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The Long-Term Mortality Predictors in Hypertrophic Cardiomyopathy Patients with Low Risk of Sudden Cardiac Death

Ani Kardiyak Ölüm Riski Düşük Olan Hipertrofik Kardiyomiyopati Vakalarında Uzun Dönem Mortalite Tahmin Edicileri

ABSTRACT

Objective: Hypertrophic cardiomyopathy (HCM) is a common hereditary cardiac disorder. Clinical presentations in the Turkish population may differ from those observed in other countries. This study aimed to evaluate the relationship between the sudden cardiac death (SCD) risk score and long-term mortality in low-risk HCM patients and to identify predictors of long-term mortality. Additionally, it investigated the clinical characteristics and outcomes of HCM patients at a tertiary cardiology center.

Method: Between 2004 and 2021, a total of 340 HCM patients without implantable cardioverter defibrillators were followed at a single tertiary cardiology center in Türkiye. This was a retrospective study. The HCM Risk-SCD score was used to integrate demographic and clinical variables to estimate the predicted five-year risk of death. Patients with an HCM Risk-SCD score of less than 4% were divided into three equal tertiles, ranging from low to high SCD scores. These tertiles were then compared.

Results: Our study identified older age [hazard ratio (HR) 95% confidence interval (CI): 1.048 (1.018-1.080)], a history of cerebrovascular accident [HR 95% CI: 3.675 (1.158-11.656)], and elevated neutrophil count [HR 95% CI: 1.450 (1.250-1.681)] as independent risk factors for long-term mortality in the cohort with HCM Risk-SCD < 4%. The receiver operating characteristic (ROC) curve demonstrated that the optimal HCM Risk-SCD threshold for predicting long-mortality in the overall study cohort was > 1.79, with 55% sensitivity and 55% specificity (area under the curve (AUC): 0.60, 95% CI: 0.52-0.69, P < 0.001). No statistically significant difference in long-term mortality was observed among the tertiles in the Kaplan-Meier analysis (P = 0.296).

Conclusion: Advanced age, cerebrovascular accident, and elevated neutrophil count are independent predictors of long-term mortality in patients with an HCM Risk-SCD score < 4%. Patients classified as low risk should undergo further evaluation using complementary tools to help prevent SCD.

Keywords: Hypertrophic Cardiomyopathy Risk-Sudden Cardiac Death score, Hypertrophic cardiomyopathy, mortality

ÖZET

Amaç: Hipertrofik kardiyomiyopati (HKMP) yaygın görülen kalıtsal bir kardiyak hastalıktır ve klinik seyri Türk popülasyonunda, diğer uluslara göre farklılıklar gösterebilir. Bu çalışma, HKMP hastalarında ani kardiyak ölüm skoru düşük olanlar ile uzun vadeli mortalite arasındaki ilişkiyi ve uzun vadeli mortalitenin öngörücülerini incelemiştir. Ayrıca Türkiye'deki üçüncü basamak bir kardiyoloji merkezindeki HKMP hastalarının klinik özelliklerini ve sonuçlarını araştırmayı amaçlamıştır.

Yöntem: Çalışma, 2004–2021 yılları arasında Türkiye'deki tek bir üçüncü basamak kardiyoloji merkezinde takip edilen, implante edilebilir kardiyoverter defibrilatörü olmayan 340 HKMP hastasından oluşmuştur. Çalışma retrospektif olarak yürütülmüştür. Demografik ve klinik değişkenler, öngörülen 5 yıllık riskle birlikte HKMP Risk-ani kardiyak ölüm skoru kullanılarak bir araya getirilmiştir. HKMP Risk-ani kardiyak ölüm skoru <%4 olan hastalar ani kardiyak ölüm skoru düşükten yükseğe olacak şekilde 3 eşit gruba ayrılmış ve daha sonra birbirleriyle karşılaştırılmıştır.

Bulgular: Çalışmamızda ileri yaş [HR %95 CI, 1.048 (1.018-1.080)], serebrovasküler olay insidansı [HR %95 CI, 3.675 (1.158-11.656)] ve yüksek nötrofil sayısı [HR %95 CI, 1.450 (1.250-1.681)] HKMP Risk-ani kardiyak ölüm skoru < %4 olan hastalarda uzun dönem

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mortalite için bağımsız risk faktörleri olarak belirlendi. ROC eğrisi, genel çalışma kohortunda uzun dönem mortaliteyi tahmin etmek için HCM Risk-SCD'nin optimum değerinin %55 duyarlılık ve %55 özgüllük ile > 1.79 olduğunu ortaya koydu [eğri altında kalan alan (AUC): 0.60, %95 CI: 0.52-0.69, P < 0.001). Kaplan-Meier eğrisinde hastalar arasında uzun dönem mortalite açısından istatistiksel olarak anlamlı bir fark saptanmadı (P = 0,296).

