Canadian Journal of Cardiology 35 (2019) 1791–1799

Systematic Review/Meta-analysis

Variable and Limited Predictive Value of the European Society of Cardiology Hypertrophic Cardiomyopathy Sudden-Death Risk Model: A Meta-analysis

Jie Wang, MD,[a,‡] Zhipeng Zhang, BMSci,[a,‡] Yuancheng Li, BMSci,[a] Yuanwei Xu, BMSci,[a] Ke Wan, MD,[b] and Yucheng Chen, MD[a]

[a] *Department of Cardiology, West China Hospital, Sichuan University, Chengdu, Sichuan, China*

[b] *Department of Geriatrics, West China Hospital, Sichuan University, Chengdu, Sichuan, China*

See editorial by Maron et al., pages 1626–1628 of this issue.

ABSTRACT

Background: We performed a systematic review and meta-analysis to assess the discrimination performance of the 2014 European Society of Cardiology (ESC) sudden cardiac death (SCD) risk-prediction model for hypertrophic cardiomyopathy (HCM).

Methods: We searched the PubMed, Embase and Web of Science, CNKI, WanFang, and China Biology Medicine disc (CBMdisc) databases for English and Chinese articles validating the risk model. The model's discrimination performance with cutoff points of 4% and 6% based on extracted information was calculated. The extracted C statistic and calculated area under the curve (AUC) with 95% confidence intervals (CIs) of all studies were weighted and summarized. Heterogeneity was quantified through I^2 statistics; sensitivity analysis and publication bias were assessed with Egger's test.

Results: We included 13 studies validating the model's usefulness. We concluded that the model has excellent specificity, although it has poor sensitivity when setting a recommended cutoff value of 6% for

RÉSUMÉ

Introduction : Nous avons réalisé une revue systématique et une méta-analyse pour évaluer la capacité de discrimination du modèle de prédiction du risque de mort subite d'origine cardiaque (MSOC) lors de cardiomyopathie hypertrophique (CMH) de la Société européenne de cardiologie (SEC).

Méthodes : Nous avons effectué des recherches dans les bases de données PubMed, Embase et Web of Science, CNKI, WanFang et China Biology Medicine disc (CBMdisc) pour trouver des articles anglais et chinois qui portaient sur la validation du modèle de risque. Nous avons calculé la capacité de discrimination du modèle à des seuils critiques de 4 % et de 6 % selon les données extraites. La statistique C extraite et la surface sous la courbe (SSC) calculée avec des intervalles de confiance (IC) à 95 % de toutes les études ont été pondérées et résumées. Nous avons quantifié l'hétérogénéité à l'aide des statistiques I^2 et nous avons évalué l'analyse de sensibilité et les biais de publication à l'aide du test d'Egger.

Hypertrophic cardiomyopathy (HCM) is an autosomal dominant genetic disease with a prevalence of 1:500 in the general adult population.[1] Generally, most HCM cases have benign prognoses. However, sudden cardiac death (SCD) is the most frequent devastating clinical event, with an incidence of 0.5% to 1% per year in patients with HCM;[2] therefore, early identification of patients with HCM at high risk of SCD and providing them with effective treatment strategies, including implantable cardioverter-defibrillators (ICDs) to prevent SCD, is important.

Although the 2011 American College of Cardiology Foundation/American Heart Association (ACCF/AHA) and 2003 American College of Cardiology/European Society of Cardiology (ACC/ESC) guidelines have some related recommendations on how these high-risk patients with HCM can be identified,[3] related validation studies have reported that these models have limited performance in discriminating high-risk and low-risk persons.[4,5] In 2014, the ESC[2] proposed a novel SCD risk-prediction model for HCM based on a study[6] that recruited 3066 European patients with HCM, and advised that high-risk patients with a 5-year SCD risk $\geq$ 6% should be offered ICD implantation and that ICD implantation may be considered when the 5-year SCD-risk model score is 4% to 6%. Subsequently, some external validation studies have been reported from different centres and

Received for publication December 31, 2018. Accepted May 5, 2019.

‡These authors contributed equally to this work.

Corresponding author: Dr Yucheng Chen, Cardiology Division, Department of Medicine, West China Hospital, Sichuan University, Guoxue Xiang No. 37, Chengdu, Sichuan 610041, China. Tel.: 86-18980602149; fax: 86-028-85422836.

E-mail: chenyucheng2003@163.com

See page 1798 for disclosure information.

https://doi.org/10.1016/j.cjca.2019.05.004

identifying high-risk patients with HCM. In addition, there was moderate discrimination value (global C statistic = 0.75, 95% CI, 0.67-0.83; cutoff point of ≥ 4%; AUC = 0.69, 95% CI, 0.62-0.75; cutoff point of ≥ 6%; AUC = 0.65, 95% CI, 0.59-0.72). Subgroup analysis by region showed slightly weaker predictive ability for North America. There was no significant publication bias (all $P > 0.05$); sensitivity analysis did not change the results significantly.

Conclusions: The 2014 ESC HCM SCD risk-prediction model has excellent specificity and poor sensitivity and has moderate discrimination performance. In addition, it may have lower prediction value for North America compared with other regions.

Résultats : Nous avons choisi 13 études qui portaient sur la validation de l'utilité du modèle. Nous avons conclu que le modèle a une excellente spécificité, bien qu'il ait une sensibilité médiocre lorsque l'on fixe la valeur limite recommandée de 6 % pour déterminer les patients exposés à un risque élevé de CMH. De plus, la valeur de discrimination était modérée (statistique C globale = 0,75, IC à 95 %, 0,67-0,83; seuil critique ≥ 4 %; SSC = 0,69, IC à 95 %, 0,62-0,75; seuil critique ≥ 6 %; SSC = 0,65, IC à 95 %, 0,59-0,72). L'analyse en sous-groupes de régions a montré une capacité prédictive légèrement plus faible pour l'Amérique du Nord. Il n'y a eu aucun biais de publication (tous $P > 0,05$); l'analyse de sensibilité n'a pas significativement changé les résultats.

