ORIGINAL RESEARCH ARTICLE

Validation of the hypertrophic cardiomyopathy risk-sudden cardiac death calculator in Asians

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ABSTRACT

Objective The hypertrophic cardiomyopathy (HCM) risk-sudden cardiac death (SCD) calculator endorsed by the 2014 European Society of Cardiology has not been independently validated in the Asians. We aimed to investigate whether the HCM Risk-SCD calculator effectively predicts SCD in Korean HCM population.

Methods An observational, longitudinal cohort study was performed in 730 patients with HCM from 2007 to 2017. The primary endpoint was a composite of SCD and appropriate implantable cardioverter-defibrillator (ICD) therapy.

Results During a follow-up period of 4288 person-years, 16 (2.2%) patients reached the primary endpoint. This validation study revealed a calibration slope of 0.892 and C-statistics of 0.718. The primary endpoint occurred in 1.1% (7/615), 4.6% (3/65) and 12.0% (6/50) of low-risk, intermediate-risk and high-risk groups, respectively. Although most patients (85.2%) without the primary endpoint were classified into the low-risk group, 7 of 11 SCD (63.6%) occurred in the low-risk group. In univariable and multivariable analysis, sex (woman) was significantly associated with the primary endpoint and emerged as independent predictor. The addition of sex to the HCM Risk-SCD calculator significantly improved the predictive value of the primary endpoint (net reclassification improvement 0.557, p=0.015).

Conclusions In the Korean HCM population, the HCM Risk-SCD calculator had a high negative predictive value and accuracy for predicting SCD or appropriate ICD therapy, but misclassified a few patients experiencing the primary endpoint as low-risk or intermediate-risk groups.

INTRODUCTION

Hypertrophic cardiomyopathy (HCM), a myocardial disorder with an autosomal dominant inheritance, but with no gene mutation identified in about half, is a major cause of sudden cardiac death (SCD) in young adults.[1 2] Although SCD is the most devastating complication, implantable cardioverter-defibrillator (ICD) implantation is known to reduce SCD risk in patients with HCM at high risk.[3] Despite its proven benefit, as a sizeable proportion of patients with HCM with ICD can experience one or more inappropriate shocks, risk stratification for SCD is of utmost importance for the effectiveness and appropriateness of ICD strategy.[4]

The 2014 European Society of Cardiology (ESC) guidelines on diagnosis and management of HCM recommended the use of the HCM Risk-SCD calculator to decide whether to implant ICD for primary prevention by estimating 5-year risk of SCD based on the first validation study from six participating European centres.[5] However, subsequent validation studies conducted in different population had contradictory results depending on cohorts involved.[6 7] Recently, an international multicentre larger cohort study (14 centres from the USA, Europe, the Middle East and Asia) enrolling more than 3700 patients with HCM was performed and gave a further evidence of the positive impact of the HCM Risk-SCD calculator.[8] Nevertheless, only 385 Asian patients with HCM were included, and there was no further analysis of ethnic subgroups.[8] Thus, limited data are currently available regarding whether the HCM Risk-SCD calculator can be properly applied to the Asians. This study aimed to investigate whether the HCM Risk-SCD calculator effectively predicts SCD events including appropriate ICD therapy in a large cohort of Korean HCM population.

METHODS

Study design and population

This observational cohort consisted of 808 patients with HCM diagnosed between 2007 and 2017 at two tertiary referral centres. The diagnosis of HCM was based on left ventricular (LV) hypertrophy, defined as maximal LV wall thickness (LVWT) ≥15 mm, in the absence of abnormal loading conditions that sufficiently explains LV hypertrophy by transthoracic echocardiography (TTE).[9] Some patients with apical HCM with a maximal LVWT of 14 mm were included based on its unique morphology with the diagnostic support by cardiac MRI. Patients with the following conditions were excluded: (1) competitive athletes, (2) Noonan syndrome, Fabry disease, glycogen storage disease, cardiac amyloidosis, mitochondrial disease and congenital heart disease, (3) patients who underwent myectomy or alcohol septal ablation and (4) candidates for secondary prevention.

