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Identifying Mitral Valve Prolapse at Risk for Arrhythmias and Fibrosis From Electrocardiograms Using Deep Learning

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Abstract

BACKGROUND—Mitral valve prolapse (MVP) is a common valvulopathy, with a subset developing sudden cardiac death or cardiac arrest. Complex ventricular ectopy (ComVE) is a marker of arrhythmic risk associated with myocardial fibrosis and increased mortality in MVP.

OBJECTIVES—The authors sought to evaluate whether electrocardiogram (ECG)-based machine learning can identify MVP at risk for ComVE, death and/or myocardial fibrosis on cardiac magnetic resonance (CMR) imaging.

METHODS—A deep convolutional neural network (CNN) was trained to detect ComVE using 6,916 12-lead ECGs from 569 MVP patients from the University of California-San Francisco between 2012 and 2020. A separate CNN was trained to detect late gadolinium enhancement (LGE) using 1,369 ECGs from 87 MVP patients with contrast CMR.

RESULTS—The prevalence of ComVE was 28% (160/569). The area under the receiver operating characteristic curve (AUC) of the CNN to detect ComVE was 0.80 (95% CI: 0.77–0.83)

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

APPENDIX For supplemental methods, figures, and tables, please see the online version of this paper.

and remained high after excluding patients with moderate-severe mitral regurgitation [0.80 (95% CI: 0.77–0.83)] or bileaflet MVP [0.81 (95% CI: 0.76–0.85)]. AUC to detect all-cause mortality was 0.82 (95% CI: 0.77–0.87). ECG segments relevant to ComVE prediction were related to ventricular depolarization/repolarization (early-mid ST-segment and QRS from V_1, V_3, and III). LGE in the papillary muscles or basal inferolateral wall was present in 24% patients with available CMR; AUC for detection of LGE was 0.75 (95% CI: 0.68–0.82).

CONCLUSIONS—CNN-analyzed 12-lead ECGs can detect MVP at risk for ventricular arrhythmias, death and/or fibrosis and can identify novel ECG correlates of arrhythmic risk. ECG-based CNNs may help select those MVP patients requiring closer follow-up and/or a CMR.

Keywords

artificial intelligence; computers; echocardiography; valvular heart disease

Mitral valve prolapse (MVP) is a common valvulopathy affecting over 170 million worldwide.[1,2] Although a subset of MVP patients (0.14%–1.8% yearly)[3–6] will develop sudden cardiac arrest (SCA) or sudden cardiac death (SCD), predictors of this devastating outcome are not well-defined. Inverted or biphasic T waves have been described in the inferior electrocardiogram (ECG) leads with a prevalence ranging between 30 and 78% in selected, retrospective studies of patients with SCD/SCA.[4,7] However, inferior T-wave abnormalities are present in 40% of MVPs even if no history of ventricular arrhythmia.[8] QT prolongation and QT dispersion in malignant MVP syndrome have been described in some, but not all, studies.[9–11] An easily obtainable and fully automated “surveillance” tool in MVP would provide substantial clinical value to quickly identify those at higher arrhythmic risk within large clinical cohorts of mostly benign MVPs.

Previously, SCD/SCA in MVP has been linked to severe mitral regurgitation (MR).[6] Other studies have reported a high arrhythmic risk in a bileaflet phenotype with mild MR, T-wave abnormalities in the inferior ECG leads, and complex ventricular ectopy (ComVE-defined as frequent pleomorphic premature ventricular contractions [PVCs], couplets/triplets, or nonsustained ventricular tachycardia [NSVT]) (Figure 1).[4,7,12] The bileaflet phenotype is often associated with mitral annular disjunction (MAD) and focal fibrosis in the papillary muscles or inferolateral base of the left ventricle.[7,13–16] However, bileaflet involvement and focal fibrosis are not consistent findings.[7,17–20] Regardless of leaflet involvement or degree of MR, ComVE is detected in 80 to 100% of MVPs prior to SCA or SCD. ComVE is associated with myocardial fibrosis and is linked to higher all-cause mortality.[4,7,21]

