ORIGINAL ARTICLE

Sudden cardiac death in hyperthrophic cardiomyopathy: Comparison of predictive models

La mort subite dans la cardiomyopathie hypertrophique: Comparaison des modèles prédictifs

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Abstract

Introduction: Sudden cardiac death (SCD) risk stratification for primary prevention in patients with sarcomeric hypertrophic cardiomyopathy (HCM) has recently been reinforced by the establishment of a new model by the American College of Cardiology (ACC). This algorithm was characterized by a different approach compared to the previous HCM Risk Score.
Aim: The objective of this study was to compare risk stratification using both the European society of cardiology (ESC) and the ACC risk scores.
Methods: This was an observational, cohort-type prognostic study with retrospective data collection. Patients were classified according to their rhythmic risk estimated by both models and followed for a period of at least one year.
Results: Forty-seven patients were followed over a mean period of 32,4 months. The mean age of our patients was 55 years ± 14 years. We found a weak concordance between the two models (Kappa = 0.28). Four patients (9 %) presented arrhythmogenic events. The ACC algorithm indicated the implantation of an implantable cardioverter defibrillator (ICD) for these four patients whereas the HCM Risk Score indicated only two. The American algorithm had a better predictive potency with an area under the ROC curve of 0.785 compared to 0.654 with the HCM Risk Score with an NRI of 0.35. However, the number of ICDs to be implanted according to this algorithm was increased by 1.6 times.
Conclusion: The ACC algorithm was more efficient in detecting high-risk patients, but it considerably increased the number of ICDs indicated.

Key words: Hyperthrophic cardiomyopathy, Sudden cardiac death, Tachyarrhythmia.

Résumé

Prérequis: La stratification du risque de mort subite (MS) en prévention primaire chez les patients atteints de cardiomyopathie hypertrophique (CMH) sarcomérique s'est renforcée récemment par l'établissement d'un nouveau modèle par l'American College of Cardiology (ACC). Cet algorithme s'est caractérisé par une approche différente par rapport à l'ancien CMH Risk Score.
But: L'objectif de ce travail était de comparer la stratification de risque selon les deux méthodes.
Méthodes: Il s'agissait d'une étude observationnelle, pronostique de type cohorte avec un recueil de données rétrospectif. Nous avons classé les patients à l'inclusion selon leur risque rythmique selon les deux modèles et suivis pendant au moins un an.
Résultats: Quarante-sept patients ont été suivis sur une période moyenne de 32.4 mois. L'âge moyen de nos patients était de 55 ans ±14 ans. Nous avons retrouvé une faible concordance entre les deux modèles (Kappa =0,28). Quatre patients (9%) avaient eu un évènement rythmique. L'algorithme de l'ACC avait permis d'indiquer l'implantation d'un défibrillateur automatique implantable (DAI) pour ces quatre patients tandis que le CMH Risk Score n'en avait indiqué que deux. L'algorithme américain avait un meilleur pouvoir prédictif avec une aire sous la courbe de ROC de 0,785 par rapport à 0,654 du CMH Risk Score avec un NRI à 0.35. Cependant, le nombre de DAI à implanter selon cet algorithme avait augmenté de 1,6 fois.
Conclusions: L'algorithme de l'ACC était plus performant pour détecter les patients à haut risque mais il a augmenté considérablement le nombre des DAI indiqués.

Mots clés: Cardiomyopathie hypertrophique, Mort subite, Tachyarythmie

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Introduction

The Hypertrophic cardiomyopathy (HCM) is the most frequent hereditary cardiomyopathy. Its prevalence is 0.2% in the general population. This condition is associated with high rates of mortality ranging around 4 to 6% (1,2). The sudden cardiac death (SCD) is the most common cause. This complication is the most severe and dreadful manifestation of the disease; especially in young and athletic population (1,2). The incidence of SCD is roughly estimated at 0,5 to 1 % (1,3). It's usually caused by a ventricular tachyarrhythmia initiated by a specific trigger (supraventricular tachyarrhythmia, sudden drop in vascular resistances during physical stress, myocardial ischemia, conduction system disorder) (4).

The primary prevention of SCD is at the forefront of the HCM management and it's based on implantable cardioverter defibrillator (ICD) implantation for patients with high rhythmic risk. Nevertheless, the selection of such patients is a tough task: the course of the disease is particularly heterogenous making the risk estimation difficult. Different scientific societies had been working on this matter and studies allowed the establishment of algorithms to sort patients by their SCD risk and therefore a better selection for ICD implantations. As a result, the prognosis of the HCM is in constant improvement with a mortality rate actually at 1 to 2% (1,2).