Because the HCM Risk-SCD calculator endorsed by the 2014 ESC guidelines cannot be applied in a few conditions, that is, age <16 or >80 years, left atrial (LA) diameter ≤28 or ≥67 mm, LV outflow tract (LVOT) pressure gradient ≤2 or ≥154 mm Hg and maximal LVWT ≤10 or ≥35 mm, patients with aforementioned conditions were carefully excluded.[2] Additionally, after excluding 78 patients with inappropriate or missing data for the HCM Risk-SCD calculator, 730 patients with HCM were included in the final analysis. Each patient with

HCM was followed either until the occurrence of SCD or appropriate ICD therapy, death from any cause or by the end of the study follow-up (31 December 2017). Patients were censored when they underwent heart transplantations due to end-stage HCM.

The study conforms to the principles of the Helsinki declaration. Written informed consent from the subjects was waived due to retrospective analyses of prospective HCM registry.

Risk factors and profiles

Patients diagnosed with HCM underwent clinical assessment including comprehensive history-taking, TTE and 24 hours Holter monitoring to evaluate risk factors at baseline. Seven factors required to calculate the 5-year SCD risk by the HCM Risk-SCD calculator were collected: (1) age at first evaluation, (2) maximum LVWT by TTE (mm), (3) LA diameter in parasternal long axis view (mm), (4) maximal LVOT pressure gradient (mm Hg, either resting or provocative), (5) a family history of SCD in one or more first-degree relatives under 40 years of age or in a first-degree relative with confirmed HCM at any age, (6) a history of unexplained syncope and (7) non-sustained ventricular tachycardia (NSVT) ≥3 beats at a rate of ≥120 beats per minute and lasting <30 seconds, documented by 24 hours Holter monitoring. Only patients with HCM with complete data were included for final analyses.

The HCM Risk-SCD calculator

We calculated the 5-year risk of SCD for each individual patient with HCM using the HCM Risk-SCD calculator provided in the 2014 ESC guidelines.[10] The estimated 5-year risk of SCD was stratified into three categories for ICD recommendations: low-risk (<4%, ICD generally not considered), intermediate-risk (4 to <6%, ICD can be considered) or high-risk (≥6%, ICD should be considered).

Primary endpoint

The primary endpoint was a composite of SCD and appropriate ICD therapy, which were identical to the HCM Risk-SCD study endpoints. Appropriate ICD therapy was defined as defibrillator shocks that was discharged to treat tachyarrhythmic events originating from ventricles. Antitachycardia pacing was not considered as appropriate ICD therapy.[10] Patients with ICD were evaluated regularly by an experienced electrophysiologist with interrogation of devices. The deaths and their causes were ascertained by the National Death Registration Records of Korea.

Statistical analysis

Normally distributed continuous variables are expressed as mean±SD and the categorical variables are shown in number and percentage. For comparison, the Student's t-test or the Mann-Whitney U test was used for continuous variables, and the χ^2 test or the Fisher's exact test was used for categorical variables. The event rate (%) was calculated by dividing the number of patients with the primary endpoint by the follow-up duration and presented as per 100 person-years. The event-free survival was estimated by the Kaplan-Meier method and compared using the log-rank test. HRs were calculated using Cox regression and presented with 95% CI and p value. The proportional hazards assumption was verified by using log-minus-log plots of survival functions for categorical variables and time-dependent Cox models with interaction between each covariate and a function of survival time for all covariates.

Table 1 Baseline clinical characteristics of the study populations

Variable	Study population n=730
Demographic data	
Age, years	57.1±14.3
Sex, male	551 (75.5)
SBP, mm Hg	127.0±16.6
DBP, mm Hg	76.6±11.5
Body mass index, cm/m^2	25.2±3.1
Echocardiographic data	
Maximal LVWT, mm	18.3±3.7
Maximal LVWT, ≥30 mm	7 (1.0)
LA size, mm	44.2±6.8
Peak LV outflow track pressure gradient, mm Hg	15.2±25.5
LV end-diastolic dimension, mm	47.5±5.2
LV ejection fraction, %	64.5±6.7
Risk factors	
Family history of sudden cardiac death	91 (12.5)
Non-sustained ventricular tachycardia	144 (19.7)
Unexplained syncope	98 (13.4)
Comorbidities	
Hypertension	292 (40.0)
Diabetes	122 (16.7)
Dyslipidaemia	182 (24.9)
Atrial fibrillation	118 (16.2)
Stroke	71 (9.7)
Ischaemic heart disease	96 (13.2)

Values presented as mean±SD for continuous variables and as the number (%) for categorical variables.
DBP, diastolic blood pressure; LA, left atrium; LV, left ventricle; LVWT, left ventricular wall thickness;SBP, systolic blood pressure.