Conclusions : Le modèle de prédiction du risque de MSOC lors de CMH de la SEC a une excellente spécificité et une sensibilité médiocre, ainsi qu'une capacité de discrimination modérée. La valeur de prédiction peut en outre être plus faible pour l'Amérique du Nord que pour les autres régions.

populations; however, their results have been inconsistent. Some studies confirmed the positive value of the model,[7,8] whereas others do not support its use.[9,10] Recently, O'Mahony et al. examined 7291 patients from 6 related validation studies and concluded that the prevalence of SCD endpoints was 1.01% (95% confidence interval [CI], 0.52-1.61) in patients with HCM and a model 5-year SCD risk < 4%, 2.43% (95% CI, 1.23-3.92) in patients with scores of 4% to 6% and 8.4% (95% CI, 6.68-10.25) in patients with scores of ≥ 6%, which suggested the model's accurate risk evaluation.[11] However, no currently published meta-analysis has assessed the model's value by the C statistic in different regions or populations or summarized the model's performance by traditional markers such as sensitivity and specificity and positive and negative predictive value. Therefore, we performed the current systematic review and meta-analysis identifying all articles validating the 2014 ESC HCM SCD risk-prediction model to evaluate its value synthetically.

Methods

The systematic review was conducted in accordance with the guide by Debray et al.[12] We used a generic search strategy that included the terms *hypertrophic cardiomyopathy* or *HCM* and *European Society of Cardiology* or *ESC* in the title and abstract. The PubMed, Embase, Web of Science, CNKI, WanFang, and China Biology Medicine disc (CBMdisc) databases were searched from October 2014, when the first internal validation study[6] was published, to October 2018. Inclusion criteria were any published study validating the 2014 ESC HCM SCD risk-prediction model in English and Chinese. All prospective or retrospective studies were included. We excluded studies from which we could not extract any discrimination statistics (C statistic or the area under the curve [AUC]) and calculate the model performance when setting a cutoff point of 4% or 6% from the presented data. Two reviewers screened all identified citations (titles + abstracts) independently for inclusion. Full articles were obtained for all included or possibly included citations and screened for inclusion. Two reviewers extracted the data independently. Any discrepancy was resolved by a third statistician. In addition, the reference list of each article was reviewed to identify any additional relevant articles. Figure 1 presents the detailed criteria.

The following information was extracted from each study identified in our review: patient characteristics (age, sex, and geographical distribution); number of patients in validated cohorts; follow-up duration; number of SCD or equivalent to SCD cases; and measures of model discrimination, including C statistic or AUC with 95% CI. SCD was defined as instant and unexpected death occurring within the first hour of the onset of symptoms in a person who was otherwise in stable condition. Equivalent SCD included appropriate ICD shock (defined as intervention triggered by ventricular fibrillation or rapid ventricular tachycardia at > 200 beats per minute) or successful resuscitation after cardiac arrest. In addition, to analyze the model discrimination statistically when using a 4% or 6% cutoff point, as proposed by the 2014 ESC guidelines on HCM diagnosis and management, we also extracted information that included the total number of patients and the number of SCD events or equivalent to SCD based on a 4% and 6% cutoff if available, respectively. An AUC of 0.70 was considered to indicate moderate discriminative ability.[13,14] The quality of the included studies was evaluated from the **Ch**ecklist for critical **A**ppraisal and Data Extraction for Systematic **R**eviews of prediction **M**odelling **S**tudies (CHARMS), based on guideline recommendations.[12,15]

Continuous variables were expressed as the mean and standard deviation (SD), and median or interquartile range (IQR), if acquirable. Categorical variables were expressed as n (%), if available. Receiver operating characteristic curve analysis, sensitivity, specificity, and the positive and negative predictive values were used to evaluate the model's discrimination performance with a cutoff point of 4% and 6%, based on extracted information. The C statistic or AUC with 95% CI of each study was weighted according to study size and summarized using random-effects meta-analysis. Heterogeneity was quantified through I^2 statistics, with I^2 statistic of 25%, 50%, and 85% corresponding to low, moderate, and high heterogeneity, respectively.[16] To explore heterogeneity, we conducted subgroup analysis by age, sex, follow-up period, publication year, region, and sample size. Finally, we performed sensitivity analysis and assessed potential publication

bias based on Egger's test.[16] Statistical analysis was performed using STATA MP 14.0 (Stata Corp LP, College Station, TX) and MedCalc (version 13.0; Ostend, Belgium). $P < 0.05$ was considered statistically significant.

Results

Our search strategy identified a total of 687 articles. After screening based on the inclusion and exclusion criteria, 13 articles remained (Fig. 1): 12 external validation studies involving > 9000 patients and 1 original validation study[6] involving 3066 patients. Four studies did not report the C statistic or AUC with 95% CI. Two and 3 articles did not provide information used for analyzing the AUC with discriminate performance, sensitivity, specificity, and positive and negative predictive values, when setting a cutoff point of 4% and 6%, respectively. Therefore, the final evaluation included 9 articles used for meta-analysis with the global C statistic, which varied from single-centre studies to large multicentre studies on 9651 patients with HCM. Eleven and 10 articles were included for assessing the model's performance when setting a cutoff value of 4% and 6%, respectively. Overall, 6 cohorts were from European countries, which included 4 single-country studies (Germany,[17] the Netherlands,[8] Italy,[18] the UK[19]) and 2 from international collaborative cohorts.[6,20] Three cohorts were from Asia (China,[21,22] Japan[23]), 2 were from North America (the US),[9,10] and 1 was from South America (Argentina[24]). We excluded an international collaborative study consisting of North American, European, Middle Eastern, and Asian cohorts during subgroup statistical meta-analysis by region because we could not obtain original data from different regions.[7]

Table 1 shows the population characteristics of the studies. The mean age of the derivation cohorts was 52.0 ± 6.3 years; the median size of the validation cohorts was 604 (IQR, 248-1719). The mean follow-up duration was 5.4 ± 2.2 years. Tables 2 and 3 show the model's discrimination performance with a cutoff point of 4% and 6%, based on extracted information that included the total number of patients and the number of SCD events or equivalent to SCD based on a cutoff of 4% and 6%.