There are actually two methods for risk stratification commonly used. The European HCM_Risk Score of 2014 (3) and the most recent American college of Cardiology (ACC) algorithm of 2020 (2). These two methods are largely validated by trials (5,6). However, the coexistence of two different modi operandi for the same risk estimation have left many practitioners with a measure of uncertainty regarding the most reliable option to use to identify highest-risk patients for whom primary prevention of SCD events with ICDs is indicated (7).

The aim of this study was to compare those two options in an observational, cohort-type prognostic study with retrospective data collection. Patients were diagnosed during the 2017-2020 period with a follow-up period of at least one year. Patients were classified according to their rhythmic risk estimated by both models.

Methods

HCM was defined by a wall thickness ≥15 mm in one or more LV myocardial segments as measured by any imaging technique (echocardiography,CMR) that is not explained solely by loading conditions (11).

We included patients diagnosed with sarcomeric HCM (including patients implanted for primary prevention) in the cardiology department of ABDERRAHMAN MAMI hospital Ariana Tunisia in the period from January 2017 to December 2020. The rhythmic risk was assessed for all patients using the two methods.

Then the patients were followed for period of at least one year. Follow-up data were obtained by hospital visits, hospitalization files and telephone contact with patients or family members.

We collected clinical data (symptoms, hospitalizations and death) and electrocardiographic data (ventricular or supraventricular arrythmias on EKG,Holter and ICD interrogations).

The primary end point was a SCD, a sustained ventricular arrythmia or an appropriate ICD shock during follow-up.

We didn't include patients with a history of previous ventricular tachyarrhythmias with hemodynamical instability (secondary prevention), patients with associated conditions that can cause arrhythmias and finally the patients with clinical, echocardiographic or MRI imaging signs consistent with a non-sarcomeric origin of the hypertrophy.

We excluded patients with incomplete clinical, imagery or electrical data.

Transthoracic echocardiographic studies were performed for all the included patients. We measured: The left ventricular ejection fraction, the maximum thickness of the myocardium, the anteroposterior diameter of the left atrium, the peak instantaneous outflow gradient (at rest and after Valsalva maneuvers) (8). We detected mitral valvular and sub valvular apparatus anomalies and the existence of systolic anterior movement (SAM) (8). We sorted patients by the hypertrophy pattern using the modified Maron classification (9,10).

Cardiovascular magnetic resonance (CMR) imaging studies were performed in all included patients with a INGENIA 1.5T OMEGA HP (Philps). The data collected was: The maximum thickness of the myocardium, indexed myocardial mass, the existence of a sub-aortic obstruction, the existence of anomalies of the mitral valvular and sub valvular apparatus, the existence of an apical aneurysm, perfusion defects and areas of late gadolinium enhancements (LGE). If the LGE reaches at least 15% of the myocardium or three segments, it is considered extensive (31-33).

ESC Risk model:

Using patients survey, echocardiographic and EKG findings we gathered data about: age, maximal left ventricular thickness, anteroposterior diameter of the left atrium, history of family SCD, non-sustained ventricular tachycardia (NSVT), unexplained syncope and the peak instantaneous outflow gradient. Those finding allowed to calculate a percentage of predicted SCD event rates over 5 years (3). Based on this score, patients are stratified into 3 risk subsets for ICD recommendations: low risk (<4%); intermediate risk (4%-6%); and high risk (≥6% over 5 years) (11).

ACC algorithm:

The estimation of the SCD risk was based on clinical data (age, personal and family history of sudden death or sustained ventricular arrhythmias and history of unexplained syncope) imaging data (maximum myocardial thickness, the existence of an apical aneurysm, the left ventricular ejection fraction (LVEF) and the large areas of LGE) and electrocardiographic data (presence of NSVT).

This algorithm classifies patients according to their risk to: High rhythmic risk group: Patients with at least one of the following criteria:

- A family history of sudden death
- Maximum myocardial thickness ≥ 30 mm

- Unexplained Syncope
- An apical aneurysm
- A LVEF < 50%.

Intermediate rhythmic risk group: patients with no high-risk criteria and with at least one of these criteria:

- The presence of NSVT.
- The presence of extended LGE.

Low rhythmic risk group: patients with none of the criteria mentioned above (2).

We calculated absolute frequencies and relative frequencies (percentages) for the qualitative variables. We calculated means, medians and standard deviations and determined extreme values for quantitative variables. Percentage comparisons were made using Pearson's chi-square test or Fisher's exact two-tailed test. The link between two quantitative variables was studied by the Pearson correlation coefficient.

We calculated the Kappa score to assess the concordance between the two methods used.