Sonuç: İleri yaş, serebrovasküler olay ve yüksek nötrofil sayısı HKMP Risk-ani kardiyak ölüm skoru <4% hastalarında uzun vadeli mortalite için bağımsız risk faktörleridir. Düşük riske sahip bu hastalar ani kardiyak ölümü önlemek için ek araçlarla daha fazla değerlendirilmelidir.

Anahtar Kelimeler: HKMP Risk-ani kardiyak ölüm skoru, Hipertrofik kardiyomiyopati, mortalite

Hypertrophic cardiomyopathy (HCM) is a hereditary cardiomyopathy characterized by abnormal thickening of the left ventricle (LV) in the absence of other causes.[1] According to several studies, the overall prevalence of HCM in adults is 0.2%.[2]

Diagnosis is typically made based on the presence of symptoms (most commonly dyspnea, chest pain, palpitations, or syncope), or through incidental findings such as abnormalities on a 12-lead electrocardiogram (ECG), detection of a murmur, or cardiac imaging during familial screening. The pathophysiology of HCM involves multiple mechanisms, including myocardial ischemia, autonomic dysfunction, diastolic dysfunction, mitral regurgitation (MR), dynamic left ventricular outflow tract obstruction (LVOTO), and arrhythmias.[3]

While the majority of HCM patients remain asymptomatic, a significant proportion experience complications such as atrial fibrillation (AF), heart failure, or sudden cardiac death (SCD) during their lifetime.[4] One study found that 51% of SCD cases in HCM were attributable to malignant arrhythmias. Long-term outcome studies suggest that advances such as the use of implantable cardioverter-defibrillators (ICDs), modern cardiovascular pharmacotherapy, and timely interventions for high-risk individuals have reduced HCM-related mortality to less than 1.0% per year.[4-6] Despite current guidelines not recommending ICD placement in patients with low-risk HCM Risk-SCD scores, the mortality rate in this group remains noteworthy and requires further investigation.[7] A study by Pay et al.[8] demonstrated that while the HCM Risk-SCD model is effective in identifying patients at high risk for SCD, the sensitivity of the score declines progressively as the score increases. According to their findings, there is a lack of evidence regarding predictors of long-term mortality in patients with an HCM Risk-SCD score < 4 %, a group classified as low risk for SCD, yet associated with the highest model sensitivity. The present study aims to address this gap in the literature by examining the clinical characteristics and long-term outcomes of HCM patients managed at a tertiary care center. The primary endpoint of the study was defined as all-cause long-term mortality.

ABBREVIATIONS

AF	Atrial fibrillation
CI	Confidence interval
CMRI	Cardiac magnetic resonance imaging
ECG	Electrocardiogram
EF	Ejection fraction
ESC	European Society of Cardiology
HCM	Hypertrophic cardiomyopathy
HR	Hazard ratio
ICDs	Implantable cardioverter-defibrillators
LA	Left atrium
LV	Left ventricle
LVOTO	Left ventricular outflow tract obstruction
MR	Mitral regurgitation
ROC	Receiver operating characteristic
SAM	Systolic anterior motion
SCD	Sudden cardiac death
TTE	Transthoracic echocardiography
VT	Ventricular tachycardia

Materials and Methods

Study Design and Participants

This retrospective study included 340 patients with HCM and an HCM Risk-SCD score < 4%, who were followed at a single tertiary cardiac center between 2004 and 2021. HCM was diagnosed based on a maximal end-diastolic wall thickness of ≥ 15 mm in any left ventricular myocardial segment, as assessed by cardiac magnetic resonance imaging (CMRI) or 2D transthoracic echocardiography (TTE), in the absence of clinical signs of pressure overload or other etiologies. Mild hypertrophy (13-14 mm) may be considered diagnostic when observed in relatives of patients with HCM, or in individuals with a positive genetic test revealing a pathogenic or likely pathogenic variant, often in a sarcomere gene.[9] Due to the absence of genetic testing data in our dataset, only patients with a maximum end-diastolic wall thickness of ≥ 15 mm were included for the diagnosis of HCM. Patients with moderate to severe aortic stenosis, hypertensive cardiomyopathy, athlete's heart, hypertrophy due to systemic diseases, and other secondary causes of LV hypertrophy, including anteroapical post-infarction obstruction and stress cardiomyopathy, were excluded. To avoid diagnostic ambiguity, hypertensive patients with an end-diastolic wall thickness < 15 mm, as well as those who showed a reduction in wall thickness following antihypertensive therapy, were also excluded. In hypertensive patients with a maximum end-diastolic wall thickness of ≥ 15 mm, additional criteria supporting the diagnosis of HCM were evaluated. These included the presence of systolic anterior motion (SAM), cardiac MRI findings indicative of HCM, and a family history of the disease.[5,10] A comprehensive review of the electronic medical database was conducted to collect demographic, clinical, and echocardiographic data. Based on post-diagnosis clinical criteria, the HCM Risk-SCD

Table 1. Baseline Clinical Characteristics of Patients with Hypertrophic Cardiomyopathy Risk-Sudden Cardiac Death (HCM Risk-SCD) < 4%, Grouped by Risk Tertiles