In general, the risk-prediction model exhibited varied discrimination ability. Six studies showed modest discrimination performance with C statistic of 0.61-0.86.[6-8,17,19,20] Liebregts et al. only included patients with HCM after alcohol septal ablation, which was a significantly different population from the other included cohorts.[20] We excluded that study when setting a cutoff point of 4% or 6% because we could not extract statistics to calculate the model performance. Two studies from China[22] and Argentina[24] showed good discrimination, with C statistic of 0.93, whereas low discrimination was reported in the US (C statistic = 0.48 [95% CI, 0.31-0.64]).[9] However, we report moderate discrimination value, with C statistic of 0.75 (95% CI, 0.67-0.83) when using random effects in nine studies (Fig. 2A). Similarly, modest discrimination performance with AUC of 0.69 (95% CI, 0.62-0.75) was identified when a

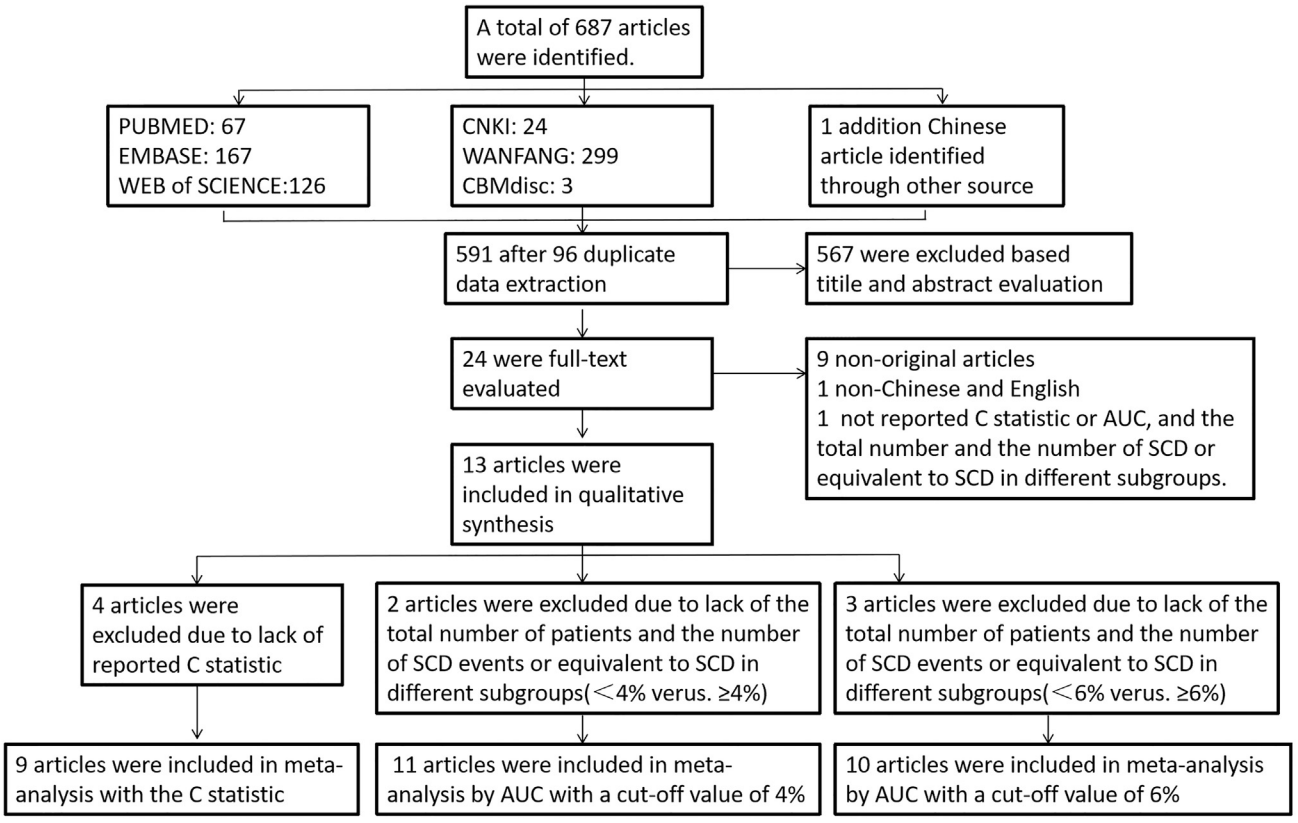

Figure 1. Literature search flow diagram. SCD, sudden cardiac death; AUC, area under the curve.

Table 1. Characteristics of 2014 ESC SCD risk-prediction model validation studies in HCM included in the systematic review

Article	Region	Validation population	Age (years)	Sex (male, %)	SCD events (n)	Time of follow-up (years)	No. of HCM patients in the validation model	C statistic (95% CI)	Sensitivity (%)*	Specificity (%)*
O'Mahony et al.[6] (2014)	Europe	UK, Spain, Greece, Italy	48 ± 17	64	84	5.7 (2.8, 9.2)	3066	0.70 (0.68-0.72)	Not given	Not given
Vriesendorp et al.[8] (2015)	Europe	Netherlands	49 ± 16	66	42	7.7 ± 5.3	706	0.69 (0.57-0.82)	Not given	Not given
Nakagawa et al.[23] (2018)	Asia	Japan	66 (54,74)	56	31	5.2 (3.5, 6.9)	370	Not given	Not given	Not given
O'Mahony et al.[7] (2018)	North America; Europe; Middle East; Asia	USA, Europe, Middle East and Asia	48 ± 17	64	44	5.4 (2.8, 8.5)	2147	0.70 (0.68-0.72)	Not given	Not given
Desai et al.[10] (2018)	North America	USA	50 ± 14	63	109	8.8 ± 4	1809	0.48 (0.31-0.64)	Not given	Not given
Li et al.[21] (2017)	Asia	China	43 ± 14	60.9	8	1.0 (0.6,1.5)	207	Not given	Not given	Not given
Zhu et al.[22] (2017)	Asia	China	60.2 ± 12.8	66.2	5	2.69 ± 1.36	172	0.93(0.85,1)	Not given	Not given
Leong et al.[19] (2018)	Europe	UK	52 ± 16	66.0	14	5.6±3.8	288	0.86 (0.78, 0.94)	57.0	82.0
Doesch et al.[17] (2017)	Europe	Germany	55.5 (mean)	41	17	4 (median)	117	0.73 (0.59,0.87)	71.0	70.0
Maron et al.[9] (2015)	North America	USA	46.9	65.5	35	5.0 (mean)	1629	Not given	Not given	Not given
Liebregts et al.[20] (2017)	Europe	Germany; Netherlands; Czech Republic; Scandinavia	58 ± 14	53	66	6.5 ± 4.2	844	0.61(0.52,0.69)	41.0	76.0
Fernández et al.[24] (2016)	South America	Argentina	51 ± 18	62.7	14	8.6 ± 4.3	502	0.93 (0.89-0.95)	Not given	Not given
Magrì et al.[18] (2016)	Europe	Italy	49 ± 16	69.0	25	3.7 (2.2,5.7)	623	Not given	Not given	Not given

CI, confidence interval; ESC, European Society of Cardiology; HCM, hypertrophic cardiomyopathy; No., number; SCD, sudden cardiac death.
*The sensitivity and specificity refer to a specific risk estimation cutoff from every validation study available.