To identify the threshold value that makes it possible to properly discriminate between two groups of individuals according to an objective variable, we conducted the analysis of the Receiver Operating Characteristic (ROC) curve. In order to draw the curves, each method was transformed into a binary classifier (indication for ICD: intermediate and high risk and no indication for ICD: low risk).

The area under the ROC curve defines the value of C-statistic. This value gives the probability that a randomly selected patient who experienced an event has a higher risk score than a patient who did not experience the event (12).

The Net Reclassification Improvement (NRI) is the statistical tool we used to assess the improvement in model performance offered by a new classification method (ACC algorithm) compared to a reference method (HCM Risk score).

Statiscal analysis were carried out using the SPSS 24.0 software.

Results

47 patients were included (figure 1). The mean follow-up duration was 32.4 months (minimum of 12 months and maximum of 52.8 months).

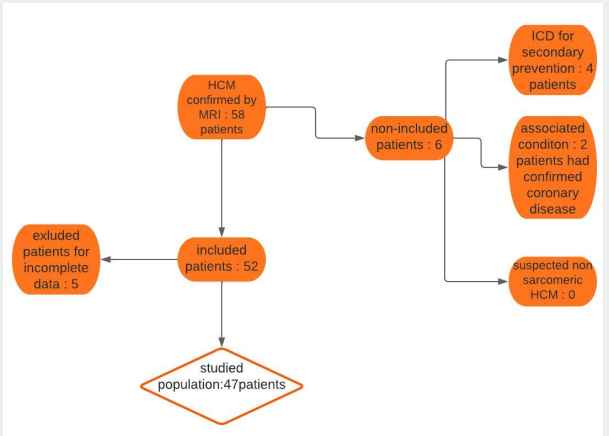

Figure 1. flow chart of patients diagnosed with HCM during the designated period.

The mean age was 55 years ±14 (minimum 23 and maximum 74 years). There were 23 male patients with a sex ratio of 1,04.

Baseline characteristics of the 47 included patients are shown in Table 1.

Table 1. Baseline characteristics of 47 patients.

Parameter	Number of patients (percentage)
Male	23 (49%)
Female	24 (51%)
Family history of SCD	5 (11%)
syncope	11 (23%)
NSVT	15 (32%)
Maximal LV wall thickness, mean (SD), mm (TTE)	22 (5)
Left atrial dimension, mean (SD), mm (TTE)	38 (7)
Left ventricular outflow tract obstruction (TTE)	18 (38%)
LV wall thickness > 30 mm (MRI)	2 (4%)
Apical aneurysm (MRI)	3 (6%)
LVEF < 50% (MRI)	4 (9%)
Large areas of LGE	28 (60%)

LGE: Late Gadolinium Enhancement, LV: Left ventricle, MRI: Magnetic Resonance Imaging, NSVT: non sustained ventricular tachycardia, SCD: Sudden Cardiac Death, SD: Standard Deviation, TTE: Trans-Thoracic echocardiography.

The implantation of an ICD was indicated for 7 patients, one of whom had refused implantation:

- Female patient aged 72, with family a history of sudden death. The patient consulted for episodes of unexplained syncope. She had a high risk according to European recommendations (HCM Risk Score of 7.69%) and a high risk according to American recommendations (family history of sudden death, personal history of syncope). The patient was implanted with a dual-chamber ICD.
- Male patient aged 61, with a family history of sudden death. He had a high risk according to the HCM Risk Score (7%) as well as a high risk according to the ACC algorithm (family history of sudden death). He was implanted with a dual-chamber ICD.
- Male patient aged 64, with a history of unexplained syncope. He had an intermediate risk according to the HCM Risk Score (4.15%) and a high risk according to the ACC algorithm (unexplained syncope). He was implanted with a single-chamber ICD.
- Male patient aged 27, with a family history of sudden death. He had a high risk according to the HCM Risk Score (11.83%) as well as a high risk according to the ACC algorithm (family history of sudden death). He was implanted with a dual-chamber ICD.
- Male patient aged 73 years who had a low risk according to the HCM Risk Score (3.27%) and an intermediate risk according to the ACC algorithm (extensive late gadolinium enhancement, and NSVT). He was implanted with a dual-chamber ICD.
- Male patient aged 40, who had HCM at the dilation stage and an impaired systolic function of the left ventricle. He was at intermediate risk according to the HCM Risk Score (5.22%) and at high risk according to the ACC algorithm (impairment of left ventricular systolic function). He was implanted with a CRT-D as a

treatment for the LVEF impairment.

Table 2 summarize the distribution of patients according to their rhythmic risk estimated by HCM Risk Score and ACC algorithm.

