REVIEW

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Risk factors of sudden cardiac death in hypertrophic cardiomyopathy

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Purpose of review
Hypertrophic cardiomyopathy (HCM) is one of the leading causes of sudden cardiac death (SCD) in younger people and athletes. It is crucial to identify the risk factors for SCD in individuals with HCM. This review, based on recent systematic literature studies, will focus on the risk factors for SCD in patients with HCM.

Recent findings
An increasing number of studies have further explored the risk factors for SCD in patients with HCM, and new risk markers have emerged accordingly. In addition, more accurate SCD risk estimation and stratification methods have been proposed and continuously improved.

Summary
The identification of independent risk factors for HCM-related SCD would likely contribute to risk stratification. However, it is difficult to predict SCD with absolute certainty, as the annual incidence of SCD in adult patients with HCM is approximately 1%. The review discusses the established risk factors, such as a family history of SCD, unexplained syncope and some new risk factors. Taken together, the findings of this review demonstrate that there is a need for further research on individual risk factors and that SCD risk stratification in HCM patients remains a clinical challenge.

Keywords
hypertrophic cardiomyopathy, prediction model, risk factors, sudden cardiac death

INTRODUCTION

Hypertrophic cardiomyopathy (HCM) is an autosomal-dominant genetic cardiomyopathy characterized by asymmetric abnormal hypertrophy of the left ventricular muscle and nondilated left ventricle (LV) [1]. The estimated general population prevalence is at least 1 out of 500 [2–4], and HCM is one of the leading causes of sudden cardiac death (SCD) in younger people and athletes, and SCD can be as the first manifestation of HCM occurring in asymptomatic or younger patients without warning [5]. The annual incidence of SCD in adult patients with HCM is approximately 1%, and far higher in paediatric patients with HCM [6–8]. Therefore, identifying the risk factors for SCD and screening out potential HCM patients at a high risk of SCD to guide prevention strategies has become significant.

In 2011, the American College of Cardiology Foundation (ACCF)/American Heart Association (AHA) published clinical practice guidelines [8] to assess the risk factors for SCD among patients with HCM and proposed five established clinical risk factors: including a family history of SCD; recently unexplained syncope; nonsustained ventricular tachycardia (NSVT); maximum left ventricular wall thickness; and an abnormal blood pressure response during exercise. The introduction of the above five noninvasive clinical markers offer a low cumulative positive predictive value of approximately 20% and

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KEY POINTS

- Sudden cardiac death (SCD) is the most devastating complication of HCM occurring in asymptomatic or younger patients without warning.
- Identifying the risk factors of SCD with HCM patients and screening potential high-risk patients can save more HCM patients' life.
- The location of LGE plays as an important role as the presence of LGE in predicting SCD with HCM patients.
- The genetic information may help to improve the prediction model of sudden cardiac death in HCM.

a rather high negative predictive value of approximately 95% [9]. Therefore, it seems compulsory to search for new risk factors for SCD in patients with HCM.

In 2014, the European Society of Cardiology (ESC) [10] created a SCD-risk prediction model that provides a 5-year SCD risk score for HCM patients. Several new risk factors, including age, left atrial diameter (LAD) and left ventricular outflow track obstruction (LVOTO), were added. The latest 2020 AHA/ACCF guidelines [11▪] have added HCM with left ventricular systolic dysfunction, left ventricular apical aneurysm (LVAA) and extensive late gadolinium enhancement (LGE) on cardiac magnetic resonance (CMR) imaging as established clinical risk factors for SCD in HCM patients. In addition, relevant studies have also reported some other risk factors associated with SCD risk, such as the B-type natriuretic peptide (BNP) level, atrial fibrillation and the New York Heart Association (NYHA) functional class. The purpose of this study was to perform a systematic literature review of publications on clinical risk factors for SCD in patients with HCM in recent years to provide a reference for clinical therapy decision-making.

FAMILY HISTORY OF SUDDEN CARDIAC DEATH

The definition of a family history of SCD is that one or more first-degree relatives under 40 or 50 years of age who died incidentally within 1 h (witnessed) or 24 h (asymptomatic observation) after the symptom appeared [1,10,12▪▪,13]. Although the definition varies, there is a consensus that SCD events in first-degree relatives increase an individual's risk of SCD [11▪,12▪▪,13,14]. Compared with HCM patients without an obvious family history, patients with a family history of SCD had a 20% increased risk of SCD [14]. Because of the familial clustering of risk, a family history of SCD is a Class IIa recommendation for ICD insertion in the ACCF/AHA guidelines and is included in the HCM Risk-SCD Calculator (ESC website) [10,12▪▪].