Table 2. Characteristics for a cutoff point of 4% in 2014 ESC SCD risk-prediction model validation studies in HCM included in the systematic review

	Risk-SCD score <4%		Risk-SCD score ≥4%								
Article	All HCM patients (n)	SCD events (n)	All HCM patients (n)	SCD events (n)	AUC (95% CI) for cutoff point 4%	Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Negative predictive value (%)	The number of ICDs needed to prevent 1 major event	The number of individuals with a major event without an ICD
O'Mahony et al.[6] (2014)	2110	24	956	60	0.71 (0.69-0.72)	71.4	70.0	6.3	98.9	16	88
Vriesendorp et al.[8] (2015)	Not given	Not given	Not given	Not given	Not counted	-	-	-	-	-	-
Nakagawa et al.[23] (2018)	305	17	65	14	0.65 (0.60-0.70)	45.2	85.0	21.5	94.4	5	18
O'Mahony et al.[7] (2018)	1524	16	623	28	0.68 (0.66-0.70)	63.6	71.7	4.5	99.0	22	95
Desai et al.[10] (2018)	1169	121	640	50	0.53 (0.51-0.56)	29.2	64.0	7.8	89.6	13	10
Li et al.[21] (2017)	122	1	85	7	0.74 (0.68-0.8)	87.5	60.8	8.2	99.2	12	122
Zhu et al.[22] (2017)	157	2	15	3	0.76 (0.69, 0.83)	60.0	92.8	20.0	98.7	5	79
Leong et al.[19] (2018)	230	6	58	8	0.69 (0.64, 0.75)	57.1	81.8	13.8	97.4	7	38
Doesch et al.[17] (2017)	121	8	28	9	0.69 (0.61, 0.77)	52.9	85.6	32.1	93.4	3	15
Maron et al.[9] (2015)	1285	48	344	33	0.60 (0.58, 0.63)	40.7	79.9	9.6	96.3	10	27
Liebregts et al.[20] (2017)	472	Not given	352	Not given	Not counted	-	-	-	-	-	-
Fernández et al.[24] (2016)	387	0	115	14	0.90 (0.87, 0.92)	100	79.3	12.2	100	8	∞
Magrì et al.[18] (2016)	423	10	200	15	0.61 (0.57, 0.66)	60.0	69.1	7.5	97.6	13	42

AUC, area under the curve; CI, confidence interval; ESC, European Society of Cardiology; HCM, hypertrophic cardiomyopathy; ICD, implantable cardioverter-defibrillators; SCD, sudden cardiac death.

Table 3. Characteristics for a cutoff point of 6% in 2014 ESC SCD risk-prediction model validation studies on HCM included in the systematic review

Article	SCD risk < 6%		SCD risk ≥ 6%		AUC (95% CI) for 6% cutoff point	Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Negative predictive value (%)	The number of ICDs needed to prevent 1 major event	The number of individuals with a major event without an ICD
	All HCM patients (n)	SCD events (n)	All HCM patients (n)	SCD events (n)							
O'Mahony et al.[6] (2014)	2597	41	469	43	0.69 (0.67-0.70)	51.2	85.7	9.2	98.4	11	63
Vriesen-dorp et al.[8] (2015)	Not given	Not given	Not given	Not given	Not counted	-	-	-	-	-	-
Nakagawa et al.[23] (2018)	335	21	35	10	0.62 (0.57-0.67)	32.3	92.6	28.6	93.7	4	16
O'Mahony et al.[7] (2018)	1850	21	297	23	0.70 (0.68, 0.72)	52.3	87.0	7.7	98.7	13	88
Desai et al.[10] (2018)	1495	149	314	22	0.53(0.50, 0.55)	12.9	82.2	7.0	90.0	14	10
Li et al.[21] (2017)	164	Not given	43	Not given	Not counted	-	-	-	-	-	-
Zhu et al.[22] (2017)	165	4	7	1	0.58 (0.51, 0.66)	20.0	96.4	14.3	97.6	7	41
Leong et al.[19] (2018)	260	7	28	7	0.71 (0.66,0.76)	50.0	92.3	25.0	97.3	4	37
Doesch et al.[17] (2017)	139	13	10	4	0.60 (0.51,0.67)	23.5	95.5	40.0	90.6	3	11
Maron et al.[9] (2015)	1497	65	132	16	0.56 (0.54-0.59)	19.8	92.5	12.1	95.7	8	23
Liebregts et al.[20] (2017)	619	Not given	205	Not given	Not counted	-	-	-	-	-	-
Fernández et al.[24] (2016)	426	2	76	12	0.86 (0.83, 0.89)	85.7	86.9	15.8	99.5	6	213
Magrì et al.[18] (2016)	536	13	87	12	0.68 (0.64,0.71)	48.0	87.5	13.8	97.6	7	41

AUC, area under the curve; CI, confidence interval; ESC, European Society of Cardiology; HCM, hypertrophic cardiomyopathy; ICD, implantable cardioverter-defibrillator; SCD, sudden cardiac death.

≥ 4% cutoff value was used for the model assessment (Supplemental Fig. S1A), and an AUC of 0.65 (95% CI, 0.59-0.72) when the cutoff value was 6% (Fig. 3A). In addition, based on available information from original validation studies, we found that the model had low sensitivity (range [41.0%, 71.0%]) and high specificity (range [70.0%, 82%]) (Table 1).

When we used a cutoff value of ≥ 4% for assessing the model (Table 2), excellent sensitivity of the model was found for China[21] (87.5%) and Argentina[24] (100%), and moderate sensitivity was reported for the European countries (range [52.9%, 71.4%]). However, poor sensitivity was reported for Japan (45.2%) and North America (40.7% and 29.2%). In addition, the model had moderate-to-good specificity (range [60.8%, 92.8%]) and excellent negative predictive value (range [89.6%, 100%]). Specifically, the positive predictive value of the model performed poorly (range [4.5%, 32.1%]). In addition, the numbers of ICDs needed to prevent 1 major event and individuals with major events without ICDs for a cutoff point of 4% were presented in Table 2. The number of ICDs needed to prevent 1 major event in other external validation studies was lower than that in the initial derivation study of O'Mahony et al.,[6] with the exception of the study from a multicentre study.[7] However, the number of individuals with major events without ICDs in other external validation studies was also lower than that in the initial derivation study of O'Mahony et al.,[6] with the exception of the studies from O'Mahony et al.,[7] Li et al.,[21] and Fernández et al.[24]

