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EDITORIAL COMMENT

Machine Learning to Predict Future Disease-Specific Outcomes

The Brave New Frontier*

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"By far, the greatest danger of artificial intelligence is that people conclude too early that they understand it."

—Eliezer Yudkowsky[1]

The broad concept of artificial intelligence (AI), of which machine learning (ML) is a key component, is exploding into the world stage at a dizzying pace and is poised to play a pivotal role in predicting outcomes across various fields and industries because of its ability to analyze data, identify patterns, and make predictions or decisions based on that data. In medicine, ML models can be trained to leverage various patient-related factors (demographics, clinical history, laboratory results, and imaging data) to identify relevant features that potentially correlate with disease outcomes.

Given the increased likelihood of sudden cardiac death in patients with hypertrophic cardiomyopathy (HCM), extensive research has been generated in this field to develop robust risk prediction tools that have been endorsed by various guidelines to help identify high-risk HCM patients who would benefit from primary prevention internal cardioverter defibrillator.[2,3] However, there is a major gap in tools that can effectively predict risk for major adverse cardiac events (MACE) in HCM-related mortality and morbidity (eg, congestive heart failure, stroke, and so on). Developing a better understanding of predictors of MACE will be important in the future, with increasing emphasis on HCM diagnosis and more patients achieving a normal lifespan.

In this issue of *JACC: Asia*, Rhee et al[4] incorporate the use of ML to correlate with MACE in HCM patients. The authors utilize the SHapley Additive exPlanations (SHAP) method to determine the relative importance of each feature incorporated into the best predictive ML model. The increased precision of ML-based modeling using widely available echocardiographic imaging and baseline clinical characteristics to identify features associated with MACE in the model is impressive. In total, 2,111 patients with HCM (age 61.4 ± 13.6 years; 67.6% men) were analyzed.

During the median 4.0 years of follow-up, MACE occurred in 341 patients (16.2%). Among the 4 ML models, the logistic regression model achieved the best area under the receiver-operating curve (AUROC) of 0.800 for MACE, 0.789 for all-cause death, 0.798 for heart failure admission, and 0.807 for stroke. The discriminant ability of the logistic regression model remained excellent when applied to the external validation cohort for MACE (AUROC: 0.768), all-cause death (AUROC: 0.750), and heart failure admission (AUROC: 0.806). This technique has the potential to make risk assessment practical, accessible, and easy, guiding future risk assessments. There are many strengths to the current report, including 2 large derivation and validation cohorts from different institutions, utilization of widely available imaging and clinical variables, and excellent correlation of 4 ML models with observed outcomes except stroke.

However, the current report is not free of significant limitations. It is interesting to note that depending upon the outcome chosen, the ML models report different variables (eg, AF for heart failure admission, age for MACE and death). Although not

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necessarily a limitation, this is important to keep in mind as we develop larger predictive models worldwide. The findings need to be replicated in a broader and more ethnically diverse population across the world. Lack of incorporation of advanced imaging techniques is another major limitation. There is not adequate transparency about understanding of disease severity at baseline, and the duration of follow-up is relatively short. Additionally, testing the performance of these newer predictive models against the traditional models is important to inform future guidelines.

For most consumers of medical information, different ML techniques (including the SHAP analysis utilized in the current report) is too complicated to understand. Although SHAP is assumed to be model-agnostic, is excellent at feature selection (by quantifying the impact of each feature on model predictions), and can be applied to various types of models, it does not fully capture the intricacies of complex models or model-specific behaviors. There are some additional potential problems with SHAP analyses, including assumption of feature independence (which is unrealistic in medicine) and sensitivity to the distribution of data and perturbations in the data set (such that small changes can result in significant variation and exaggerated interpretation). Although a major issue with ML is the "black-box" nature of proprietary software, the SHAP analysis is an important step in the right direction for broader applicability. However, although SHAP values offer insights into model predictions, they may not provide a complete understanding of the underlying black-box model, as they give feature-level explanations but not a holistic view of the model's decision-making process.

In conclusion, the current report is a crucial step in leveraging AI and ML to understand the role of various clinical and imaging markers in development of a broad endpoint of MACE (not just sudden cardiac death) in HCM patients. However, as a society, as we rapidly rumble toward increasing AI and ML applications, we need to hold ourselves accountable to do the following: 1) ensure availability of accurate, high-quality, diverse, and large-scale training and validation data sets; 2) have clinically validated tools to enhance trust from our patients and increase adoption by health care professionals; and 3) have fair, unbiased predictive tools while protecting patient privacy.

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