Proceedings of the 2023 Design of Medical Devices Conference
DMD2023
April 17-19, 2023, Minneapolis, MN, USA

DMD2023-2989

ARRHYTHMIC SUDDEN DEATH SURVIVAL PREDICTION MODEL FOR HYPERTROPHIC CARDIOMYOPATHY PATIENTS: AN INTERPRETABLE MACHINE LEARNING ANALYSIS

Nasibeh Zanjirani Farahani, Ph.D.
Mayo Clinic
Rochester, MN

Moein Enayati, Ph.D.
Mayo Clinic
Rochester, MN

Andredi Pumarejo, M.D.
Mayo Clinic
Rochester, MN

Mateo Alzate Aguirre, M.D.
Mayo Clinic
Rochester, MN

Christopher Scott, Ph.D.
Mayo Clinic
Rochester, MN

Konstantinos Siontis, M.D.
Mayo Clinic
Rochester, MN

Martijn Bos, MD, Ph.D.
Mayo Clinic
Rochester, MN

Jeffrey B. Geske, M.D.
Mayo Clinic
Rochester, MN

Michael J. Ackerman, M.D., Ph.D.
Mayo Clinic
Rochester, MN

Adelaide M. Arruda-Olson, M.D., Ph.D.
Mayo Clinic
Rochester, MN

ABSTRACT

Hypertrophic Cardiomyopathy (HCM) is an inheritable heart disease with the highest rate of sudden cardiac death (SCD) in young adults. Implantable Cardioverter Defibrillator (ICD) therapy is recommended for HCM patients at high risk for SCD. Reviewing the recent clinical literature revealed the potential to improve the selection of candidates for ICD implantation. The current study uses information extracted from echocardiography reports to evaluate HCM patients with ICD and aims to provide a comparative insight into patients who benefited the most from the device therapy, including shock and anti-tachycardia pacing (ATP). The proposed interpretable machine learning approach has used the XGboost algorithm. The model's performance was considered satisfactory, as evidenced by an accuracy score of 81% and an area under the receiver operating characteristic curve (AUC) value of 69% and SHapley Additive exPlanations (SHAP) identified common properties of HCM patients in each category and provided high-level reasoning and foundation for a clinical decision support tool.

Keywords: Hypertrophic Cardiomyopathy, Arithmetic sudden cardiac death, Implantable Cardioverter Defibrillator, Machine Learning, SHapley Additive exPlanations (SHAP), survival prediction model

1. INTRODUCTION

Hypertrophic Cardiomyopathy HCM is an inheritable heart disease affecting as many as 20 million people worldwide and more than 700,000 Americans annually [1, 2]. Diagnosing HCM is often challenging as clinical presentation varies and physical examination is often unrevealing. Many patients are completely asymptomatic and often identified incidentally or after experiencing an adverse outcome [3]. These adverse outcomes include sudden cardiac death (SCD), heart failure, and atrial fibrillation, with an associated risk for ischemic stroke [4, 5]. Implantable cardioverter-defibrillator (ICD) is the recommended treatment for lowering HCM mortality, indicated for patients at greatest risk for SCD. However, existing risk stratification strategies sometimes disagree regarding risk assessment and can misclassify risk for SCD. HCM patients at high risk of SCD might not be correctly selected for ICD implantation [6], underscoring the importance of developing personalized, accurate, and cost-effective models for identifying HCM patients at high risk for SCD [7].

Recent developments in machine learning algorithms have shown significant success in developing different tools to identify HCM patients, including echocardiography [8] and ECG [9]. Enayati, et al. [10] have highlighted the potential application of artificial intelligence in evaluating ICD therapies

of HCM patients. Several algorithms are proposed to help with the clinical interpretation of the results to tackle the black box effect. SHapley Additive exPlanations (SHAP) is a popular algorithm used to explain clinical prediction models. For example, it was used to interpret the results of an XGBoost model, predicting all-cause mortality in patients with heart failure [11, 12] In this pilot project, we have developed an interpretable machine-learning approach to predict the arrhythmic event survival of HCM patients.