We conducted category-free net reclassification improvement (NRI)[11] and integrated discrimination improvement (IDI) analyses[12] to assess the reclassification ability of 5-year SCD risk when sex factor (woman) was added to the HCM Risk-SCD calculator. The 95% CI and p values for these measures were obtained using R packages (nricens for NRI and survIDINRI for IDI).

A two-sided p value of <0.05 was considered statistically significant. All statistical analyses were performed with R programming V.3.2.4 (R core Team, 2017) and the SPSS V.25 (IBM Corp, 2017).

Validation of the HCM Risk-SCD calculator

The calibration plot for HCM Risk-SCD score was used to refer to the agreement between the observed and predicted probability of the primary endpoint. The C-index was calculated to measure the discriminative ability of the HCM Risk-SCD calculator, sex and both.

Ischaemic heart disease (IHD) can be considered a potential risk factor of SCD by diminishing LV dysfunction. To assess the impact of IHD on the accuracy of the calculator, HCM Risk-SCD calculator was revalidated as a sensitivity analysis after excluding patients with IHD.

RESULTS

Baseline characteristics

The study enrolled a total of 730 patients with HCM (aged 57.1±14.3 years; 551 men (75.5%)). The baseline clinical characteristics are shown in table 1. The mean values of maximal LVWT and LA size were shown to be higher than the reference

Table 2 Primary endpoints according to the HCM Risk-SCD calculator

	Estimated HCM Risk-SCD category		
	Low (<4%)	Intermediate (4%–6%)	High (≥6%)
Patient, n (%)	615 (84.2)	65 (8.9)	50 (6.8)
Primary endpoint, n (%)	7 (43.8)	3 (18.8)	6 (37.5)
SCD	7 (63.6)	2 (18.2)	2 (18.2)
Appropriate ICD therapy	0 (0.0)	1 (20.0)	4 (80.0)
5 years event rate (95% CI)*	0.84 (0.31 to 1.82)	3.73 (0.77 to 10.9)	10.3 (3.76 to 22.3)

*Event rate presented as per 100 person-years.
HCM, hypertrophic cardiomyopathy; ICD, Implantable cardioverter-defibrillator; SCD, sudden cardiac death.

range of echocardiographic data.[13] Seven patients had a maximal LVWT ≥30 mm, all of whom did not achieve the primary endpoint. Eleven patients had an LV ejection fraction (LV-EF) ≤50% and one of them reached the primary endpoint; the patient was classified as intermediate-risk group.

Primary endpoint

During a mean follow-up duration of 4288 person-years, 16 (2.2%) patients reached the primary endpoint, 11 of whom had SCD. Among 21 patients (2.9%) who had an ICD implanted for primary prevention, five received appropriate ICD discharge for ventricular tachyarrhythmia. Thus, the event rate of the primary endpoint was 0.37 per 100 person-years (95% CI 0.21 to 0.61) at 1 year, 1.12 (0.64–1.82) at 3 years and 1.87 (1.07–3.03) at 5 years, respectively. The table 2 demonstrates the primary endpoint according to the HCM Risk-SCD calculator.

Validation of the HCM Risk-SCD calculator

The calibration plot of HCM Risk-SCD score illustrated a good agreement between the observed and predicted risk of primary endpoint (R^2=0.835) (figure 1). The C-statistics for the HCM Risk-SCD calculator was 0.718 (95% CI 0.562 to 0.852). The proportion of patients with the primary endpoint in the HCM Risk-SCD category was 1.1% (7/615), 4.6% (3/65) and 12.0% (6/50) (figure 2). Among the five patients who received appropriate ICD therapy, four (80.0%) were in the high-risk group