UNEXPLAINED SYNCOPE

Unexplained syncope is defined as one episode of an unexplained loss of consciousness within the previous 6 months. Syncope commonly occurs in one of four patients with HCM but is difficult to estimate for multiple causes, such as supraventricular arrhythmia, sinus node dysfunction and complete heart block [15]. Several studies have shown that unexplained syncope is a marker for an increased risk of SCD [7,10,13,16]. Both the ACCF/AHA guidelines (Class IIa) and the ESC guidelines include unexplained syncope in ICD decision-making. Spirito *et al.* [17] demonstrated that the relative risk of SCD in patients with recent unexplained syncope (<6 months) was five-fold higher than that in patients without syncope. However, older patients (≥40 years of age) with remote episodes of syncope (>5 years before initial evaluation) did not show an increased risk of SCD.

NSVT

NSVT refers to three or more consecutive ventricular beats with a frequency of at least 120 beats per minute lasting for less than 30 s [18]. NSVT is very common in HCM, with a high incidence rate of 20–30% in HCM patients over the age of 40 years [18,19]; hence, the positive predictive value of NSVT for SCD is not high, so NSVT alone is not sufficient to warrant ICD insertion [8,10]. A study suggested that NSVT is predictive of SCD only when it occurs repeatedly or is associated with symptoms [20]. Another study showed that NSVT was associated with a greater risk of SCD in HCM but only in patients 30 years old or less, and the frequency, duration and rate of the NSVT did not have predictive value [18].

MAXIMUM LEFT VENTRICULAR WALL THICKNESS

Left ventricular wall thickness is the maximum end-diastolic dimension within the chamber. The greatest thickness measured at any location of the LV is considered to represent the maximum wall thickness. Studies have shown left ventricular wall thickness at least 30 mm is independently associated with SCD [10,13,21,22], and as a Class IIa recommendation for ICD insertion in ACCF/AHA guidelines [8]. However, a binary cutoff for decision-making ignores the stepwise increase in the risk of gradations of left

ventricular hypertrophy. Use of left ventricular thickness as a continuous variable within the HCM Risk-SCD Calculator likely provides a more inclusive assessment of risk in this regard [12▪▪].

ABNORMAL EXERCISE BLOOD PRESSURE RESPONSE

Abnormal blood pressure response is defined as failure of a SBP increase of more than 20 mmHg or an SBP decrease of 10 mmHg during exercise [23]. An abnormal blood pressure response to exercise occurs in more than one of three of HCM patients [24]. Most studies show that abnormal blood pressure response corresponds to increased SCD risk for younger patients with HCM (under 40 years old) [9,13,25,26], and the prognostic value of abnormal blood pressure response in patients aged more than 40 years is not known.

HYPERTROPHIC CARDIOMYOPATHY RISK-SUDDEN CARDIAC DEATH TOOL

The 2014 ESC guidelines on the diagnosis and management of HCM [10] recommends the HCM Risk-SCD tool to stratify the 5-year SCD risk. Some of the factors in the ESC model are the same as those in the ACCF/AHA approach (left ventricular wall thickness, family history of SCD and syncope), but the ESC model also includes age, outflow tract gradient and LAD. The output of the HCM Risk-SCD tool places patients into one of three 5-year SCD risk categories: less than 4%, 4–6% and more than 6%. ICDs are not recommended for the lower-risk group, may be considered for the intermediate-risk group and should be considered for the higher-risk group. Statistical validation in two retrospective cohorts concluded that the ESC model had a better discriminative C-statistic than the existing 'risk factor' approach [27,28]. In 2018, a large, international, multicentre cohort study further confirmed that this risk-SCD tool can provide accurate prognostic information and can be used to guide the prevention of SCD [29]. However, the application of the HCM risk-SCD tool in a real-world cohort of 1629 AHA risk-stratified patients found that only 20% who had suffered SCD or appropriate shocks were deemed ''high risk' by the ESC risk model [30].

LEFT VENTRICULAR SYSTOLIC DYSFUNCTION

Left ventricular systolic dysfunction is defined as left ventricular ejection fraction (LVEF) less than 50% by echocardiography. Some studies advocated that left ventricular systolic dysfunction should be considered another risk factor for SCD [31–33], and patients with LVEF of 35% or less are at a high risk of SCD [34,35]. Currently, guideline recommends that ICD is used to reduce the risk of death in patients with severely reduced LVEF ($\leq$ 35%) as primary prevention and cardiac arrest survivors as secondary prevention [36].