2. MATERIALS AND METHODS

In this pilot project, we have focused on a large cohort of HCM patients with ICDs evaluated at Mayo Clinic. Before conducting the study at Mayo Clinic, this work was approved by the Institutional Review Board (IRB). Finding HCM patients who had documented life-threatening arrhythmic events required many phases, shown in Figure 1. The study design for developing an interpretable machine-learning model for identifying HCM patients at risk of life-threatening arrhythmic events is shown in Figure 2.

Initial Cohort Identification: In Mayo Clinic, 6276 patients between 2004-2019 had confirmed HCM based on the chart review by expert clinicians. After reviewing the device implantation records of these patients, 2,263 had ICDs implanted and were selected for this project. Six patients did not approve research authorization and were excluded from the study. After reviewing the patient's information, 1,893 patients with available EHR and echo reports were selected for this study. 72% were males with a median (IQR) age of 49 (35-60) years, and the average length of follow-up time was 4.3 years. Another round of data collection was needed to recognize the patients who had survived arrhythmic events.

Outcome Data Collection: HCM patients with ICD underwent device interrogation at routine intervals or as needed if clinically indicated (e.g., after experiencing a shock). All ICD interrogation reports were retrieved from the institutional data warehouse of the Unified Data Platform.

All reports were reviewed, and natural language processing algorithms extracted relevant information for each event. [13]

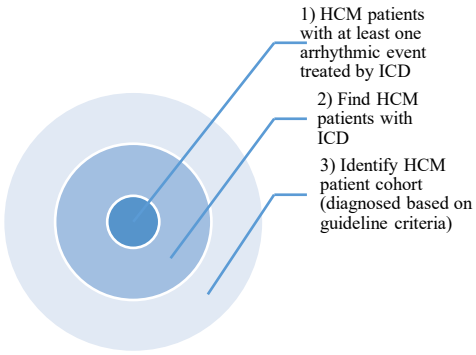

FIGURE 1: STEPS FOR IDENTIFICATION HCM PATIENTS WHO SURVIVED A LIFE-THEREATHENING ARRHYTHMIA TREATED BY ICD

This information was reported as semistructured data for the next round of review.

Defibrillator threshold testing reports were excluded. The events were divided into four categories for manual review: Device therapy events included: 1) shocks, 2) anti-tachycardia pacing (ATP), or 3) both ATP and shock for treatment of ventricular tachycardia or ventricular fibrillation events 4) inappropriate shocks. A manual review of ICD interrogation reports validated all events and ICD therapies. In the final phase, 235 patients were selected, and these were considered cases for developing this survival prediction model.

Data Preparation: We selected patients with ICD who had never had any equivalent death events for the control group. Patients who died for unknown reasons were excluded. Cases and controls were matched 1 to 4 based on age and sex. Demographic information and echo features were extracted from EHR and the first echo report of each patient. Table 1 shows a summary of the baseline characteristics of these patients.

Modeling: For *feature* selection, we referred to echo measurements for HCM identification from Farahani et al. [8] and patient demographics. In literature, several classification methods, such as random forest [8], XGBoost, a popular supervised-learning algorithm, and regression, were suggested