	Patient Groups by HCM Risk-SCD Tertiles			P
	Tertile 1 (n = 114)	Tertile 2 (n = 113)	Tertile 3 (n = 113)	
Age, years	56 ± 12	59 ± 13	64 ± 12	<0.001
Male gender, n (%)	69 (60.5)	72 (63.7)	79 (69.9)	0.323
Diabetes mellitus, n (%)	22 (19.3)	18 (15.9)	15 (13.3)	0.466
Insulin-dependent diabetes mellitus, n (%)	4 (3.5)	2 (1.8)	2 (1.8)	0.607
Hyperlipidemia, n (%)	20 (17.5)	16 (14.2)	14 (12.4)	0.537
Hypertension, n (%)	52 (45.6)	50 (44.2)	41 (36.3)	0.307
Chronic obstructive pulmonary disease, n (%)	7 (6.1)	5 (4.4)	6 (5.3)	0.847
Cerebrovascular accident, n (%)	5 (4.4)	7 (6.2)	3 (2.7)	0.432
Atrial fibrillation, n (%)	23 (20.2)	37 (32.7)	27 (23.9)	0.084
Coronary artery disease, n (%)	44 (38.6)	37 (32.7)	36 (31.9)	0.509
Percutaneous coronary intervention, n (%)	18 (15.8)	9 (8.0)	15 (13.3)	0.188
Coronary artery bypass grafting, n (%)	9 (7.9)	8 (7.1)	6 (5.3)	0.731
Chronic kidney disease, n (%)	9 (7.9)	14 (12.4)	6 (5.3)	0.156
Heart failure with preserved ejection fraction, n (%)	4 (3.5)	13 (11.5)	14 (12.4)	0.038

Values are presented as mean ± standard deviation, median (25^{th}–75^{th} interquartile range), or n (%). HCM Risk-SCD, Hypertrophic Cardiomyopathy Risk-Sudden Cardiac Death.

score was calculated for each patient, following the guidelines established by the European Society of Cardiology (ESC). The ESC recommends using the HCM Risk-SCD score, a seven-parameter model, to estimate the five-year risk of SCD.[9] This scoring system classifies patients into low-risk (five-year risk of SCD < 4%), intermediate-risk (4-6%), or high-risk (≥ 6%) categories.[5] Of the 389 HCM patients, 49 with intermediate or high five-year SCD risk scores were excluded, and the study was conducted on the remaining 340 low-risk patients. These 340 patients were divided into three equal tertiles, with increasing SCD risk probability from tertile 1 to tertile 3. The SCD risk probabilities for patients in tertile 1, tertile 2, and tertile 3 were 1.1 (0.9-1.2), 1.7 (1.5-1.8), and 2.5 (2.2-3.0), respectively. Only patients who had not received an ICD were included in the study. All data were obtained from the patients' initial clinical evaluation. The study was conducted in strict accordance with the principles outlined in the Declaration of Helsinki and its subsequent amendments. Ethical approval was granted by the Health Sciences University Hamidiye Scientific Research Ethics Board (Approval Number: 28/17, Date: 30.12.2022).

Echocardiography

Transthoracic echocardiography was performed in accordance with the current recommendations of the American Society of Echocardiography.[11] Experienced cardiologists performed TTE using either the Vivid 7 system (GE Vingmed Ultrasound AS, Horten, Norway) or the Philips EPIQ 7C ultrasound system (Philips Healthcare, Andover, Mass, USA), both equipped with an X5-1 matrix-array transducer. The LV ejection fraction (EF) was calculated using the modified Simpson's method, and end-diastolic and end-systolic LV volumes were assessed. Maximum LV wall thickness was measured in parasternal long- and short-axis views and recorded as the greatest observed wall thickness. LV outflow tract obstruction was defined as a peak instantaneous outflow gradient ≥ 30 mmHg at rest or during provocation, as measured by continuous-wave Doppler. The anterior motion of the mitral valve during systole was assessed using M-mode imaging.

Statistical Analysis

Statistical analyses were performed using the Statistical Package for the Social Sciences, version 20.0 (SPSS; IBM, Armonk, New York, USA). Based on the HCM Risk-SCD score assessed at admission, the study population was divided into three groups (tertiles 1 to 3), starting from the lowest risk. Baseline characteristics, TTE measurements, laboratory results, and medical treatments were compared among the groups. The Kolmogorov-Smirnov test was used to assess the normality of data distribution. Continuous variables with a normal distribution were expressed as mean (standard deviation, SD), while those not normally distributed were presented as median (Q1-Q3). The median (interquartile range) was used to present quantitative variables. The Kruskal-Wallis test was applied to compare continuous variables with skewed distributions. Categorical variables were presented as percentages and numbers, and Pearson's chi-square test was used for their comparison. Hazard ratios (HRs) were reported with 95% confidence intervals (CIs), and a two-tailed p-value of < 0.05 was considered statistically significant. Independent risk factors for long-term mortality were identified using univariable and multivariable Cox regression analyses (enter method). To identify independent predictors of long-term mortality, multivariable Cox regression analysis included variables with a p-value of 0.05 in the univariable analysis. Cut-off values for HCM Risk-SCD and long-term mortality, with the highest sensitivity and specificity, were determined using nonparametric receiver operating characteristic (ROC) curve analysis. The Kaplan-Meier and log-rank tests were used to compare long-