We have previously demonstrated that machine learning-based methods can be applied to accurately analyze raw ECG data to discriminate patients with and without MVP.[22] Here we investigate whether ECGs can discriminate the “arrhythmic” from the “non-arrhythmic” MVP phenotype. Specifically, we hypothesize that an ECG-based deep-learning model can: 1) identify MVP at risk for ComVE, including those that will develop sustained VT or ventricular fibrillation; 2) identify novel ECG correlates of MVP-related myopathy and arrhythmic risk beyond traditional ECG criteria, and across mono or bileaflet MVP subtypes; 3) select those MVPs at risk for myocardial fibrosis on cardiac magnetic

resonance (CMR) imaging; and 4) predict all-cause mortality and cardiac death, including sudden arrhythmic death.

METHODS

STUDY POPULATION.

We identified 638 consecutive MVP cases between January 2012 and December 2020 who had at least one ECG and echocardiogram at the University of California-San Francisco (UCSF). Nine patients were excluded because of concomitant arrhythmogenic conditions: hypertrophic cardiomyopathy (n = 2), sarcoidosis (n = 2), Wolff-Parkinson-White (n = 1), ischemic (n = 2) and nonischemic (n = 2) cardiomyopathy with left ventricular (LV) ejection fraction ≤35% (Figure 2). An additional 60 patients were excluded because of lack of ECGs or presence of atrial fibrillation, PVCs, paced rhythms or right/left bundle branch on ECG (Figure 2). All remaining 569 MVP subjects had demographic, clinical, ECG, echocardiographic, and (if available) CMR study data already extracted and organized in an online research database as part of a UCSF MVP Registry (Central Illustration).

Mortality data and cause of death occurring during the study period were obtained through the review of medical records and the Social Security Death Index. In addition to all-cause mortality, we defined a composite outcome of cardiac death (nonarrhythmic and arrhythmic, the latter inclusive of sudden arrhythmic death, and cardiac arrest/implantable cardioverter defibrillator (ICD) placement due to ventricular fibrillation or sustained VT). UCSF Institutional Review Board approval was obtained for this study. Patient's informed consent was exempted by the Institutional Review Board because of the retrospective nature of the study.

CARDIAC IMAGING.

MVP was defined as systolic leaflet displacement of one or both leaflets >2 mm beyond the mitral annulus in a parasternal or apical 3-chamber long-axis echocardiographic view (Figure 1). When quantitative assessment of MR was not available, its severity was based on visual estimation of the regurgitant jet. The presence of MAD was assessed qualitatively as a separation between the left atrial wall at the level of MV junction and the LV free wall in the parasternal long axis or apical views.[13] LV end-diastolic/end-systolic volumes, ejection fraction, and mass were quantified and indexed to body surface area. Right ventricular dilatation was defined as a basal diameter ≥4.2 cm in the 4-chamber view. Right ventricular systolic dysfunction was assessed qualitatively.

CMR was conducted through the UCSF CMR Core using a 3.0-T Discovery MR750w scanner (GE Healthcare). Breath-hold cine imaging and late gadolinium enhancement (LGE) assessment were performed as previously described.[23]

IDENTIFICATION OF STUDY GROUPS.

We extracted raw ECG voltage data for 2 study groups: patients with and without ComVE. ComVE was defined as: >5% burden of PVCs (isolated and/or in couplets/triplets) or presence of NSVT on 48-hour Holter or 2-week event monitor[4,21] or inpatient telemetry

strips. Pleomorphic PVCs were defined as PVCs of at least 2 different morphologies. NSVT was defined as >3 PVCs with a rate >100 beats/min lasting <30 seconds.[12] Sustained VT was defined as tachycardia of ventricular origin with a rate >100 beats/min and lasting >30 seconds.[12]

Given the known association of MVP with myocardial fibrosis,[7,15,20] we performed a separate analysis classifying all MVP patients regardless of ComVE status into 2 groups: patients with LGE and patients without LGE.