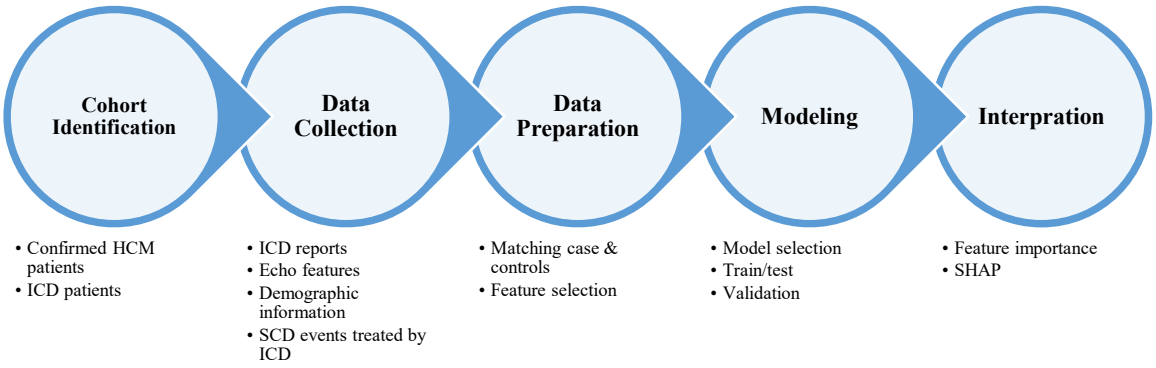

FIGURE 2: PHASES FOR DEVELOPMENT OF AN INTRPETABLE MACHINE LEARNING MODEL FOR IDENTIFICATION HCM PATIENTS AT RISK OF LIFE-THERATENING ARRHYTHMIC EVENTS

TABLE 1: BASELINE CHARACTERISTICS TABLE OF MOST IMPORTANT ECHO MEASUREMENTS

	Median (IQR)		P value
	ICD patients with no event (N=940)	ICD patients with an event (N=235)	
Age at first echo, year	49 (36, 60)	49 (35, 60)	0.72
Male sex, no (%)	668 (71.7%)	167 (71.7%)	1
Body surface area, m^2	2.1 (1.9, 2.2)	2.1 (1.8, 2.2)	0.76
Interventricular septum diastolic thickness, mm	19 (15, 24)	19 (15, 24)	0.96
Left ventricular mass, g/m2	303 (237, 393)	313 (240, 403)	0.35
Left ventricular outflow tract gradient, mmHg	3.1 (2.1, 4.3)	3.1 (2.3, 4.1)	0.82
Mitral valve E/A, ratio	1.3 (0.9, 1.7)	1.4 (1, 2)	0.06
Mitral valve deceleration time, ms	199 (165, 244)	173 (150, 222)	0.001
Mitral valve lateral annulus E/e', ratio	11.4 (8, 15.9)	11.1 (7.9, 15)	0.40
Global longitudinal strain, %	-13 (-16, -10)	-12 (-15, -10)	0.09
Thickest segment of the wall, mm	23 (20, 27)	26 (23, 30.5)	0.01

to classify large datasets [11]. In this study, we used the XGBoost method to classify HCM patients in two groups in sparse datasets as a powerful algorithm with a built-in function to deal with the sparsity of echo data.

Interpretation: As recommended in recent publications[11], SHAP modeling was used for result interpretation and presentation to clinicians. In a SHAP value graph, the colors red and blue are used to represent the direction and magnitude of the effect of a feature on a prediction.

3. RESULTS AND DISCUSSION

The proposed survival prediction model focuses on HCM patients who had experienced at least one successfully treated event compared to a control group of HCM patients who had no events. We purposefully excluded ICD patients who had died despite having the device, as there are specific clinical reasons for those cases. The selected patients from these two groups were matched at 1 to 4 (case/control) based on their age at their first echocardiogram and sex. Each patient's demographic information and echocardiographic measurements were extracted from related databases to train an XGBoost machine learning model. The model achieved an acceptable performance (accuracy of 81%, AUC of 69%, sensitivity of 89%, and specificity of 53%), and these results were interpreted using SHAP. The use of AUC for rare cases is controversial because the rare class constitutes an exceedingly small amount of data [14]. Although the classification solution is expected to predict the rare class, the algorithms are deviated more towards predicting the majority class since their loss functions try to perform well in calculating the error rate without considering the distribution of the feature.