Table 2. Laboratory, Echocardiographic, and Clinical Findings in Patients with Hypertrophic Cardiomyopathy Risk-Sudden Cardiac Death (HCM Risk-SCD) < 4%, Stratified by Risk Tertiles

	Patient Groups by HCM Risk-SCD Tertiles			P
	Tertile 1 (n = 114)	Tertile 2 (n = 113)	Tertile 3 (n = 113)	
Laboratory Variables				
Hb, (g/dL)	13.4 (11.7–15.1)	13.5 (11.9–14.7)	13.9 (12.0–15.1)	0.402
Lymphocyte count, (%)	2.0 (1.4–2.5)	2.0 (1.4–2.5)	1.9 (1.5–2.4)	0.567
Monocyte count, (%)	0.53 (0.40–0.66)	0.51 (0.42–0.66)	0.53 (0.44–0.69)	0.197
Neutrophil count, (cells/μL)	7.3 (6.5–8.4)	7.6 (6.7–9.2)	7.6 (6.7–9.7)	0.129
Platelet count, (10^3/μL)	229 (193–292)	233 (203–274)	224 (184–265)	0.253
Creatinine, (mg/dL)	0.9 (0.8–1.0)	0.9 (0.8–1.1)	0.9 (0.8–1.0)	0.633
Urea, (mg/dL)	25 (19–34)	25 (21–43)	25 (20–38)	0.535
AST, (U/L)	23 (19–39)	24 (19–36)	25 (20–39)	0.633
ALT, (U/L)	20 (16–29)	22 (15–35)	21 (14–31)	0.609
TSH, (mIU/L)	1.4 (0.8–2.5)	1.6 (1.1–2.3)	1.5 (1.0–2.1)	0.336
Albumin, (mg/dL)	4.1 (4.0–4.4)	4.1 (4.0–4.5)	4.1 (4.0–4.4)	0.453
Glucose, (mg/dL)	99 (95–115)	100 (92–116)	99 (92–117)	0.933
HbA1c, (%)	5.5 (5.4–6.0)	5.5 (5.4–5.8)	5.4 (5.4–5.7)	0.528
Total cholesterol, (mg/dL)	199 (178–225)	203 (164–223)	200 (166–217)	0.710
LDL, (mg/dL)	123 ± 35	117 ± 37	120 ± 34	0.346
HDL, (mg/dL)	40 ± 11	41 ± 20	40 ± 16	0.802
Triglycerides, (mg/dL)	146 (100–198)	157 (100–219)	151 (97–193)	0.410
Medical Therapy				
Beta-blocker use, %	97 (85.1)	98 (86.7)	98 (86.7)	0.918
Echocardiographic Parameters				
Ejection fraction, %	60 (55–60)	60 (55–60)	60 (60–60)	0.022
LVEDD, (mm)	45 (41–50)	47 (42–50)	46 (42–50)	0.143
LVESD, (mm)	27 (23–30)	27 (24–31)	27 (23–31)	0.625
Maximal wall thickness, (mm)	17 (16–19)	18 (16–21)	19 (17–24)	<0.001
LV outflow gradient, (mmHg)	25 (20–33)	28 (21–35)	29 (22–32)	0.190
LV outflow gradient > 50 mmHg, n (%)	4 (3.4)	9 (7.9)	3 (2.8)	0.140
LA diameter, (mm)	39 (36–44)	45 (37–50)	44 (39–50)	<0.001
Clinical Findings According to HCM Risk-SCD Score				
Syncope, n (%)	4 (3.5)	3 (2.7)	16 (14.2)	<0.001
Positive family history of SCD, n (%)	1 (0.9)	3 (2.7)	9 (8.0)	0.015
Non-sustained VT, n (%)	5 (4.4)	2 (1.8)	11 (9.7)	0.024
Long-term mortality, n (%)	2 (1.8)	16 (14.2)	11 (9.7)	0.003

All values are expressed as mean ± standard deviation, median (25^{th}–75^{th} interquartile range), or n (%). ALT, Alanine Transaminase; AST, Aspartate Transaminase; Hb, Hemoglobin; HbA1c, Hemoglobin A1c; HCM Risk-SCD, Hypertrophic Cardiomyopathy Risk-Sudden Cardiac Death; HDL, High-Density Lipoprotein; LA, Left Atrium; LDL, Low-Density Lipoprotein; LV, Left Ventricle; LVEDD, Left Ventricular End-Diastolic Dimension; LVESD, Left Ventricular End-Systolic Dimension; TSH, Thyroid-Stimulating Hormone; VT, Ventricular Tachycardia.

term survival between groups, which were formed based on the optimal cut-off value derived from the ROC curve.