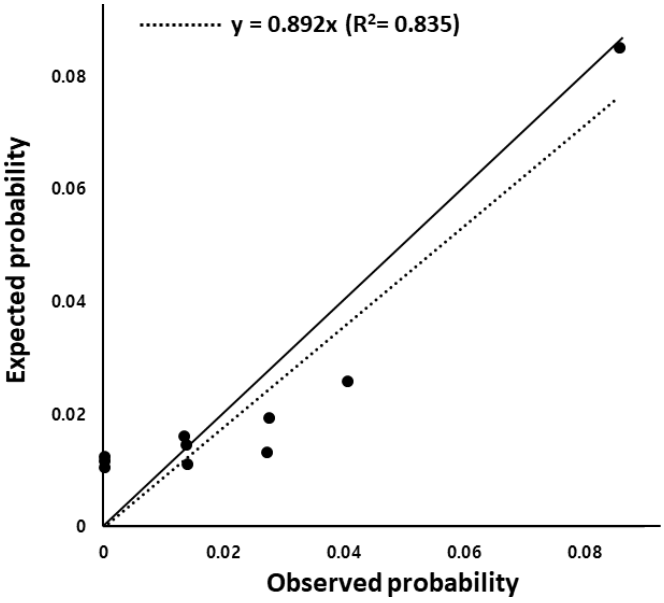
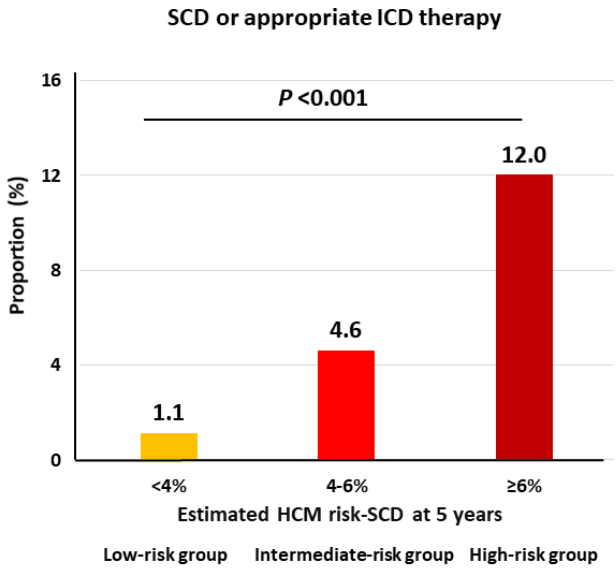


Figure 1 Calibration plot of the hypertrophic cardiomyopathy risk-sudden cardiac death score.



	Low-risk group	Intermediate-risk group	High-risk group
Estimated risk	<4%	4-6%	≥6%
Total number	615	65	50
Event number	7	3	6

Figure 2 The proportion of primary endpoint in three risk groups stratified by HCM Risk-SCD calculator. HCM, hypertrophic cardiomyopathy; ICD, implantable cardioverter-defibrillator; SCD, sudden cardiac death.

with no one in the low-risk group. The HCM Risk-SCD calculator generally well predicted the risk of the primary endpoint. Specifically, the intermediate-risk group had a 3.76 times higher risk of the primary endpoint than the low-risk group (p=0.055), while the high-risk group had a 10.9 times higher risk than the low-risk group (p<0.001) (table 3). As shown in figure 3, event-free survival rate was the worst in the higher risk group. Results were not changed in patients without IHD (online supplementary figure 1, and online supplementary tables 1 and 2).

Of note, although most patients (85.2%) without the primary endpoint could be classified into the low-risk groups, 7 of 11 SCD (63.6%) occurred in the low-risk group. Overall, the low-risk group (43.8%) and intermediate-risk group (18.8%) significantly contributed to the primary endpoint (figure 4). Online supplementary table 3 summarises the details of these seven patients.

Independent risk factors for the primary endpoint

The table 4 compares the differences in the baseline risk factors according to whether the primary endpoint was achieved or not. The primary endpoint occurred more frequently in women (p=0.036). Patients with the primary endpoint had a significantly larger mean LA size (p=0.009). Although mean LV-EF was significantly different between the two groups, they were within the normal range in both groups and the proportion of patients with LV-EF less than 50% was not different (p=0.22).