Figure 3 shows the result of SHAP in two graphs. On the right side, the local explanation summary shows the relationship between an echo measurement and the outcome. Red means the increase in the value of a measurement, and blue shows the decrease. The positive values of SHAP translate as the occurrence of an arrhythmic event based on the XGBoost model. The mean absolute SHAP values on the left side illustrate global feature importance. These are the top features based on their mean absolute SHAP value and impact on the model output. The thickest segment of the wall, left ventricular outflow tract obstruction, and mitral valve deceleration time are the top three features in predicting the successful treatment of an arrhythmic event in a patient with an ICD. Global longitudinal strain and left ventricular mass are the next features. The second section of Figure 3 shows how a measurement can impact the model output. The thickest wall segment, left ventricular outflow tract gradient

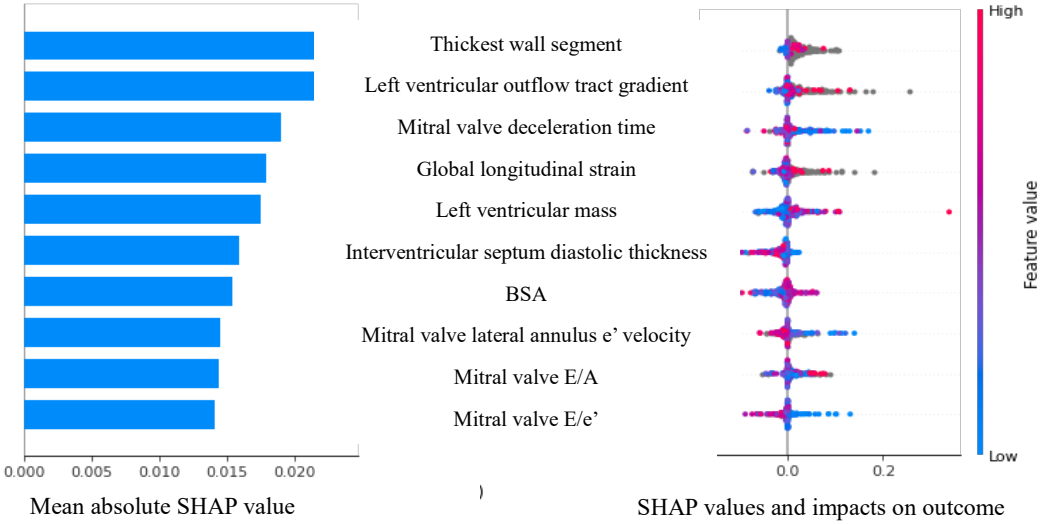

FIGURE 3: SHAP VALUES SHOW THE IMPACT OF EACH FEATURE ON THE MODEL OUTPUT.

and mass, BSA, and mitral valve E/A were found to be independently associated with an increased risk of arrhythmic events in patients with ICDs. However, these measurements are not consistently tracked for all patients.

Additionally, events were less likely to be detected in patients with longer mitral valve declaration time or lower mitral valve E/e' values. While the importance of mitral valve lateral annulus e' velocity on outcome is apparent, the SHAP model was unable to clearly define its directional relationship. Therefore, further research is necessary to understand how these variables impact the risk stratification for SCD.

One limitation of echocardiographic studies is the absence of specific HCM-related measurements in control subjects. For instance, Figure 3 highlights that the thickest wall segment, a leading predictor of adverse events, may not be consistently documented. Not all patients may have global strain values. However, the proportion of arrhythmic events was higher for patients with fewer negative values. Also, as Figure 3 shows, the blue and red dots overlap for certain echo measurements, implying the potential occurrence of misclassifications.

4. CONCLUSION

In this project, a prediction model for HCM patients based on their echocardiography report and demographic information was developed. This model classified patients at higher risk for experiencing an arrhythmic event. This data may be additive to existing SCD risk stratification in guiding ICD decision-making. This model was interpreted by an advanced technique to provide more clinical insights for experts.

REFERENCES

[1] J. B. Geske *et al.*, "Women with hypertrophic cardiomyopathy have worse survival," *Eur Heart J,* vol. 38, no. 46, pp. 3434-3440, Dec 7 2017, doi: 10.1093/eurheartj/ehx527.