When we used a cutoff value of ≥ 6% for assessing the model (Table 3), poor sensitivity of this predictive model was found for the recruited studies (range [12.9%, 52.3%]), with the exception of the study from Argentina[24] (85.7%). Moreover, sensitivity for North America (12.9% and 19.8%) was inferior to that for other regions. The positive predictive value of this model was also poor (ranged [7.0%, 40%]). However, its specificity (range [82.2%, 96.4%]) and negative predictive value performed excellently (range [90.0%, 99.5%]). Similarly, the number of ICDs needed to prevent 1 major event in other external validation studies was lower than that in the initial derivation study of O'Mahony et al., with the exception of the studies from O'Mahony et al.[7] and Desai et al.[10] However, the number of patients with major events without ICDs in other external validation studies were also lower than that in the initial derivation study of O'Mahony et al.,[6] with the exception of the studies from O'Mahony et al.[7] and Fernández et al.[24]

The pooled C statistic results for 9 articles exhibited significant interstudy heterogeneity ($I^2 = 96.6\%$, $P < 0.001$). Subgroup analyses by age, sex, follow-up period, and publication year did not reveal any potential source of heterogeneity except for sample size and region (Fig. 2B and Fig. 4). The subgroup for sample size < 700 had a significantly larger C statistic than the subgroup for sample size ≥ 700 (C statistic = 0.89, 95% CI, 0.82-0.95 vs 0.68, 95% CI, 0.65-0.71; Fig. 4), with decreased heterogeneity. Subgroup analysis by region involved only one study each in Asia, South America, or North America. However, the model's predictive ability appeared slightly weaker for North America if roughly analyzed (C statistic = 0.48, 95% CI, 0.31-0.64, Fig. 2B). Egger's test showed no significant publication bias ($t = 0.16$, $P = 0.88$).

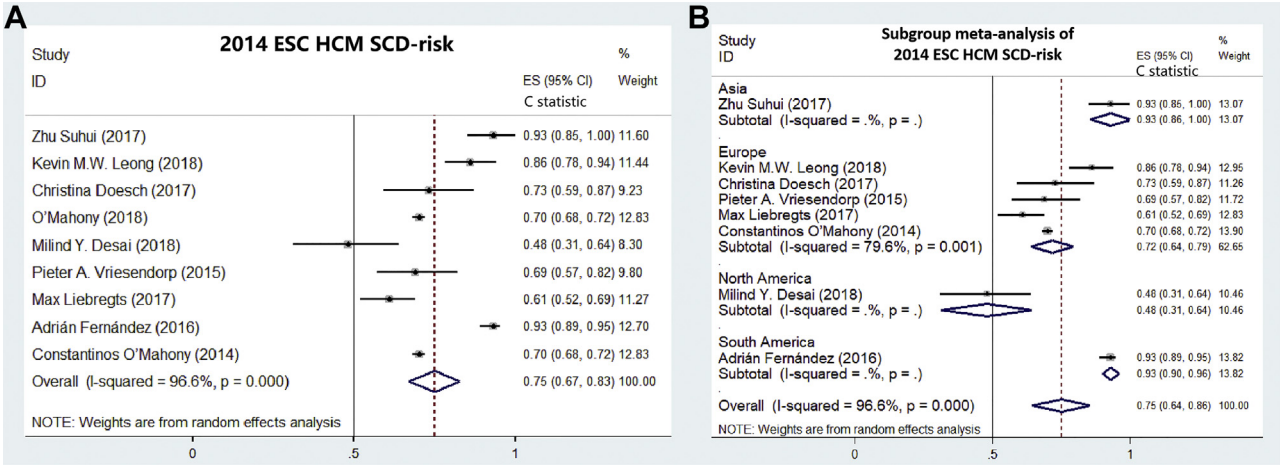

Figure 2. Forest plot of extracted performance statistics with C statistic (**A**). Subgroup meta-analysis of C statistic by the model based on geographic distribution (**B**). CI, confidence interval; ESC, European Society of Cardiology; HCM, hypertrophic cardiomyopathy; SCD, sudden cardiac death.

There was considerable heterogeneity among 11 studies when using calculated AUC with a cutoff of 4% ($I^2 = 98.0\%$, $P < 0.001$).[6,7,9,10,17-19,21-24] Similarly, subgroup analysis revealed that the AUC for North America was much lower than that for other regions (AUC = 0.56, 95% CI, 0.50-0.63; Supplemental Fig S1B], whereas sample size did not appear to contribute to the potential heterogeneity. Publication bias was not detected by Egger's test ($t = -0.55$, $P = 0.595$).

The overall calculated AUC with a cutoff value of 6% was 0.65 (95% CI, 0.59-0.72), with significant heterogeneity among 10 studies ($I^2 = 97.7\%$, $P < 0.001$).[6,7,9,10,17-19,22-24] Subgroup analysis also suggested that the C statistic for North America was remarkably inferior to that for other regions (AUC = 0.54, 95% CI, 0.50-0.58; Fig. 3B). Similarly, we did not find that sample size was a source of heterogeneity. Publication bias was also not observed ($t = -0.82$, $P = 0.437$).

The overall effect size remained robust when each study was removed in turn (Fig. 5 and Supplemental Fig. S2).

Discussion

The current systematic review summarizes 13 different published studies invalidating the 2014 ESC HCM SCD risk-prediction model. The main findings are that (1) there was moderate discrimination ability when using the global C statistic or the AUC with the recommended cutoff value of 4% and 6% in meta-analysis of the model; (2) this model had excellent specificity and negative predictive value based on all recruited validation studies; and (3) this model had poor sensitivity and poor positive predictive value when a recommended cutoff of 6% was set for identifying high-risk patients with HCM, which indicates that it is