Table 2. distribution of patients according to their rhythmic risk.

		Risk level (ACC algorithm)			Total
		low	intermediate	high	
Risk level (HCM Risk Score)	Low	21	8	7	36
	intermediate	0	2	5	7
	High	0	0	4	4
	Total	21	10	16	47

ACC: American College of Cardiology, HCM: Hypertrophic cardiomyopathy.

Twenty (43%) patients were sorted differently according to the model used. Therefore, we found a weak concordance between the two models (Kappa = 0.28).

Those twenty patients were always reclassified as in a higher risk category by the ACC algorithm. As a result, the number of ICDs to be implanted increased by 1,6 times.

Four patients (9%) developed primary end point during follow up. Their characteristics are shown in table 3.

The ACC algorithm predicted the occurrence of the primary endpoint for these four patients (Sensitivity:100%, Specificity: 49%) whereas the HCM Risk Score predicted only two (Sensitivity=50%, Specificity=95%).

Table 3. characteristics of patients with the primary end-point.

Sex	Age	Primary end-point	Risk level (HCM Risk Score)	Risk level (ACC algorithm)	ICD implantation	Appropriate shock
female	62	SCD	Low	Intermediate	no	N/A
Male	27	Electrical storm	high	High	yes	yes
Male	40	VT	intermediate	High	Yes (CRT-D)	yes
Male	57	VT	low	High	no	N/A

ACC: American College of Cardiology, CRT-D: Cardiac Resynchronization Therapy-defibrillator, HCM: Hypertrophic Cardiomyopathy, SCD: Sudden Cardiac Death, VT: ventricular tachycardia.

The two patients left unprotected by the CMH Risk Score were:

- A 57-year-old man with no family history of HCM or syncope. This patient was classified as low risk according to European recommendations (HCM risk score of 3.31%) and high risk according to American recommendations (LVEF < 50%) therefore he had not benefited from an ICD. He died from a hemodynamically unstable sustained VT refractory to reduction.
- A 62-year-old woman. She was at low rhythmic risk according to European recommendations (HCM risk score at 1.43%) and at intermediate rhythmic risk according to American recommendations (extended contrast enhancement on MRI). She had not been implanted with an ICD. The patient died at home while sleeping.

The ROC curves for the two methods are illustrated in figure 2.

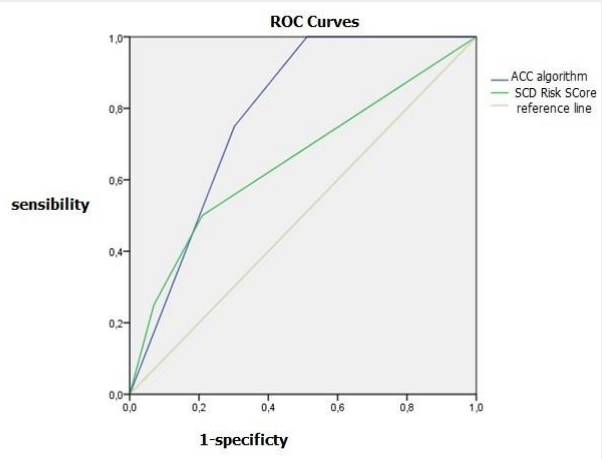

Figure 2. ROC Curves for the ACC algorithm and the SCD Risk Score.

Both curves are above the reference line indicating a positive predictive potency. Nevertheless, the area under the curves and the c-statistics (0.785) of the ACC algorithm are superior to those of the SCD Risk score (0.654) indicating a better predictive value.

The NRI for the ACC algorithm was positive (0.35) indicating an improvement of the detection of high-risk patients in comparison with the HCM Risk Score (4 patients protected VS 2).

Discussion

Since 2014, the estimation of the rhythmic risk of patients with sarcomeric hypertrophic cardiomyopathy has been largely based on the calculation of the European HCM Risk score. A new strategy was established in 2020 by the ACC. It has been proposed as a substitution for the European score for the American population. With the arrival of a new method estimating the same risk, questions about similarity and efficiency of the two options began to rise. We found poor agreement between the two strategies. In fact, 43% of patients were classified differently depending on the model chosen (kappa =0.28). The ACC algorithm allowed a better appreciation of the rhythmic risk with a positive NRI of 0.35. It thus made it possible to detect two patients who developed sudden death or a sustained ventricular arrhythmia during follow-up and who would not be previously considered to be patients at risk. This model has strong predictive power with an area under the ROC curve of 0.785. He was able to predict all patients who had sudden death or a ventricular tachyarrhythmia. However, and despite its good sensitivity, this algorithm had low specificity and tended to considerably increase the number of ICDs prescribed. In our cohort, the number of ICDs had raised by 1.6 times and to eventually save two more patients we would have to implant 16 mores ICDs.