[2] M. S. Maron, E. L. Lanuario, E. J. Rowin, and B. J. Maron, "Global Dissemination and Implementation of Contemporary Management Principles for Hypertrophic Cardiomyopathy and Role of the International HCM Summit," (in eng), *Am J Cardiol,* vol. 172, pp. 146-149, Jun 1 2022, doi: 10.1016/j.amjcard.2022.01.036.

[3] J. B. Geske, S. R. Ommen, and B. J. Gersh, "Hypertrophic Cardiomyopathy: Clinical Update," *JACC Heart Fail,* Apr 5 2018, doi: 10.1016/j.jchf.2018.02.010.

[4] B. J. Maron, "Clinical Course and Management of Hypertrophic Cardiomyopathy," *N Engl J Med,* vol. 379, no. 7, pp. 655-668, Aug 16 2018, doi: 10.1056/NEJMra1710575.

[5] S. R. Ommen *et al.*, "2020 AHA/ACC Guideline for the Diagnosis and Treatment of Patients With Hypertrophic Cardiomyopathy: Executive Summary: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines," *Circulation,* vol. 142, no. 25, pp. e533-e557, Dec 22 2020, doi: 10.1161/CIR.0000000000000938.

[6] K. M. W. Leong *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,* vol. 121, no. 3, pp. 349-355, Feb 1 2018, doi: 10.1016/j.amjcard.2017.10.027.

[7] D. M. Popescu *et al.*, "Arrhythmic sudden death survival prediction using deep learning analysis of scarring in the heart," *Nature Cardiovascular Research,* vol. 1, no. 4, pp. 334-343, 2022/04/01 2022, doi: 10.1038/s44161-022-00041-9.

[8] N. Z. Farahani *et al.*, "Application of Machine Learning for Detection of Hypertrophic Cardiomyopathy Patients from Echocardiogram Measurements," in *2021 Design of Medical Devices Conference*, 2021, vol. 2021 Design of Medical Devices Conference, V001T02A009, doi: 10.1115/dmd2021-1078. [Online]. Available: https://doi.org/10.1115/DMD2021-1078

[9] K. C. Siontis *et al.*, "Detection of hypertrophic cardiomyopathy by an artificial intelligence electrocardiogram in children and adolescents," (in eng), *Int J Cardiol,* vol. 340, pp. 42-47, Oct 1 2021, doi: 10.1016/j.ijcard.2021.08.026.

[10] M. Enayati *et al.*, "Deep Unsupervised Clustering of Sparse Echo Data to Identify Patients for Implantation of Cardioverter-Defibrillator," in *2022 Design of Medical Devices Conference*, 2022, vol. 2022 Design of Medical Devices Conference, V001T01A008, doi: 10.1115/dmd2022-1074. [Online]. Available: https://doi.org/10.1115/DMD2022-1074

[11] K. Wang *et al.*, "Interpretable prediction of 3-year all-cause mortality in patients with heart failure caused by coronary heart disease based on machine learning and SHAP," *Computers in Biology and Medicine,* vol. 137, p. 104813, 2021/10/01/ 2021, doi: https://doi.org/10.1016/j.compbiomed.2021.104813.

[12] S. M. Lundberg and S.-I. Lee, "A unified approach to interpreting model predictions," *Advances in neural information processing systems,* vol. 30, 2017.

[13] K. C. Siontis *et al.*, "Natural language processing of implantable cardioverter-defibrillator reports in hypertrophic cardiomyopathy: A paradigm for longitudinal device follow-up," (in eng), *Cardiovasc Digit Health J,* vol. 2, no. 5, pp. 264-269, Oct 2021, doi: 10.1016/j.cvdhj.2021.05.005.

[14] J. Davis and M. Goadrich, "The relationship between Precision-Recall and ROC curves," presented at the Proceedings of the 23rd international conference on Machine learning, Pittsburgh, Pennsylvania, USA, 2006. [Online]. Available: https://doi.org/10.1145/1143844.1143874.