For ComVE and LGE analyses, all ECGs following the first echocardiographic diagnosis of MVP were included. The data were divided into training (80%), development (10%), and test (10%) data sets, split randomly by patient. All ECGs from patients with or without ComVE or LGE were given a respective label and used for algorithm training and testing. We then examined the performance of the trained ComVE algorithm to discriminate ECGs from patients that experienced all-cause mortality and cardiac death, separately. For these analyses, we deployed the trained ComVE algorithm on all ECGs for a patient within 1 year of their ComVE adjudication date and evaluated the algorithm's performance to discriminate mortality outcomes in the test data set.

ALGORITHM DEVELOPMENT.

We trained separate deep convolutional neural networks (CNNs) to predict ComVE and LGE from a 12-lead ECG voltage matrix of size 2,500 × 12. The model had a one-dimensional ResNet architecture[24] and was initialized from a previously described pretrained model,[25] keeping all layers trainable. See the Supplemental Appendix for additional statistical details.

EXAMINING ECG SEGMENTS MOST STRONGLY CONTRIBUTING TO PREDICTIONS.

To examine the ECG segments contributing most strongly to ComVE or LGE prediction, we trained models using a parallel machine learning approach which has been previously reported and that was designed for increased interpretability.[22]

RESULTS

In the cohort of 569 patients with MVP (160 or 28% with ComVE), we analyzed a total of 6,916 ECGs. Of 160 ComVE MVPs, 75 (47%) had more severe arrhythmic presentations (either SCD, VF/SCA, ICD, sustained ventricular fibrillation, or need for radiofrequency catheter ablation, alone or in combination) (Table 1). Twenty individuals (12% of the ComVE group, 3% of the total MVP sample) experienced SCD or an aborted cardiac arrest. Of the 20 who underwent radiofrequency catheter ablation, all had pleomorphic ectopy except 4, who had right bundle branch block morphology PVCs (therefore excluding the possibility of right ventricular outflow tract ventricular tachycardia). Of the 85 (53%) without severe arrhythmic presentations, 74 had NSVT with or without ≥5% PVCs, and 11 had only ≥5% PVCs (all pleomorphic) without NSVT. The ComVE and non-ComVE groups had similar demographics, prevalence of cardiovascular risk factors, and coronary artery disease (Table 1). There was a greater proportion of patients with bileaflet MVP and MAD in the ComVE group.

Baseline ECG characteristics, including the presence of inverted or biphasic T waves, did not differ between those with and without ComVE. There was a higher proportion of patients with bileaflet involvement and LGE among those with ComVE. Compared to the non-ComVE group, LV volumes were larger despite similar LV systolic function and degree of MR.

PERFORMANCE OF A CNN TO PREDICT ComVE.

In the test data set for ComVE, the CNN had an AUC to detect ComVE of 0.80 (95% CI: 0.77–0.83) (Figure 3A, Table 2); sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) are shown in Figure 3B and Table 2). The CNN score was higher in the overall ComVE group (Figure 4A). Within the ComVE group, those with ComVE requiring radiofrequency catheter ablation or with sustained VT or ventricular fibrillation arrest/ICD or with SCD, ie, the "progressors," had a higher overall ComVE CNN score compared to ComVE who did not progress (Figure 4B). When plotted over time from the date of ComVE diagnosis, ComVE CNN scores of MVPs without ComVE were mostly below the ComVE threshold, while scores of ComVE MVPs were generally above (Figure 4C). Interestingly, those with ComVE with progression exhibited an increase in CNN score over time, while those without progression exhibited an overall flat to slight downtrend in CNN score. MVPs with ComVE (either with or without progression) had an early drop in ComVE CNN score within the first third of total follow-up time after ComVE diagnosis (Figure 4C). Among those with ComVE, initiation of nodal agents or antiarrhythmic medications was more common in the first third of total follow-up time (3 years) after ComVE diagnosis compared to before ComVE diagnosis (19% vs 6%, respectively, $P < 0.05$), which may explain the decrease in ComVE CNN score. MVP patients without ComVE did not exhibit the same early drop in ComVE CNN score, and the use of nodal agents or antiarrhythmics was less common in this group (Table 1). The model can be optimized to achieve sensitivity or specificity ≥90% (Supplemental Table 1).

PREDICTING ALL-CAUSE MORTALITY AND CARDIAC DEATH.