The HCM Risk Score allowed a good assessment of rhythmic risk with an area under the ROC curve of 0.654 and had a higher specificity for identifying patients unlikely to have events, but this score could not predict the rhythmic complication in two patients and therefore could not protect them by indicating the implantation of an ICD.

The two strategies are different and this is largely explained by different methods of estimation and distinct considered risk factors.

Whil The estimation of the rhythmic risk with the HCM Risk score was based on the study of all the factors that may be linked to SCD and the evaluation of the degree of their link using coefficients allowing ultimately all items to be incorporated into a percentage calculation (The items are linked and the existence of a single isolated criterion does not necessarily lead to ICD implementation). In contrast, the ACC algorithm is based on several works establishing a relationship between each of the clinical (13,14), electrical (15), or imaging (16-19) elements and the occurrence of sudden death. Therefore, each item is considered on its own as an independent risk factor requiring prevention. Moreover, the American college recommends the use of CMR to asses maximal wall thickness, LVEF and to detect a possible apical aneurysm (2) in opposition to the HCM risk score who is mainly based on TTE. And, as demonstrated by anterior works, TTE and MRI do not allow a similar assessment of anatomical and geometric parameters (20,21).

Apart from the history of sudden death in the family, syncope and NSVT, which are common to the two models, the two strategies use distinct items to estimate the rhythmic risk. Left ventricle out tract obstruction (LVOTO), age, and left atrial diameter were not considered independent risk factors for sudden death by the ACC algorithm.

The good sensitivity of the ACC algorithm is also pinpointed through previous large cohorts (7,22) and can be explained by the great contribution of CMR in general and the LGE analysis specifically. As a matter of fact, an extensive LGE is greatly correlated to SCD events (19) and it sometimes had better performances than the ACC algorithm itself (23).

In contrast the low sensibility could be an impediment to its current use (6): The common resort to this algorithm then comes up against the considerable rise in the economic burden, especially in a developing country undergoing economic constraints such as Tunisia.

The low sensitivity of the HCM Risk Score can be explained by the fact that it is a mathematical tool that calculates a percentage. It assigns coefficients to the different parameters: This score assesses the risk of sudden death from a complex, heterogeneous pathology with an unpredictable course using a rigid statistical model (24). However, the good specificity of the score could potentially decrease implants in low-risk patients (7) and limit the resort to unnecessary ICD implantations.

Certain genetic mutations were associated with higher risk of SCD (25-28). For example, Arg[403]Gln, Arg[719] Trp, and Arg[453]Cys mutations affecting ß-MyHC (28). Nevertheless, neither method has incorporated those mutations as risk factors.

The results of our study on a Tunisian population are consistent with the major international works focusing on the subject of the comparison between the two methods. But, it's important to consider the specific characteristics of HCM population in Tunisia: HCM are often diagnosed in advanced stage associated with heart failure and frequent SCD. Moreover, genetics studies demonstrated very rare and complex mutations (29,30). Those facts suggest a different course of the pathology (29,30). A large national registry can eventually allow us to study the rhythmic risk factors while taking into account the characteristics specific to the Tunisian patient. Thus, optimizing care and rationalizing the use of ICD implantation.

Moreover, new techniques and predictors of SCD are been brought to light every now and then. Those new method could actually revolutionize our understanding of the matter and refine the decision physicians take to prevent those events. we could mention for example the myocardial strain (34) the topography of LGE in CMR (35) and even some artificial intelligence models featuring machine learning techniques (36).

Our study has some limitations:

- It included a number of patients who could constitute a representative sample of the population with HCM. However, a cohort of 47 patients remains a limited number that does not allow for formal conclusions. A longer period can eventually allow a better detection of rhythmic events.
- No genetic mapping was done for our population.
- The retrospective nature of data collection.

Despite those limitations, and despite failing to demonstrate the superiority of one method over the other, this study was the first in Tunisia that tried to confront the two strategies on a face to face and therefore, attempt to clear the confusion regarding the choice of a better method. We noticed the similarity of our results with larger international cohorts.

Conclusions

The two methods of risk estimation yield different results for the same patients. The ACC algorithm was more efficient in detecting high-risk patients, but it considerably increased the number of ICDs indicated. In the other hand, The ESC model is associated with higher specificity for identifying patients unlikely to have events, potentially decreasing implants in low-risk patients, but it's still limited by a lower sensibility. Further investigations are to be made (with more patients, longer follow-up periods and genetic mapping) to take in consideration the particularities of Tunisian HCM population.

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