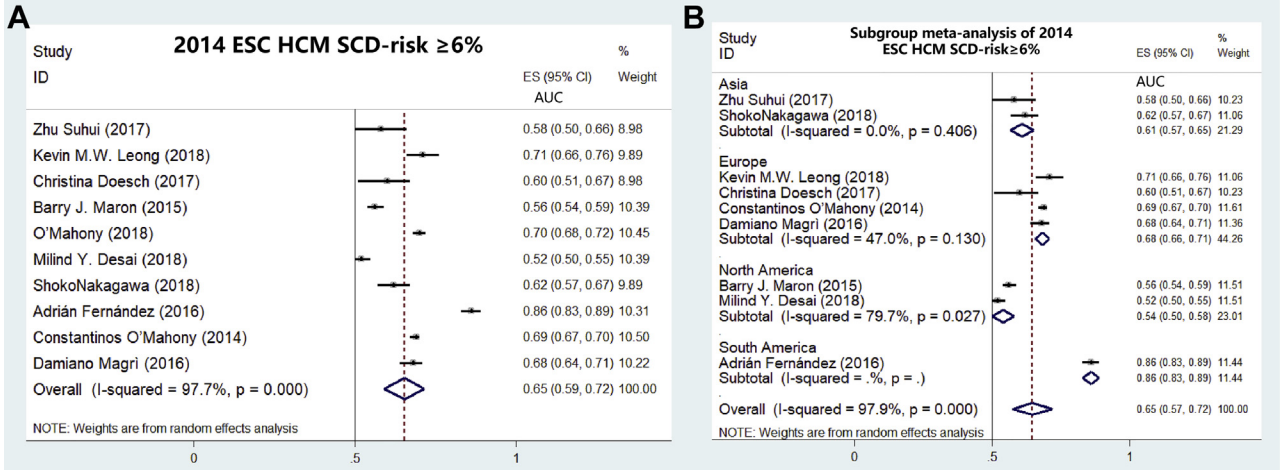

Figure 3. Forest plot of calculated performance statistics with AUC with a cutoff point 6% **(A).** Subgroup meta-analysis of AUC with a cutoff of 6% **(B)** by the model based on geographic distribution. AUC, area under the curve; CI, confidence interval; ESC, European Society of Cardiology; HCM, hypertrophic cardiomyopathy; SCD, sudden cardiac death.

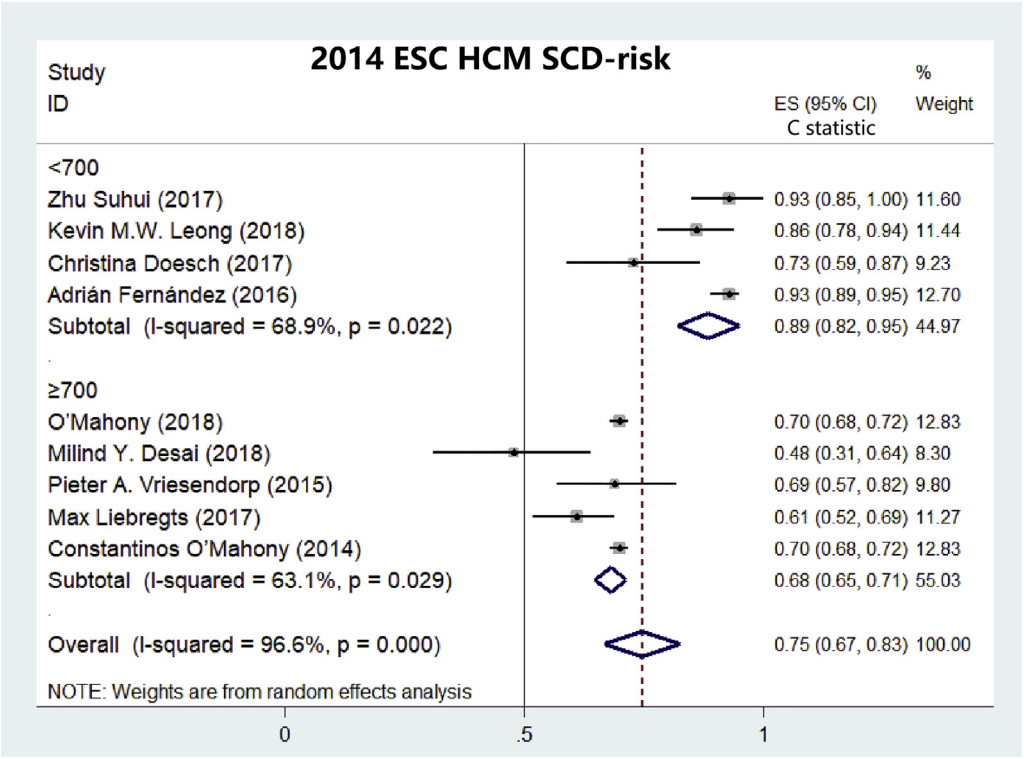

Figure 4. Subgroup meta-analysis of C statistic by model based on sample size with a cutoff point of 700. CI, confidence interval; ESC, European Society of Cardiology; HCM, hypertrophic cardiomyopathy; SCD, sudden cardiac death.

likely to miss a subgroup of high-risk HCM. Moreover, there may be a trend for the model having lower prediction performance for North America compared with other regions.

At present, 2 main models are used for identifying patients with HCM and at high risk for SCD, 1 of which is the North American model[3] based on 5 binary risk factors, in which the presence of any leads to consideration of ICD implantation. This strict evaluation of the North American model is sensitive but not very specific, with limited discriminative power.[6] For example, Maron et al.[9] recruited 1629 patients with HCM from 3 centres and found that only 10% of ICD implantations, based on previous guideline recommendations, experienced appropriate discharge. Our study found that the 2014 ESC model has excellent specificity and negative predictive value, which may avoid overtreatment with ICD interventions. However, the poor sensitivity and poor positive predictive value of this model may mean it is likely to miss a subgroup of high-risk patients with HCM.

The model's performance among patients with HCM has been controversial. Zhu et al. (n = 172), [22] Li et al. (n = 207), [21] and Nakagawa et al. (n = 370)[23] found that it was valuable for predicting SCD in Chinese or Japanese HCM cohorts. A recent validation from an international collaborative multicentre study also reported that the model yielded accurate SCD risk information (calibration slope: 1.02, 95% CI, 0.93-1.12; C-index:

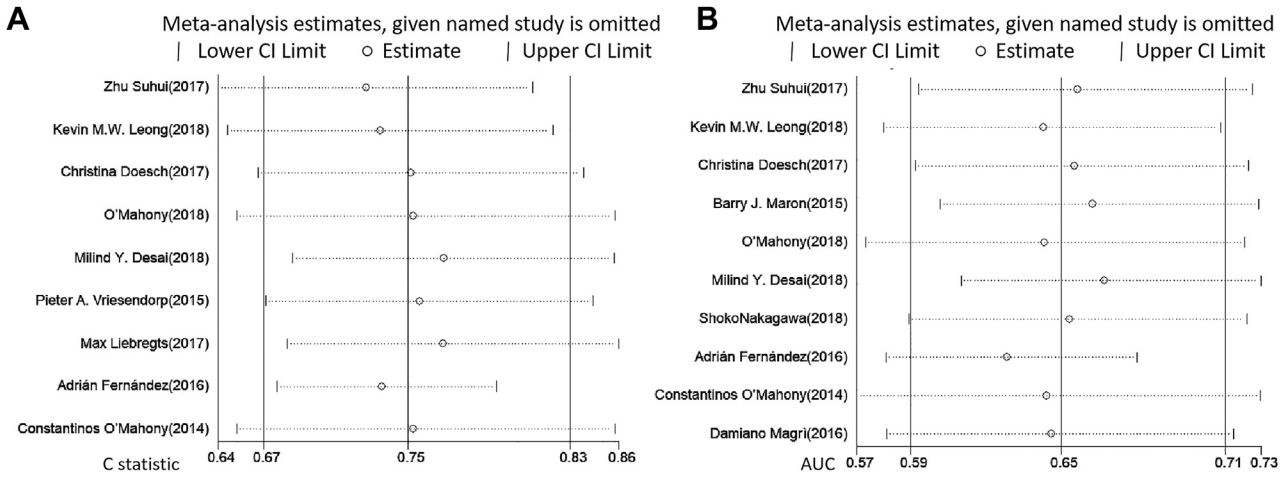

Figure 5. Sensitivity analysis of the extracted C statistics (**A**) and calculated area under the curve (AUC) with a cut-off point of 6% (**B**).

0.70, 95% CI, 0.68-0.72; D-statistic: 1.17, 95% CI, 1.05-1.29); furthermore, it confirmed the value of a cutoff point of 6% in clinical decision making.[7] Studies from Europe and South America have confirmed the risk benefit for ICD implantation when using the model, with moderate-to-high predictive value. Moreover, Vriesendorp et al., [8] Fernández et al., [24] and Zhu et al.[22] validated the model's positive impact compared with other previous predictive approaches. However, in contrast, Desai et al.[10] and Maron et al.[9] used data from 3 centres in North America and showed that the model had high negative predictive value and was less reliable for predicting risk of SCD. Having recruited all validation cohorts of the model, we suggest that it is a moderate predictive model, which is consistent with most previous validation studies, except the studies from North America. However, it is worth noting that our study had heterogeneity limitations, although we also detected the potential source of heterogeneity due to sample size and region.

Subgroup analysis by sample size revealed decreased heterogeneity when using the C statistic rather than the AUC with a 4% and 6% cutoff. The main reason contributing to bias is possibly the AUC results based on our calculations from the presented data rather than the model's original predictive score from each participant, which may have compromised some information. Therefore, we could not exclude the heterogeneity by sample size when validating the model using the 4% or 6% cutoff values, owing to the lack of original data. In addition, the C statistic in the subgroup for sample size < 700 was significantly higher than that in the subgroup for sample size ≥ 700, which indicates that validation of the model in more large and multicentre populations remains necessary.

Of interest, our study shows that regional distribution may determine the heterogeneity. Although there was no obvious decreased heterogeneity ($I^2 = 94.0\%$, $P < 0.001$) in North America in subgroup analysis by region in the model with a 4% cutoff value, it is unsurprising, as there were only 2 studies from North America, and there was no overlapping 95% CI between these 2 validations. However, it was very obvious that the C statistic was lower than that for any other region, and there was also no overlapping 95% CI compared with other regions. Our research suggests that the model may have different power for predicting the SCD risk in different regions or HCM populations, especially in North America. Many reasons contributed to the poor performance of the model in North America. One reason may be the differences in specific recruited HCM patient populations, such as hypertrophic obstructive cardiomyopathy (HOCM) populations, and the regional diversity of management strategies for patients with HCM. Desai et al.[10] only recruited patients with HOCM, and a high proportion of the patients underwent surgical myectomy, which may alter some of the risk factors in the model, and there was a significantly lower observed event rate than expected. Another reason may be the higher rate of ICDs in North American cohorts. Maron et al. reported that the rate of ICDs was 28%,[9] whereas Fernández et al. reported that 19% experienced ICDs,[24] which can lead to higher sensitivity for potentially significant but clinically benign ventricular tachycardia detection. Another possible reason for the poor performance is the low risk of sudden death events in North American cohorts. Maron et al. reported 2% sudden death events, [9] whereas Fernández et al. reported 3% incidence.[24] However, validation via more populations and centres is needed to validate the model in North America.

An increasing number of validation studies on the model have suggested that it may have incremental and improved power for prediction when other factors are added. Magri et al.[18] reported that the minute ventilation/CO_2 production (VE/VCO_2) slope might improve SCD risk stratification in HCM cases classified at low-to-intermediate SCD with a score of $< 4\%$. In addition, cardiovascular magnetic resonance (CMR) has a unique advantage in myocardial tissue feature assessment using late gadolinium enhancement (LGE) for detecting myocardial fibrosis, and previous studies have confirmed the extent LGE is related to SCD risk in HCM.[25-29] Furthermore, Doesch et al. reported that LGE could be considered an additional risk marker, except the current model parameters, in the model.[17] Our study further emphasizes the moderate discrimination performance of the model and the poor ability for predicting SCD risk in North America. New prediction models or the addition of risk factors, such as LGE, to the current model may be warranted to improve the power of predicting SCD in HCM.

Our study included retrospective studies, and models derived from retrospective data may inherently include bias and be subject to confounding. Also, we included only 2 studies from North America; therefore, it is necessary to validate the power of the model in more large and multicentre HCM populations in North America. Finally, we did not acquire original data from the authors, so all analysis was based only on the presented information.

Conclusion

We have determined that the 2014 ESC HCM SCD risk-prediction model has excellent specificity and negative predictive value, but it has poor sensitivity and poor positive predictive value when setting a recommended cutoff value of 6% for identifying high-risk patients with HCM, which indicates that it is likely to miss a subgroup of high-risk patients with HCM. In addition, the current meta-analysis reveals that the model has modest discrimination performance, and it may be underpowered for predicting SCD risk when used for patients with HCM in North America.

Funding Sources

This work was supported by a grant from the National Natural Science Foundation of China, People's Republic of China (81271531), 1.3.5 project for disciplines of excellence, West China Hospital, Sichuan University, China (No: ZYJC18013) and Sichuan province science and technology support grant, China (2015SZ0176).

Disclosures

The authors have no conflicts of interest to disclose. All authors had access to the data and played a role in writing the manuscript.

References

1. Maron BJ, Gardin JM, Flack JM, et al. Prevalence of hypertrophic cardiomyopathy in a general population of young adults echocardiographic analysis of 4111 subjects in the CARDIA study. Circulation 1995;92:785.