Results

In this study, 340 patients with an HCM Risk-SCD score < 4% were divided into three equal tertiles based on increasing SCD risk probability. Patients were followed for an average of 55.5 ± 12.7 months. Tertile 1 (lowest risk) included 114 patients, while tertiles 2 and 3 each comprised 113 patients, with tertile 3 representing the highest SCD risk. The mean age in tertile 3 was 64 ± 12 years, which was significantly higher than in the other tertiles. The incidence of heart failure with preserved EF was also significantly greater in tertile 3. Apart from these findings, no differences were observed in demographic or clinical characteristics among the tertiles. Table 1 summarizes the demographic and clinical features of the study population.

Table 3. Univariable and Multivariable Analyses of Long-Term Mortality in Patients with Hypertrophic Cardiomyopathy Risk-Sudden Cardiac Death (HCM Risk-SCD) < 4%

	Univariable Analysis		Multivariable Analysis	
	P	HR (95% CI)	P	HR (95% CI)
Age	<0.001	1.058 (1.029-1.087)	0.002	1.048 (1.018-1.080)
Chronic obstructive pulmonary disease	0.043	2.973 (1.034-8.542)	0.061	3.198 (0.949-10.783)
Cerebrovascular accident	0.014	3.765 (1.310-10.823)	0.027	3.675 (1.158-11.656)
Heart failure with preserved ejection fraction	<0.001	7.323 (3.454-15.528)	0.451	1.511 (0.516-4.425)
Neutrophil count	<0.001	1.463 (1.314-1.629)	<0.001	1.450 (1.250-1.681)
LV outflow gradient	<0.001	1.074 (1.049-1.099)	0.056	1.033 (0.999-1.069)
LA diameter	<0.001	1.104 (1.055-1.154)	0.160	1.045 (0.983-1.112)
Syncope	<0.001	8.421 (3.910-18.138)	0.939	1.075 (0.169-6.839)
Positive family history for SCD	<0.001	14.562 (6.593-32.163)	0.329	2.596 (0.383-17.608)

All clinically relevant parameters were included in the model. CI, Confidence Interval; HCM Risk-SCD, Hypertrophic Cardiomyopathy Risk-Sudden Cardiac Death; HR, Hazard Ratio; LA, Left Atrium; LV, Left Ventricle.

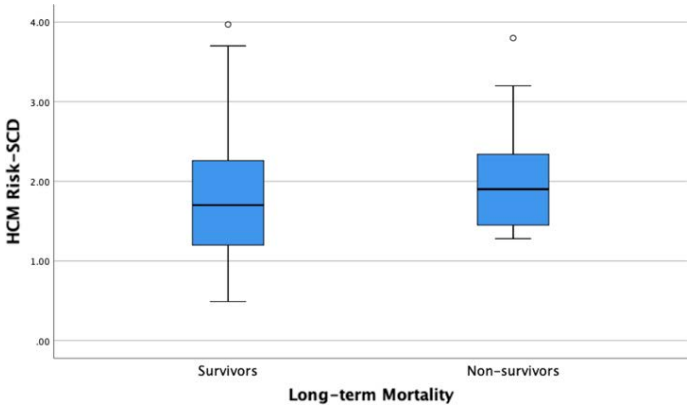

Figure 1. Box plot of long-term mortality by HCM Risk-SCD.

HCM Risk-SCD, Hypertrophic Cardiomyopathy Risk-Sudden Cardiac Death.

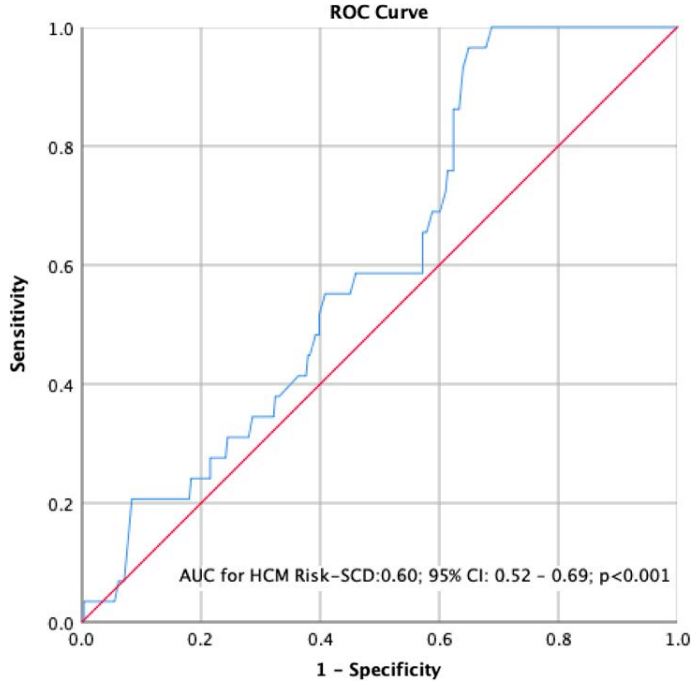

Figure 2. Receiver operating characteristic (ROC) curve analysis of HCM Risk-SCD.