Table 3 HCM Risk-SCD calculator-based risk assessment

Variable	HR	95% CI	P value
Low risk, <4%	Reference	–	–
Intermediate risk, 4%–6%	3.76	0.97 to 14.6	0.055
High risk, ≥6%	10.9	3.67 to 32.5	<0.001

HCM, hypertrophic cardiomyopathy; SCD, sudden cardiac death.

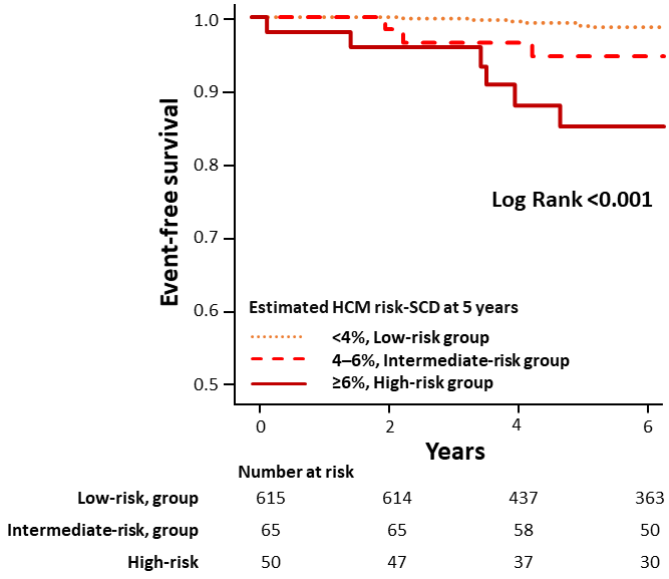


Figure 3 Kaplan-Meier curve for HCM patient by risk groups stratified by HCM Risk-SCD calculator. The primary endpoint was a composite of SCD or appropriate ICD therapy. HCM, hypertrophic cardiomyopathy; ICD, implantable cardioverter-defibrillator; SCD, sudden cardiac death.

In the univariate Cox regression analysis, sex significantly predicted the primary endpoint (online Supplementary table 4). In multivariate Cox regression analysis, the HCM Risk-SCD calculator (irrespective of continuous or categorical variable), sex (women) emerged as a predictor of the primary endpoint (online supplementary table 5). On the C-statistics for the prediction capability of the HCM Risk-SCD calculator, sex (women) had 0.630 (95% CI 0.500 to 0.761). The addition of sex (women) to the HCM Risk-SCD calculator significantly increased the C-index compared with the HCM Risk-SCD calculator alone (0.856, 95% CI 0.641 to 1.000 vs 0.718, 95% CI 0.562 to 0.852, p<0.001). In addition, compared with the HCM Risk-SCD calculator, the addition of sex (women) to the HCM Risk-SCD calculator resulted in a positive overall NRI of 0.557 (95% CI 0.089 to 1.057, p=0.015) (online supplementary table 6).

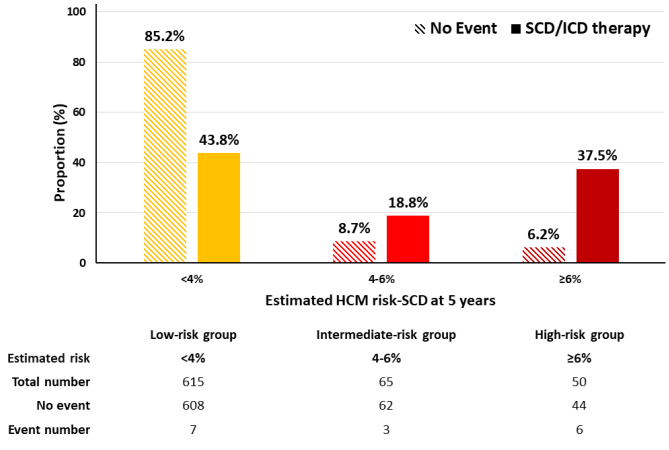


Figure 4 The distribution of patient with HCM with or without the primary endpoint in three risk groups stratified by HCM Risk-SCD calculator. HCM hypertrophic cardiomyopathy; ICD, implantable cardioverter-defibrillator; SCD, sudden cardiac death.