LEFT VENTRICULAR APICAL ANEURYSM

An apical aneurysm is defined as a discrete thin-walled dyskinetic or akinetic segment of the most distal portion of the left ventricular chamber [37]. The prevalence of SCD in HCM patients is reported to be 2.2% and SCD occur in LVAA patients over a wide range of ages [38,39]. LVAA has been associated with an increased risk of SCD and ventricular arrhythmia [14,28], but the size of the aneurysm was not shown to affect the risk of SCD [40]. Therefore, monitoring apical aneurysms in patients with HCM may be of great significance to predict the risk of SCD. In a large cohort of HCM patients at two centres, 93 of whom (4.8%) were found to have LVAAs, over 4.4 ± 3.2 years of follow-up, the rate of SCD occurrence was 4.7%/year [37].

LATE GADOLINIUM ENHANCEMENT ON CARDIAC MAGNETIC RESONANCE IMAGING

LGE-CMR is a marker of myocardial fibrosis in HCM. A growing body of studies has shown that extensive LGE is independently associated with a high risk of SCD [10,41,42]. Data from Chan *et al.* [41] showed that LGE was more powerful in predicting SCD than individual risk factors in a cohort of 1293 HCM patients, and a quantitation of at least 15% LGE demonstrated a two-fold increase in SCD, and a meta-analysis [42] demonstrated that the risk of SCD was significantly correlated with the degree of LGE, and with every 10% increase in LGE, the risk of SCD increased by 36%. However, some controversy remains as to whether LGE provides incremental information over traditional risk factors in HCM [43,44]. Recent studies showed that the extent of LGE was significantly related to the risk of SCD in patients with HCM [41,42], while other studies found that the extent of LGE was not an independent predictor of SCD in HCM [43,45]. Three pioneering studies indicated that the location of LGE was related to serious arrhythmia and SCD in HCM patients [46–48]. In our cohort study [49▪▪] including 557 HCM patients with a mean follow-up time of 83.0 months, there was a significantly

higher SCD incidence in patients with LGE outside the interventricular septum than in those with LGE in the interventricular septum only, indicating that the location of LGE plays as important a predictive role as the presence of LGE.

AGE

Studies have pointed out that SCD preferentially occurs in asymptomatic (or mildly symptomatic) children and adults younger than 35 years [8,10], while it is infrequent in patients older than 60 years [50]. Spirito *et al.* [17] assessed 1511 consecutive patients with HCM and found that the risk of SCD decreased significantly with age.

However, other authors noted that SCD in HCM is not limited to young patients and that the risk period in this disease almost runs almost through throughout life [1,51]. The impact of age on SCD risk has been investigated in only limited studies, so it is impossible to draw a definite conclusion.

LEFT ATRIAL DIAMETER OR LEFT ATRIAL VOLUME

Recent echocardiographic guidelines suggest that left atrial volume (LAV) is the most accurate method for estimating left atrial size [52,53]. Left atrial size serves as a barometer of chronic elevation in left atrial pressure, the sum total of abnormal diastolic function, mitral regurgitation and atrial arrhythmias [54]. Among patients without documented atrial fibrillation, enlarged LAD was an independent determinant of SCD risk; however, there was no significant difference in SCD risk between patients with and without enlarged LAD among patients with documented atrial fibrillation. These results suggest that the relationship between LAD and SCD is influenced by the presence or absence of atrial fibrillation in HCM patients [55].

LVOTO

LVOTO is defined as a peak instantaneous Doppler left ventricular outflow tract pressure gradient of at least 30 mmHg either at rest or with provocation [10]. Studies indicated that nonobstructive patients with a left ventricular outflow tract pressure gradient of at least 30 mmHg have two-fold risk for SCD [26]. It is also important to note that the LVOTO as a potential risk factor for SCD in HCM patients has certain limitations, because the left ventricular outflow pressure gradient is prone to dynamic and spontaneous changes and can be influenced by many environmental factors and routine daily activities [56].

GENE MUTATIONS

In the PubMed/MEDLINE database, there are more than 50 published genes and nearly 8000 variants related to HCM. *MYBPC3* and *MYH7*, encoding cardiac myosin-binding protein C (cMyBP-C) and β-myosin heavy chain (β-MHC), respectively, are the two most common affected genes. A meta-analysis of 7675 patients of HCM reported 5% SCD in *MYBPC3*, 11% in *MYH7*, 17% in *TNNT2* and 0.4% in mutation-negative HCM; in the meantime, SCD rate was significantly higher in any mutation-positive group than in mutation-negative patients [57▪▪].