AUC, Area Under the Curve; CI, Confidence Interval; HCM Risk-SCD, Hypertrophic Cardiomyopathy Risk-Sudden Cardiac Death.

Table 2 presents the laboratory data, TTE results, and clinical findings of all categorized patients. No statistically significant differences were observed among the tertiles in laboratory measurements, including neutrophil counts. Except for maximal wall thickness and left atrial (LA) diameter, all TTE measurements were statistically similar across the tertiles. Syncope, a positive family history of SCD, non-sustained ventricular tachycardia (VT) on 24-hour ECG monitoring, and long-term mortality were all significantly more common in tertile 3.

In univariate regression analysis, age, chronic obstructive pulmonary disease, cerebrovascular accident, heart failure with preserved EF, neutrophil count, LV outflow gradient, LA diameter, syncope, and a positive family history of SCD were identified as significant predictors of long-term mortality in the HCM Risk-SCD < 4% group. In the subsequent multivariate analysis, increasing age, a higher number of cerebrovascular accident events, and elevated neutrophil levels were determined to be independent predictors of long-term mortality. Table 3 presents the results of the univariate and multivariate models for long-term mortality in patients with an HCM Risk-SCD score < 4%.

Figure 1 displays a box plot of long-term mortality rates according to HCM Risk-SCD scores. This figure indicates that although patients with long-term mortality tended to have higher HCM Risk-SCD scores, the difference was not statistically significant compared to those without long-term mortality.

ROC curve analysis identified 1.79 as the optimal cut-off value for HCM Risk-SCD, with 55% sensitivity and 55% specificity for predicting long-term mortality (area under the curve (AUC): 0.60, 95% CI: 0.52-0.69, P < 0.001) (Figure 2). Using this cut-off, a Kaplan-Meier curve was generated (Figure 3). However, no statistically significant difference in long-term mortality was found between patients with HCM Risk-SCD scores above and below 1.79 (P = 0.296).

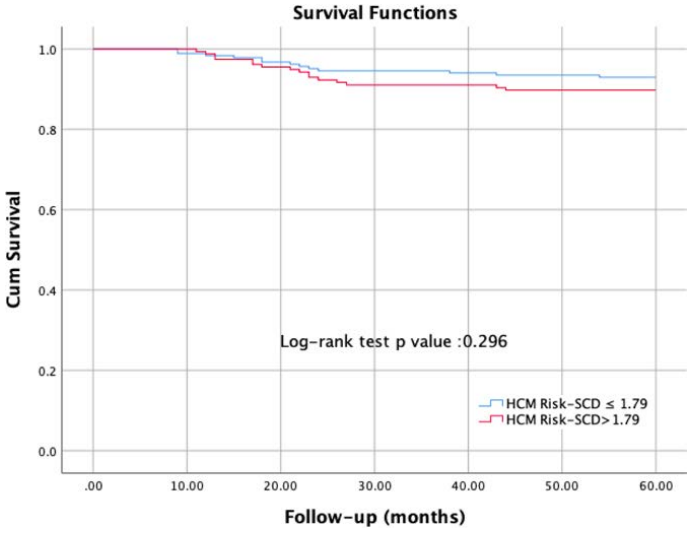

Figure 3. Kaplan-Meier curves comparing long-term mortality rates between patients with HCM Risk-SCD > 1.79 and those with HCM Risk-SCD ≤ 1.79.

HCM Risk-SCD, Hypertrophic Cardiomyopathy Risk-Sudden Cardiac Death.

Discussion

This retrospective analysis of the Turkish population revealed several important findings. Our study demonstrated that the SCD score alone lacks adequate sensitivity to predict long-term mortality in low-risk patients with an HCM Risk-SCD score < 4%. Advanced age, a history of cerebrovascular accidents, and elevated neutrophil counts were identified as independent risk factors that may improve the predictive sensitivity of the SCD score.

AF occurs in approximately 25% of patients with HCM, with an annual incidence of 2% to 3%. Our findings align with the current literature, showing that the prevalence of AF in patients with an HCM Risk-SCD score < 4% ranges from 23% to 37%.[6,12] Compared to patients in sinus rhythm, those with AF are at significantly higher risk for thromboembolism, heart failure, and mortality.[13] It is well-established that the incidence of SCD is elevated in patients with AF.[14] While multiple hypotheses have been proposed, AF is thought to contribute to SCD both by triggering ventricular arrhythmias and by creating a substrate that predisposes to them. Additionally, AF is a major risk factor for coronary artery disease, heart failure, and stroke, conditions that can directly lead to SCD. This fact should not be overlooked.[15] Although AF is not included as a risk factor in the HCM Risk-SCD score, a significant proportion of patients with AF is still observed, even among those classified as low risk.[5] We propose that the presence of AF may contribute to the reduced sensitivity of the risk score.

