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EDITORIAL COMMENT

Rethinking Risk in Mitral Valve Prolapse

The Promise of Machine Learning and Multimodal Phenotyping

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Mitral valve prolapse (MVP) is the most common valvular heart disease, affecting approximately 2% to 3% of the general population. Although the prognosis is generally benign in the absence of mitral regurgitation (MR),[1] a small, poorly defined subset of individuals remains at higher risk for malignant ventricular arrhythmias and sudden cardiac death (SCD).[2] The association between MVP and SCD has been reported with an annual incidence <1%, yet higher than in cases of idiopathic ventricular fibrillation.[3] Due to the low event rate and the lack of large prospective cohorts, risk stratification in MVP remains challenging.

In this issue of *JACC: Clinical Electrophysiology*, Tastet et al[4] provide a robust methodologic approach by integrating comprehensive clinical, electrocardiographic (ECG), and echocardiographic evaluations with unsupervised machine learning (ie, hierarchical clustering) to reveal hidden phenotypic differences in patients with MVP but no significant MR. This innovative use of artificial intelligence-generated clusters defines the arrhythmic MVP (AMVP) phenotype with greater precision, leveraging all-cause mortality as a robust endpoint. Notably, the reliance on routine echocardiographic evaluation enhances the applicability of these findings to primary care settings, where such tools are widely available.

The investigators studied 343 patients with MVP and no more than moderate MR, enrolled over 10 years from a single-center cohort at the University of California-San Francisco.[4] They focused on the incidence of arrhythmic events and mortality. Through hierarchical clustering analysis using 32 routinely obtainable variables, including demographic data, ECG intervals, and echocardiographic markers, 3 distinct MVP clusters were delineated. These clusters were not predefined by known risk factors but emerged from the data, without assumptions. This approach revealed an 83% low-risk group (Cluster 1), an intermediate-risk group (Cluster 2; 9%), and a high-risk group (Cluster 3; 8%). Most strikingly, despite only mild or trace MR, Cluster 3 exhibited significant left atrial (LA) and left ventricular (LV) structural and functional abnormalities and was associated with an HR of 5.85 for all-cause mortality relative to the low-risk group. Cluster 2, which showed greater right ventricular dysfunction and elevated pulmonary pressures, also carried a similarly high risk (HR: 5.01).

Tastet et al[4] should be commended for their innovative approach. Traditionally, the degree of MR has been central to risk stratification in MVP, and subjects without significant MR were believed to have a benign course.[5] This study identifies 2 subgroups with a very high risk of death (>40% at 6 years) despite normal LV systolic function and nonsignificant MR. More than 85% of participants had no or only mild MR, and neither MR severity nor classic anatomical features such as bileaflet prolapse, or mitral annular disjunction emerged as dominant contributors to cluster classification.[6] Conversely, functional parameters of atrial and ventricular performance, such as LA reservoir strain, LA function index, and LV global longitudinal strain, exhibited the highest predictive value. These findings emphasize subtle markers of LA and both right ventricular

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and LV remodeling, representing a potential paradigm shift. They suggest that MVP-associated arrhythmias and mortality result not only from the consequences of MR but also from underlying primary atrial and ventricular myopathic processes. This "atriopathy" and "cardiomyopathy" hypothesis is further supported by the inclusion of LA strain and right ventricular function among the top clustering features,[7] as ranked by a random forest model. The clinical implications are significant. By using widely available diagnostic tools, specifically standard echocardiography and 12-lead ECG, the authors show that advanced risk stratification can be feasibly integrated into routine clinical practice, including in primary care centers. This approach facilitates the identification of patients with MVP at elevated risk who might otherwise be regarded as low risk due to their mild MR. Although not yet universally implemented, parameters such as LA strain and mechanical dispersion can be incorporated into clinical workflows.

The study also points to the potential for individualized follow-up.[4] Patients classified within Clusters 2 and 3, although representing a minority of the cohort, exhibited substantially higher rates of arrhythmic events and all-cause mortality over a mean follow-up of 5.4 years. Identification of these high-risk individuals may trigger personalized management strategies.

While innovative, the study has inherent limitations.[4] It is a single-center study involving a limited number of patients over a long period, particularly in the high-risk clusters (Clusters 2 and 3, with 31 and 28 patients, respectively). The small cohort size in these high-risk groups is inherent to the paucity of severe arrhythmic events in MVP and the lack of systematic rhythmic risk stratification in routine practice of MVP until recent data emerged.[8] Although the hierarchical clustering method was robust and validated with sensitivity analyses, external replication is essential. Furthermore, because MVP-related arrhythmic events remain relatively rare, large-scale, multicenter validation efforts are warranted before widespread clinical adoption. Restricting the analysis to patients with less than severe MR does not allow adjustment for MR severity grade, leaving uncertainty about whether LA/LV adverse remodeling in AMVP is truly independent of MR severity. In addition, LA/LV dysfunction assessed by strain is not easily applicable to routine risk stratification in clinical practice, as strain measurements are dependent on both operator expertise and vendor-specific software. Conversely, LA function in MVP, assessed by using the LA contraction index, calculated as septal e' divided by LA volume index (both measured in routine practice), is feasible, reproducible, independent, and incremental to LA volume in MVP risk stratification.[9] Moreover, as correctly pointed out by the authors,[4] the AMVP clusters do not account for cardiac magnetic resonance imaging data, which could enhance risk prediction.[10]

The main strength of the proposed classification lies in predicting all-cause mortality, a robust endpoint.[4] However, 77% of these events were noncardiac, and only a minority were arrhythmic. The arrhythmic endpoint was a composite, dominated by frequent premature ventricular contractions and complex ventricular ectopy, including sustained or nonsustained ventricular tachycardia. Most of these events, likely captured by ambulatory ECG monitoring, did not constitute clinical events and could have been included in the classification model to improve arrhythmic event prediction. Notably, one-half ($n = 6$) of the SCD events occurred in Cluster 1, constituting a larger absolute number of deaths in that cluster compared with Clusters 2 and 3, suggesting that this classification may be insufficient to guide the selection of candidates for primary prevention of SCD using defibrillators. Although advanced imaging data were intentionally excluded, this approach may be reductive, as such data are part of guideline-recommended assessments of heart disease and associated risk, potentially improving risk prediction and mechanistic understanding.

The study by Tastet et al[4] supports the concept that MVP is not merely a valve disease but a complex condition involving atrial, ventricular, and autonomic substrates. They propose that the term "arrhythmic MVP" encompasses electromechanical dispersion, atrial myopathy, and subtle myocardial dysfunction, phenomena that may be present even in the absence of overt MR. By coupling machine learning with accessible diagnostic tools, the authors emphasize that MVP risk is not confined to regurgitant volume but reflects a broader context of myocardial function, electrophysiological dispersion, and hemodynamic interactions. This study paves the way for international cohorts with well-defined AMVP and long-term follow-up to explore this unique phenotype with artificial intelligence integration. The next steps involve validating these findings, incorporating advanced imaging techniques, and integrating them into predictive models for clinical practice.

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