Median follow-up in our cohort was 4.2 years (IQR: 2.1–6.3 years), maximum follow-up was 8.8 years, and there were a total of 154 all-cause and 85 cardiac deaths. In the test data set, the CNN had an AUC to detect all-cause mortality of 0.82 (95% CI: 0.77–0.87); sensitivity, specificity, PPV, and NPV shown in Table 2, Figure 3A, and Supplemental Figure 2 using the same CNN threshold of 0.39 used for ComVE. For the composite outcome of cardiac death, the CNN had an AUC of 0.72 (95% CI: 0.62–0.80); sensitivity, specificity, PPV, and NPV shown in Table 2, Figure 3A, and Supplemental Figure 2.

PATHOPHYSIOLOGIC CORRELATES DRIVING ComVE PREDICTION.

We conducted multiple sensitivity analyses to better understand the pathophysiologic correlates of the CNN's ability to predict ComVE from ECG alone. We excluded patients with a history of MV repair or replacement, moderate-severe or greater MR, or bileaflet MVP, and examined the ability of the trained CNN to discriminate ComVE. The vast majority (214/250 or 86%) of bileaflet MVPs had MAD. Hence, by excluding bileaflet MVP we implicitly excluded MAD and assessed the contribution of MAD-related valvular-myocardial interactions to the CNN in our sensitivity analysis. The trained CNN

performance remained robust to these exclusions, as demonstrated by similar AUCs to that of the primary analysis (Table 3).

Using a parallel machine learning-based approach, we examined which ECG segments contributed most strongly to the prediction of ComVE. The top ECG segments were related to ventricular depolarization and repolarization, such as the early-mid ST-segment and QRS segments from leads V_2-V_4, and I, III, and aVR. Early-mid portions of PR intervals (from lead I and V_5) were also among the top 10 segments important for ComVE prediction (Figure 5, Supplemental Table 3). Interestingly, after excluding patients with moderate-severe or greater MR from the cohort, both P-wave/PR interval segments were no longer important predictors (Supplemental Table 4).

PERFORMANCE OF A CNN TO PREDICT LGE.

In a subset of the cohort with CMR data (n = 87, 1,369 ECGs), we trained a separate CNN algorithm to discriminate between patients with and without CMR-detected LGE (Figure 6A).[7,15] LGE in the papillary muscles or basal inferolateral wall was present in 21 (24%) of 87 patients with available CMR. Overall, this CNN had an AUC of 0.75 (95% CI: 0.68–0.82) to predict LGE from an ECG, with a sensitivity of 100% and specificity of 54.1% in the holdout test data set (Figure 6B). For the prediction of LGE, the ECG segments which contributed most strongly were the early-mid QRS from lead I and the early-mid P-wave/PR intervals from V_1, V_6, II, and aVR (Supplemental Table 5). After excluding MVP patients with moderate-severe MR in this cohort, P-wave/PR interval segments were no longer among the most important predictors of LGE. Instead, QRS-related ECG segments showed the greatest importance to predict LGE without moderate-severe MR (Supplemental Table 6).

DISCUSSION

ComVE is detected in most patients with MVP prior to SCA or SCD, is commonly associated with myocardial fibrosis, and is linked to higher all-cause mortality.[4,7,21] In our study, we demonstrate that deep learning can be applied to standard 12-lead ECGs to: 1) identify MVP at risk for ComVE, including those that will develop sustained VT or ventricular fibrillation; 2) identify novel ECG correlates of myocardial disease and arrhythmic risk across mono or bileaflet MVP subtypes; 3) select those MVPs with CMR-detected myocardial fibrosis; and 4) predict all-cause mortality and composite cardiac death. The ability to identify ComVE, CMR-detected LGE, and all-cause mortality/cardiac death with an inexpensive, rapid, and widely available point-of-care test such as a 12-lead ECG using deep learning could markedly improve arrhythmic risk stratification in the MVP population. A recent consensus statement on arrhythmic MVP[26] recommends a periodic Holter monitor in all MVP patients regardless of symptoms, although does not specify the frequency of such monitoring when the initial Holter is negative. MVPs identified to be at risk for ComVE or LGE by ECG-based deep learning may benefit from more frequent ambulatory ECG monitoring and closer clinical and imaging follow-up.