In two comparable studies, the average age of HCM patients at assessment was 41 years; however, in our study, the average age ranged from 56 to 64 years, reflecting a comparatively older patient population.[16,17] Maron et al.[6] reported that heart failure and stroke-related mortality were more common in middle-aged and older patients. It is also well established that advancing age is associated with a higher prevalence of cardiovascular disease and AF, which in turn contributes to increased mortality rates.[18,19] The study by Alashi et al.[20] found that while elderly HCM patients had a higher overall burden of cardiovascular risk factors, they tended to have lower HCM Risk-SCD scores. In our cohort of HCM patients with a Risk-SCD score < 4%, advanced age and a history of cerebrovascular accidents were identified as independent risk factors for long-term mortality, likely due to the higher mean age of our study population compared to those in earlier studies.

Inflammation plays a crucial role in cardiovascular diseases, and elevated neutrophil levels have been linked to myocardial fibrosis and increased arrhythmogenic potential, both key contributors to SCD.[21,22] In HCM, myocardial fibrosis is characterized by ongoing low-grade systemic and local inflammation. Proposed triggers in its pathogenesis include mechanical stress, mitochondrial oxidative stress, sarcomere injury, microvascular dysfunction, and cardiomyocyte dysregulation. Myocardial fibrosis is a central factor contributing to malignant arrhythmias and reduced ventricular function in HCM.[22,23] Wang et al.[24] identified both a high neutrophil-to-lymphocyte ratio and elevated neutrophil levels as independent risk factors for all-cause mortality in patients with HCM. For the first time in the literature, our study demonstrates that patients with an HCM Risk-SCD score < 4% and elevated neutrophil counts are independently at risk for long-term mortality. A comprehensive investigation into the relationship between neutrophil count and HCM may support the inclusion of inflammatory markers, such as neutrophils, in risk assessment models or in evaluating the benefits of anti-inflammatory therapy for these patients in the future.

The average annual mortality rate reported in HCM studies is 6%; however, a comprehensive study by Jacobsen et al.[25] reported a long-term mortality rate of 16.5% over five years. Among patients with an HCM Risk-SCD score of < 4%, long-term mortality rates have ranged from 2% to 16%. Our study population consisted of patients who did not have an ICD at baseline or during follow-up. This may partially explain the observed long-term mortality rate. Although tertile 2 in our study had a lower SCD score than tertile 3, it showed a higher long-term mortality rate. While this may initially seem contradictory, our statistical analysis indicates that the SCD score has low sensitivity in predicting long-term mortality in the HCM Risk-SCD < 4% group, which may explain this unexpected outcome.

Limitations

Several limitations of our study should be noted. First, our retrospective analysis used data from a single center. The restricted patient population poses a significant limitation, as key parameters such as LV maximum wall thickness and non-sustained VT, known independent predictors of SCD in HCM, were not identified as independent predictors in our study. Therefore, our findings require validation in larger cohorts. Second, our data were limited to β-blocker use; we lacked information on other medications and septal reduction therapies, which restricts the scope of our conclusions. Cardiac biopsy was not performed to confirm the diagnosis of HCM, and the absence of genetic screening data prevented analysis of HCM-specific mutation rates. Third, the exclusion of CMR data limited our ability to perform related analyses. Furthermore, while all-cause mortality was used as the study endpoint, the specific causes of death were not included in our dataset. To confirm and clarify our findings and their therapeutic implications, larger prospective studies are necessary.

Conclusion

This retrospective study on HCM patients at a tertiary referral hospital in Türkiye demonstrated that the SCD risk score alone is insufficient for predicting long-term mortality. Advanced age, cerebrovascular accidents, and elevated neutrophil counts were identified as independent risk factors for long-term mortality among patients with an HCM Risk-SCD score < 4%. We propose that incorporating such independent risk variables may improve the predictive sensitivity of the SCD risk score.