2. Elliott PM, Anastasakis A, Borger MA, 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;35:2733-79.

3. Gersh BJ, Maron BJ, Bonow RO, et al. 2011 ACCF/AHA Guideline for the Diagnosis and Treatment of Hypertrophic Cardiomyopathy: Executive Summary: a report of the American College of Cardiology Foundation/American Heart Association Task Force on practice guidelines developed in collaboration with the American Association for Thoracic Surgery, American Society of Echocardiography, American Society of Nuclear Cardiology, Heart Failure Society of America, Heart Rhythm Society, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. J Am Coll Cardiol 2011;58:2703-38.

4. O'Mahony C, Tomeesteban M, Lambiase PD, et al. A validation study of the 2003 American College of Cardiology/European Society of Cardiology and 2011 American College of Cardiology Foundation/American Heart Association risk stratification and treatment algorithms for sudden cardiac death in patients with hypertrophic cardiomyopathy. Heart 2013;99:534-41.

5. Maron BJ, McKenna WJ, Danielson GK, et al. American College of Cardiology/European Society of Cardiology clinical expert consensus document on hypertrophic cardiomyopathy: a report of the American College of Cardiology Foundation Task Force on Clinical Expert Consensus Documents and the European Society of Cardiology Committee for Practice Guidelines. J Am Coll Cardiol 2003;42:1687-713.

6. 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;35:2010-20.

7. O'Mahony C, Jichi F, Ommen SR, et al. An international external validation study of the 2014 European Society of Cardiology Guideline on sudden cardiac death prevention in hypertrophic cardiomyopathy (evidence from HCM). Circulation 2018;137:1015-23.

8. Vriesendorp PA, Schinkel AF, Liebregts M, et al. Validation of the 2014 ESC Guidelines risk prediction model for the primary prevention of sudden cardiac death in hypertrophic cardiomyopathy. Circ Arrhythm Electrophysiol 2015;8:829-35.

9. Maron BJ, Casey SA, Garberich RF, et al. Independent assessment of the European Society of Cardiology sudden death risk model for hypertrophic cardiomyopathy. Am J Cardiol 2015;116:757-64.

10. 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;156:750-9.

11. O'Mahony C, Akhtar MM, Anastasiou Z, et al. Effectiveness of the 2014 European Society of Cardiology guideline on sudden cardiac death in hypertrophic cardiomyopathy: a systematic review and meta-analysis. Heart 2019;105:623-31.

12. Debray TP, Damen JA, Snell KI, et al. A guide to systematic review and meta-analysis of prediction model performance. BMJ 2017;356:i6460.

13. Schneeweiss S, Seeger JD, Maclure M, et al. Performance of comorbidity scores to control for confounding in epidemiologic studies using claims data. Am J Epidemiol 2001;154:854-64.

14. Ohman EM, Granger CB, Harrington RA, Lee KL. Risk stratification and therapeutic decision making in acute coronary syndromes. JAMA 2000;284:876-8.

15. Moons KG, De JG, Bouwmeester W, et al. Critical appraisal and data extraction for systematic reviews of prediction modelling studies: the CHARMS checklist. PLoS Med 2014;11:e1001744.

16. Higgins JPT. Measuring inconsistency in meta-analyses. BMJ 2003;327:557-60.

17. Doesch C, Tülümen E, Akin I, et al. Incremental benefit of late gadolinium cardiac magnetic resonance imaging for risk stratification in patients with hypertrophic cardiomyopathy. Sci Rep-Uk 2017;7:6336.

18. Magrì D, Limongelli G, Re F, et al. Cardiopulmonary exercise test and sudden cardiac death risk in hypertrophic cardiomyopathy. Heart 2016;102:274-80.

19. Leong KMW, Chow JJ, Ng FS, et al. Comparison of the prognostic usefulness of the European Society of Cardiology and American Heart Association/American College of Cardiology Foundation risk stratification systems for patients with hypertrophic cardiomyopathy. Am J Cardiol 2018;121:349-55.

20. Liebregts M, Faber L, Jensen MK, et al. Validation of the HCM Risk-SCD model in patients with hypertrophic cardiomyopathy following alcohol septal ablation. Europace 2018;20:f198-203.

21. Li WX, Liu LW, Wang J, et al. Predicting value of 2014 European guidelines risk prediction model for sudden cardiac death (HCM Risk-SCD) in Chinese patients with hypertrophic cardiomyopathy. Zhonghua Xin Xue Guan Bing Za Zhi 2017;45:1033-8.

22. Zhu SH, Li Y, Huang W, et al. Feasibility of the 2014 European guidelines risk prediction model for sudden cardiac death in hypertrophic cardiomyopathy in Chinese patients. Zhonghua Xin Xue Guan Bing Za Zhi 2017;45:404-8.

23. Nakagawa S, Okada A, Nishimura K, et al. Validation of the 2014 European Society of Cardiology sudden cardiac death risk prediction model among various phenotypes in Japanese patients with hypertrophic cardiomyopathy. Am J Cardiol 2018;122:1939-46.

24. Fernández A, Quiroga A, Ochoa JP, et al. Validation of the 2014 European Society of Cardiology sudden cardiac death risk prediction model in hypertrophic cardiomyopathy in a reference center in South America. Am J Cardiol 2016;118:121-6.

25. Weng Z, Yao J, Chan RH, et al. Prognostic value of LGE-CMR in HCM: a meta-analysis. JACC Cardiovasc Imaging 2016;9:1392-402.

26. O'Hanlon R, Grasso A, Roughton M, et al. Prognostic significance of myocardial fibrosis in hypertrophic cardiomyopathy. J Am Coll Cardiol 2010;56:867-74.

27. Flett AS, Hayward MP, Ashworth MT, et al. Equilibrium contrast cardiovascular magnetic resonance for the measurement of diffuse myocardial fibrosis: preliminary validation in humans. Circulation 2010;122:138-44.

28. White SK, Sado DM, Fontana M, et al. T1 mapping for myocardial extracellular volume measurement by CMR: bolus only versus primed infusion technique. JACC Cardiovasc Imaging 2013;6:955-62.

29. Hinojar R, Varma N, Child N, et al. T1 mapping in discrimination of hypertrophic phenotypes: hypertensive heart disease and hypertrophic cardiomyopathy: findings from the International T1 Multicenter Cardiovascular Magnetic Resonance Study. Circ Cardiovasc Imaging 2015;8:e3285.

Supplementary Material

To access the supplementary material accompanying this article, visit the online version of the *Canadian Journal of Cardiology* at www.onlinecjc.ca and at https://doi.org/10.1016/j.cjca.2019.05.004.