24 (16.2)	21 (17.2)	17 (19.5)	0.16
Risk factors, n (%)					
Non-sustained VT on Holter	80 (17.3)	27 (18.2)	22 (18.0)	18 (20.7)	0.12
Unexplained syncope	40 (8.6)	13 (8.8)	10 (8.2)	10 (11.5)	0.11
Family history of SCD	48 (10.4)	20 (13.5)	19 (15.6)	18 (20.7)	0.03
LVOTO	95 (20.5)	33 (22.3)	33 (27.0)	21 (24.1)	0.04
Maximum LV wall thickness ≥ 30mm	22 (4.8)	7 (4.7)	6 (4.9)	4 (4.6)	0.77
Echocardiography, mean ± SD					
LVEF (%)	63.3±6.7	61.2±6.3	62.5±6.2	61.0±6.0	0.79
Left atrial diameter	39.6±9.7	40.2±9.5	39.9±9.3	40.2±9.0	0.65
ICD implantation					
ICD, n (%)	48 (10.4)	15 (10.1)	13 (10.7)	9 (10.3)	0.78
Medications at discharge, n (%)					
β-Blockers	290 (62.6)	99 (66.9)	77 (63.1)	52 (59.8)	0.19
Calcium channel blockers	79 (17.1)	27 (18.2)	23 (18.9)	16 (18.4)	0.74
RAAS inhibitors	72 (15.6)	23 (15.5)	21 (17.2)	14 (16.1)	0.69
Diuretic	34 (7.3)	11 (7.4)	8 (6.6)	6 (6.9)	0.48
Amiodarone	11 (2.4)	5 (3.4)	4 (3.3)	2 (2.3)	0.65
Laboratory parameters, mean ± SD					
Pro-BNP (pg/mL)	641.0±513.5	589.4±502.0	599.0±493.5	584.0±471.1	0.32
Creatinine (umol/L)	75.2±14.2	73.9±13.9	74.1±13.8	74.2±13.6	0.52
HDRS score	4.5±2.5	10.3±2.6	16.1±1.8	22.6±3.2	<0.001

HDRS indicates 17-item Hamilton Depression Rating Scale; SD, standard deviation; BMI, body mass index; LV, left ventricle; NYHA, New York Heart Association; VT, ventricular tachycardia; SCD, sudden cardiac death; LVOTO, left ventricular outflow tract obstruction; LVEF; left ventricular ejection fraction; ICD, implantable cardioverter defibrillator; RAAS, rennin-angiotensin-aldosterone system; Pro-BNP, pro-brain natriuretic peptide.

Figure S1. Clinical profile of sudden death events and HCM-related heart failure events



HCM indicates hypertrophic cardiomyopathy; ICD, implantable cardioverter defibrillator; NYHA, New York Heart Association.