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References

1. Lee HJ, Kim J, Chang SA, Kim YJ, Kim HK, Lee SC. Major clinical issues in hypertrophic cardiomyopathy. *Korean Circ J*. 2022;52(8):563-575. [CrossRef]
2. Hada Y, Sakamoto T, Amano K, et al. Prevalence of hypertrophic cardiomyopathy in a population of adult Japanese workers as detected by echocardiographic screening. *Am J Cardiol*. 1987;59(1):183-184. [CrossRef]
3. Ommen SR, Mital S, Burke MA, et al. 2020 AHA/ACC Guideline for the diagnosis and treatment of patients with hypertrophic cardiomyopathy: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *Circulation*. 2020;142(25):e558-e631. [CrossRef]
4. Rowin EJ, Maron MS, Chan RH, et al. Interaction of adverse disease related pathways in hypertrophic cardiomyopathy. *Am J Cardiol*. 2017;120(12):2256-2264. [CrossRef]
5. Authors/Task Force members, Elliott PM, Anastasakis A, et al. 2014 ESC Guidelines on diagnosis and management of hypertrophic cardiomyopathy: The Task Force for the Diagnosis and Management of Hypertrophic Cardiomyopathy of the European Society of Cardiology (ESC). *Eur Heart J*. 2014;35(39):2733-2779. [CrossRef]
6. Maron BJ, Olivotto I, Spirito P, et al. Epidemiology of hypertrophic cardiomyopathy-related death: Revisited in a large non-referral-based patient population. *Circulation*. 2000;102(8):858-864. [CrossRef]
7. Desai MY, Smedira NG, Dhillon A, et al. Prediction of sudden death risk in obstructive hypertrophic cardiomyopathy: Potential for refinement of current criteria. *J Thorac Cardiovasc Surg*. 2018;156:750-759.e3. [CrossRef]
8. Pay L, Çetin T, Dereli Ş, et al. Validation of the HCM Risk-SCD model in patients with hypertrophic cardiomyopathy and future perspectives. *Pacing Clin Electrophysiol*. 2023;46(12):1519-1525. [CrossRef]
9. Ommen SR, Ho CY, Asif IM, et al. 2024 AHA/ACC/AMSSM/HRS/PACES/SCMR Guideline for the management of hypertrophic cardiomyopathy: A Report of the American Heart Association/American College of Cardiology Joint Committee on Clinical Practice Guidelines. *Circulation*. 2024;149(23):e1239-e1311. [CrossRef]
10. O'Mahony C, Jichi F, Pavlou M, et al. A novel clinical risk prediction model for sudden cardiac death in hypertrophic cardiomyopathy (HCM risk-SCD). *Eur Heart J*. 2014;35(30):2010-2020. [CrossRef]
11. Mitchell C, Rahko PS, Blauwet LA, et al. Guidelines for performing a comprehensive transthoracic echocardiographic examination in adults: Recommendations from the American Society of Echocardiography. *J Am Soc Echocardiogr*. 2019;32(1):1-64. [CrossRef]
12. Marian AJ, Braunwald E. Hypertrophic cardiomyopathy: Genetics, pathogenesis, clinical manifestations, diagnosis, and therapy. *Circ Res*. 2017;121(7):749-770. [CrossRef]
13. Alphonse P, Virk S, Collins J, et al. Prognostic impact of atrial fibrillation in hypertrophic cardiomyopathy: A systematic review. *Clin Res Cardiol*. 2021;110(4):544-554. [CrossRef]
14. Liao MT, Wu CK, Juang JJ, Lin TT, Wu CC, Lin LY. Atrial fibrillation and the risk of sudden cardiac arrest in patients with hypertrophic cardiomyopathy – A nationwide cohort study. *EClinicalMedicine*. 2021;34:100802. [CrossRef]
15. Waldmann V, Jouven X, Narayanan K, et al. Association between atrial fibrillation and sudden cardiac death: Pathophysiological and epidemiological insights. *Circ Res*. 2020;127(2):301-309. [CrossRef]
16. Kofflard MJ, Ten Cate FJ, van der Lee C, van Domburg RT. Hypertrophic cardiomyopathy in a large community-based population: Clinical outcome and identification of risk factors for sudden cardiac death and clinical deterioration. *J Am Coll Cardiol*. 2003;41(6):987-993. [CrossRef]
17. Cecchi F, Olivotto I, Montereggi A, Santoro G, Dolara A, Maron BJ. Hypertrophic cardiomyopathy in Tuscany: Clinical course and outcome in an unselected regional population. *J Am Coll Cardiol*. 1995;26(6):1529-1536. [CrossRef]
18. North BJ, Sinclair DA. The intersection between aging and cardiovascular disease. *Circ Res*. 2012;110(8):1097-1108. [CrossRef]
19. Feinberg WM, Blackshear JL, Laupacis A, Kronmal R, Hart RG. Prevalence, age distribution, and gender of patients with atrial fibrillation. Analysis and implications. *Arch Intern Med*. 1995;155(5):469-473. [CrossRef]
20. Alashi A, Smedira NG, Popovic ZB, et al. Characteristics and outcomes of elderly patients with hypertrophic cardiomyopathy. *J Am Heart Assoc*. 2021;10(3):e018527. [CrossRef]
21. Prabhu SD, Frangogiannis NG. The biological basis for cardiac repair after myocardial infarction: From inflammation to fibrosis. *Circ Res*. 2016;119(1):91-112. [CrossRef]
22. Becker RC, Owens AP 3rd, Sadayappan S. Tissue-level inflammation and ventricular remodeling in hypertrophic cardiomyopathy. *J Thromb Thrombolysis*. 2020;49(2):177-183. [CrossRef]
23. Raman B, Ariga R, Spartera M, et al. Progression of myocardial fibrosis in hypertrophic cardiomyopathy: Mechanisms and clinical implications. *Eur Heart J Cardiovasc Imaging*. 2019;20(2):157-167. [CrossRef]
24. Wang Z, Zhao L, He S. Relation between neutrophil-to-lymphocyte ratio and mortality in patients with hypertrophic cardiomyopathy. *Biomark Med*. 2020;14(18):1693-1701. [CrossRef]
25. Jacobsen MB, Petersen JK, Modin D, et al. Long term mortality in patients with hypertrophic cardiomyopathy – A Danish nationwide study. *Am Heart J Plus*. 2022;25:100244. [CrossRef]