Table 4 Baseline risk factors of patients with and without primary endpoint

Variable	Patients without SCD or ICD therapy, n=716 (97.8%)	Patients with SCD or ICD therapy, n=16 (2.2%)	P value
Risk factor			
Age, years	56.1±14.3	56.4±15.0	0.858
Sex, male	543 (76.1)	8 (50.0)	0.036
Maximal LV wall thickness, mm	18.3±3.7	18.7±2.8	0.621
LA size, mm	44.1±6.7	48.6±8.2	0.009
Peak LVOT pressure gradient, mm Hg	15.2±25.5	15.8±26.7	0.920
LV ejection fraction, %	64.6±6.6	59.8±6.6	0.004
LV ejection fraction <50%	10 (1.4)	1 (6.2)	0.218
Family history of SCD	85 (11.9)	6 (37.5)	0.007
Non-sustained ventricular tachycardia	136 (19.0)	8 (50.0)	0.006
Unexplained syncope	93 (13.0)	5 (31.2)	0.081

Values presented as mean±SD for continuous variables and as the number (percentages) for categorical variables.
ICD, implantable cardioverter-defibrillator; LA, left atrium; LV, left ventricle; LVOT, left ventricular outflow track; SCD, sudden cardiac death.

DISCUSSION

This is the first study to validate the HCM Risk-SCD calculator endorsed by the 2014 ESC guidelines in a large independent cohort of Korean HCM population. The two main findings of the current study can be summarised as follows: first, although the HCM Risk-SCD calculator had a good predictability for SCD or appropriate ICD therapy for primary prevention, especially in the high-risk group, it misclassified significant proportion of high-risk patients into the low- or intermediate-risk group. Second, we observed a clinical utility of the sex factor on top of the HCM Risk-SCD calculator-based risk classification.

Although most patients with HCM are asymptomatic, SCD is the most catastrophic, unexpected event.[14] In terms of primary prevention of SCD, however, models for appropriately selecting patients who require prophylactic ICD have been under debate.[4] Therefore, previous guidelines suggested similar but diverse strategies to more effectively select patients with HCM at risk of SCD in a primary prevention setting.

The 2011 American College of Cardiology Foundation (ACCF)/American Heart Association (AHA) guideline suggested three major risk factors (ie, family history of SCD, unexplained syncope and maximal LVWT ≥30 mm) and two minor risk factors (ie, NSVT and abnormal blood pressure response to exercise) to assess the risk of SCD in patients with HCM.[15] As the 2011 ACCF/AHA guideline showed limited power for SCD risk prediction, a need for a novel prediction model for SCD risk stratification was called out. O'Mahony *et al* proposed a clinical risk prediction model to improve SCD risk stratification in patients with HCM,[10] which was officially adopted as the 2014 ESC risk prediction model for primary prevention of SCD in HCM.

Since the 2014 ESC guidelines was first published, three external independent validation studies have been performed in Europe and the USA. The first was a two-centre cohort study of 706 patients with HCM from Belgium and the Netherlands, demonstrating that the HCM Risk-SCD calculator improves primary risk stratification in patients with HCM (C-index, 0.69).[6] The second was a cohort of 1629 patients with HCM

from two US tertiary referral centres; in this study, Maron *et al* reported that 59% of patients with HCM with SCD or appropriate ICD therapies were misclassified with low-risk scores.[7] Finally, a large multicentre, international study proved the positive impact of the HCM Risk-SCD prediction model in clinical decision-making.[9] In addition, a systematic review and meta-analysis involving 7291 patients with HCM again recently reported the clinical value of the HCM Risk-SCD calculator.[16]

Given that HCM is as an inherited cardiomyopathy,[17] its clinical features and prognosis are likely to be variable depending on ethnicity.[18–20] Hence, it is essential to validate the HCM Risk-SCD calculator in a separate, independent and sizeable cohort of the Asian patients with HCM. This study confirmed that the HCM Risk-SCD calculator provides useful information on selecting patients with HCM at high risk in this Korean HCM population. However, we also found a drawback of the HCM SCD-Risk calculator when applied to the Korean population, that is, the low positive predictive value; 62.5% of patients with HCM who died from SCD or received appropriate ICD therapies were classified into the low-risk or intermediate-risk groups. These findings suggest that more than 50% of patients with HCM who are actually at risk of SCD can be unprotected, illustrating that the HCM Risk-SCD calculator appears to be incomplete in the Korean HCM population to predict SCD or appropriate ICD therapy, especially when the estimated SCD risk score is <4%. Therefore, in order to better classify the risk, additional variables seem to be required.