The *MYH7* gene is localized at chromosome 14 long arm and more than 350 pathogenic variants have been documented in the *MYH7* gene in the Human Gene Mutation Database (HGMD; http://www.hgmd.cf.ac.uk). It is reported that the pathogenic variant of *MYH7* gene produces a more aggressive phenotype, characterized by younger onset age, more left ventricular hypertrophy and high risk of SCD, resulting a poor prognosis [58–60]. Furthermore, Herrera-Rodríguez *et al.* [61▪] conducted a systematic review and found that multiple site mutations in *MYH7* gene were associated with SCD of HCM, including p. Arg 453 Cys, p. Arg 1045 Leu, p. Arg 719 Trp, p. Asn 391 Thr, p. Gly 716 Arg, p. Arg 403 Gln, p. Arg 453 Cys, p. Glu 848 Gly and p. Asn 391 Thr. Moreover, study from Liu *et al.* [62] found that thr 446 pro and phe 468 leu mutations of *MYH7* gene can also lead to SCD.

Compared with *MYH7*gene mutation, most patients with heterozygous *MYBPC3* usually develop at later onset age and have a favourable disease progression [63]. However, *MYBPC3* gene mutation also found multiple loci associated with SCD in HCM, which are respectively p. Glu 542 Gln, p. Cys 719 Arg, p. Glu 334 Lys, p. Pro 108 Alafs∗9, p. Gly 1093 Cys, p. Arg 668 His, p. Arg 502 Trp, IVS 5 + 5G→C, p. F 305 Pfs∗27 and Lys 1209 Serfs∗28 [61▪]. A case report of Tong *et al.* [64] also showed that the c.2737 + 1 (IVS26) G > T mutation in *MYBPC3* gene can lead to severe ventricular hypertrophy and SCD.

The thin filament protein encoding genes *TNNT2* and *TNNI3* are less frequently affected, the mutations in the *TNNT2* gene account for 5% of patients with HCM [65]. *TNNT2* gene mutations can manifest as only mild left ventricular wall thickness, low HCM penetrance, while more severe myocyte disarray, younger patients and high incidence of SCD [66–69]. *TNNI3* gene is a subtype of troponin I and is only expressed in myocardium. Recently, Fahed *et al.* [70] studied that the *TNNI3* p. Arg 21 Cys mutation can lead to malignant HCM characterized by remarkably high rate of early onset SCD, sometimes accompanied by thinning of the myocardium and enlargement of the cardiac cavity [71].

Some other gene mutations have also been reported to be associated with SCD of HCM. Osborn *et al.* [72] demonstrate that homozygous myosin light chain 3 (*MYL3)* loss-of-function variants (c. 170C > A, c. 106G > T, c.482-1 G > A) can contribute to cardiomyopathy and SCD. *FLNC* mutations have been reported to have a high probability of SCD [73]. However, whether genetic information improves risk stratification for SCD is not known.

OTHERS

In addition to the risk factors for SCD in HCM patients mentioned above, some other risk factors have been reported. Studies have found that an increase in BNP level is related to the occurrence of malignant ventricular arrhythmia and/or SCD [74–76]. In some studies, atrial fibrillation is associated with a high risk of cardiovascular death [77,78]. And Sorajja *et al.* [77] found that only chronic atrial fibrillation was a risk factor for SCD in patients with HCM. The NYHA functional class has also been mentioned by a few researchers as a possible as a risk factor associated with SCD risk [17,79]. Currently, surface ECG analysis for fragmented QRS (fQRS) has become as a new tool to strongly predict the risk of SCD in patients with HCM and that fQRS should be considered in a model of risk stratification [80]. In a recent study including 491 consecutive HCM patients by Higuchi *et al.* [81▪], the results showed that renal dysfunction may be associated with the risk of SCD in patients with HCM. However, the results have yet to be further verified.

CONCLUSION

There are many risk factors for SCD in HCM patients. However, the identification of high-risk patients for SCD remains a challenge. Further study is required to characterize and confirm the multiple risk factors for SCD in patients with HCM in larger HCM patient cohorts. More precise risk estimates may be achievable through the incorporation of LGE in CMR and genetic information, along with machine learning analytics. However, no matter how precise the risk estimates become, there will always be tradeoffs in finding a balance between the number of lives saved and the risks of ICD implantations complications.

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Conflicts of interest

There are no conflicts of interest.

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Like most studies indicated the presence of LGE in HCM is an independent predictor of SCD, the location of LGE also plays an important role in predicting SCD.

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