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EDITORIAL COMMENT

# Event Prediction in HFpEF Using Machine Learning

## Will This Promising Model Be Applied in Practice?

Jeroen G. Valk, MSc,[a,b] Arlene John, PhD,[a] Mark J. Schuuring, MD, PhD[a,b]

Heart failure with preserved ejection fraction (HFpEF) represents an increasingly common cardiovascular condition, now accounting for almost one-half of all heart failure (HF) cases.[1] As the prevalence continues to increase, efficient risk stratification and personalized care is needed.[2] However, predicting clinical outcomes in these patients is challenging, since a substantial gap remains in literature regarding predictors for hospitalizations and mortality for HFpEF patients.[3,4] Compounding to this challenge is the shortage of health care professionals, highlighting the urgent need to improve the efficiency and personalization of patient care.[5] A potential solution is the application of machine l earning (ML) to enhance understanding of predictors of hospitalization and mortality and provide automated risk stratification to identify high-risk patients.

In this issue of *JACC: Asia*, Chang et al[6] present their innovative study that utilizes ML for risk stratification in patients with HFpEF. In their multicenter study, Chang et al[6] analyzed 6,092 HFpEF patients from the Chang Gung Research Database complimented with data from the Taiwan Death Registry. In their database, the investigators included echocardiographic features, an element not previously incorporated in HFpEF risk stratification literature.[6] The inclusion of echocardiographic features enhances the clinical relevance of the model by providing more insight into cardiac function. Using a random survival forest (RSF), Chang et al[6] identified 15 predictors for HF hospitalizations and cardiovascular-related death, achieving an area under the curve of 85.6% and 86.9% in the derivation and validation sets, respectively. Their analyses showed that an increase in the number of predictors for a patient was linked to an elevated rate of hospitalizations and mortality.

One of the strengths of the studies lies in its large, multicenter dataset, which incorporated 6,092 patients from over 20,000 screened. The database consists of 58 features, including demographic, comorbidity, baseline echocardiographic, laboratory, and medication features. The incorporation of echocardiographic features is an aspect that enhances the clinical relevance of the model, given the "echo first" strategy widely adopted in cardiology clinics worldwide.[7] Furthermore, the generalizability of the RSF model is demonstrated by its performance on the large independent validation set, which was geographically diverse due to the north-south hospital split. The consistent results across both the derivation and validation cohorts underline the model's applicability across different clinical settings.

Another strength of the study is the incorporation of partial dependency plots of the top 15 features, which enhances the explainability of the RSF model. Through these plots, insights are gained into the importance of the chosen features on the predictive performance of the model. Furthermore, through the removal of HFpEF mimics such as cardiac amyloidosis or sarcoidosis in their sensitivity analysis, Chang et al[6] demonstrated that the model's outcomes were consistent with those observed in the original analysis. The additional analysis enhances the explainability and the applicability of the model, making it more suited for clinical settings where transparency in decision-making is crucial.[8]

Despite the strengths of this study, certain limitations of this study should be addressed. First of all, concerns about the data completeness and quality arise. The investigators stated that only 37% of the

From the [a]Department of Biomedical Signals and Systems, University of Twente, Enschede, the Netherlands; and the [b]Department of Cardiology, Medisch Spectrum Twente, Enschede, the Netherlands.

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derivation set was fully complete without imputation of missing variables. Since the amount of imputation needed was not noted, the effect of missing data on the model's prediction is unknown. Moreover, the exclusion of features missing for two-thirds of the population may have resulted in the loss of potentially valuable predictors for events. Furthermore, the exclusion of HFpEF patients who were hospitalized for HF without receiving diuretic agents may have led to potential bias in the population. This exclusion criterion may result in a cohort that underrepresents stable patients, who did not require diuretic agents during hospitalization, thus limiting the generalizability of the model. Finally, there is concern regarding the reliability of the death registry, particularly how accurately cardiovascular death is recorded in the database. As cardiovascular death is 1 of the primary endpoints, this issue may pose a considerable limitation to the reliability of the results.

A closer look at the ML techniques applied in this study reveals another minor limitation. Chang et al[6] used variable importance ranking for their feature selection. Although variable importance ranking is well-incorporated in RSF models, it was not stated what method was used to determine feature importance, such as Gini impurity or permutation importance. This introduces a degree of uncertainty regarding the prioritization of the features.[9] Additionally, different methods for feature selection, such as recursive feature elimination or LASSO regularization, might have ranked features differently, potentially leading to alternative conclusions regarding which variables are most important to the predictive performance of the model.

Regardless of the limitations, this is the first study from Taiwan to identify predictors of hospitalizations and mortality, which is significant given the demonstrated variability of comorbidities and outcomes among HFpEF patients across Asia.[10] The predictive model of Chang et al[6] has the potential to enhance clinical decision-making by assisting clinicians with individual risk assessments. However, its clinical impact is yet to be determined, as its benefit is dependent on the model's agreement to current clinical risk assessment and the extent to which it simplifies or accelerates the decision-making process. Evaluating the implementation of a digital solution in clinical practice is therefore essential.[11] Further studies are needed to determine the model's clinical impact and optimal implementation into the workflow with involvement of relevant stakeholders.[12]

Looking further ahead, the future of risk prediction in HFpEF may lie in continuous risk assessment rather than relying on a single point-in-time evaluation. By integrating follow-up data into the model of Chang et al,[6] it could evolve into a tool that offers clinicians updated risk predictions at various stages of a patient's care. This shift from static to dynamic prediction would reflect the changing nature of HFpEF progression, offering more nuanced risk prediction.

In summary, Chang et al[6] developed a risk stratification model aimed at identifying high-risk patients using a large dataset of over 6,000 patients, including echocardiographic features, a novel addition in this area of research. In their study they identified 15 predictors for HF hospitalizations and CV death in HFpEF patients, contributing valuable insights to address gaps in the existing literature. Despite the strengths of this study, the clinical implementation of the predictive model is yet to be determined. Nonetheless, this study once again highlights the potential of ML for advancing personalized risk assessment for patients with HFpEF.

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**ADDRESS FOR CORRESPONDENCE:** Dr Mark J. Schuuring, University of Twente, Biomedical Signals and Systems, Drienerlolaan 5, 7522 NB Enschede, the Netherlands. E-mail: mark.schuuring@utwente.nl.

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