While the HCM Risk-SCD calculator represented a step forward in the SCD risk stratification, the accurate risk estimation remains challenging. Therefore, there is the unmet need to include new arbitrators in the HCM Risk-SCD calculator.[21] This study observed the sex factor (woman) to be important in the estimation of the risk of SCD or fatal tachyarrhythmia in this Korean HCM population. Although the significance of sex difference in the natural course of HCM remains hitherto unclear, female sex has been recently referred to as a risk factor for worse survival and progression to heart failure in HCM.[22] A large cohort study of 3673 patients with HCM revealed that female patients with HCM were older, more symptomatic, had a more advanced stage of diastolic dysfunction and obstructive physiology despite similar degree of LV hypertrophy and showed worse survival rates.[23] In addition, there have been reports on pathological differences between male and female patients with HCM.[24] In the current study, SCD or appropriate ICD therapies took place in a higher proportion in female (4.5%) patients than male (1.5%). Moreover, surprisingly, all seven patients reaching the primary endpoint despite being classified into the low-risk group by the HCM Risk-SCD calculator were women. After adjustment for confounding factors, female sex emerged as an independent risk factor the primary endpoint in this cohort. Although the relatively small number of study population do not allow for drawing a definite conclusion, we suggest that the prognosis of female patients with HCM might be less favourable, and thus the sex factor needs to be considered as an independent potential risk factor for prophylactic ICD. This may be attributed to genetic and/or hormonal effects, but more studies recruiting larger patients with HCM are required for validation of the sex factor as a significant risk for SCD.

LIMITATIONS

First, the number of patients enrolled was relatively small. However, as far as we know, this study included the largest number of Asian patients with HCM, and all of the patients were carefully followed with a complete data set. Although exclusion of missing data might introduce statistical bias, we believe that use of complete data set can guarantee the accuracy. Second, although it is reported that HCM is more prevalent in man with approximately 2:1 ratio, only 24.5% of women was recruited in this study.[25] Finally, like all the studies on the SCD risk stratification in HCM, this study retrospectively assessed and judged appropriate ICD therapies as equivalents of SCD. However, we considered only defibrillator shock, not antitachycardia pacing, as appropriate ICD therapy, because not all ventricular tachyarrhythmias cause SCD, and the ICD therapies depend mostly on different programming of devices.[26]

CONCLUSION

The HCM Risk-SCD calculator endorsed by the 2014 ESC guidelines showed a high negative predictive value and accuracy for SCD or appropriate ICD therapy in this homogeneous Korean HCM population. However, significant proportion of patients experiencing SCD events were misclassified into the low-risk or intermediate-risk group based on the HCM Risk-SCD calculator, suggesting that caution needs to be used for the application of the HCM Risk-SCD calculator to the Asian HCM population.

Key questions

What is already known on this subject?

- Hypertrophic cardiomyopathy (HCM), a myocardial disorder with an autosomal dominant inheritance, is a major cause of sudden cardiac death (SCD) in young adults. The HCM Risk-SCD calculator endorsed by the 2014 European Society of Cardiology (ESC) guidelines has been validated mostly in the Western population, but rarely in the Asian population.

What does this study add?

- This study purely including the Korean HCM population demonstrated that the HCM Risk-SCD calculator had a high negative predictive value and accuracy for SCD; however, a few patients with HCM experiencing the primary endpoint were misclassified as the low-risk or intermediate-risk groups. Apart from the HCM Risk-SCD calculator, sex (woman) emerged as independent predictor for the primary endpoint.

How might this impact on clinical practice?

- Although the HCM Risk-SCD calculator suggested by the 2014 ESC guidelines has a high negative predictive value and accuracy for SCD or appropriate ICD therapy in the Korean population, considering sex factor in conjunction with the HCM Risk-SCD calculator could provide better prognostic information to select patients with HCM at high risk.

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Patient consent for publication Not required.

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Provenance and peer review Not commissioned; externally peer reviewed.

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