PREDICTION OF ComVE AND PROGRESSION TO SEVERE ARRHYTHMIC EVENTS AND DEATH FROM 12-LEAD ECGs USING DEEP LEARNING.

We have previously shown that deep-learning ECG analysis can discriminate individuals with MVP from those without MVP. However, discrimination for "general" MVP was not as strong as that for arrhythmic MVP (ie, with ComVE) (AUC 0.77 for MVP[22] vs AUC 0.81 for ComVE in the current study) (Figure 3). These findings suggest that ECG features specific to arrhythmic MVP may be absent among mostly benign, non-arrhythmic MVP cases within a large database.

Among the ComVE "progressors" (those treated with radiofrequency catheter ablation, or with an ICD following sustained VT/ventricular fibrillation, or those with SCD), the ComVE CNN score increased over time, in contrast to those MVP with ComVE without progression. These findings suggest that the CNN has increased ability to discriminate over time those with progressive arrhythmogenicity, including those at risk for death. These findings highlight the potential to use ECG-based machine learning in a future risk prediction model inclusive of clinical and imaging data to improve risk stratification and assess the need for primary prevention ICD.

MVPs with ComVE had an early, brief drop in the ComVE CNN score which corresponded to initiation of nodal agents or antiarrhythmics within a similar time period. Interestingly, the ComVE CNN score increased or stabilized after this drop (Figure 4C), suggesting recurrence of arrhythmogenicity and decreased response to medications over time. Indeed, MVP patients developed severe arrhythmic events despite the use of medications, as previously noted.[4,7,17,23]

MVPs without ComVE also had an increase in CNN score over time (Figure 4C), albeit consistently below the threshold of 0.39. A mild increase of CNN score may occur in MVP due to pro-fibrotic conditions such as hypertension or normal aging, although it may never manifest clinically as ComVE.

Ventricular arrhythmias in MVP have been traditionally linked to 2 echocardiographic phenotypes. In the "hemodynamic" MVP subtype with severe MR, acute or chronic ventricular volume load represents an important arrhythmic trigger,[6] and even more so if associated with myocardial fibrosis.[14,17,27,28] In the "bileaflet" phenotype, abnormal annular mechanics and localized traction on the myocardium lead to replacement fibrosis and increased arrhythmogenic risk even in the absence of MR.[4,7,13,29] To investigate the contributions of these 2 important MVP phenotypes on the CNNs ability to predict ComVE, we did sensitivity analyses excluding patients with a history of MV repair or replacement, moderate-severe or greater MR, or bileaflet MVP. After such exclusions, the AUC remained largely unchanged, suggesting that its overall ability to discriminate ComVE from the ECG occurs independently from the influence of these conditions. These findings highlight that arrhythmogenicity in MVP cannot be attributed only to 2 echocardiographic phenotypes (significant MR or bileaflet MVP). As observed in true clinical scenarios, there are "gray zones" or combined phenotypes that may be equally important in causing ventricular arrhythmia in MVP. Indeed, only 20% of SCD cases in MVP can be explained by severe MR and having bileaflet MVP and/or MAD does not always translate into SCD.[3,30]

While CNN sensitivity and specificity changed with exclusions of severe MR or bileaflet MVP compared to the primary analysis, changes were reciprocal (ie, a higher sensitivity and lower specificity or vice versa) and primarily due to the use of the same model threshold as the one used for the primary analysis; overall model performance was unchanged as exhibited by a similar AUC. Importantly, high negative predictive values could be achieved in both the primary analysis and the sensitivity analyses, which is essential for an ideal screening test.

ECG SEGMENTS CONTRIBUTING TO ECG PREDICTION OF ComVE.

In our study, we used a novel, purpose-built machine learning approach to demonstrate that the top ECG segments contributing to ComVE prediction were related to ventricular depolarization and repolarization. These findings suggest an underlying MVP-related myopathy that may not be caused only by severe MR (Supplemental Table 3). Indeed, when we excluded patients with moderate-severe MR, ECG segments with the highest importance remained the ones related to ventricular activity, whereas the 2 previously included P-wave/PR interval segments were no longer in the top 10 strongest ECG segment predictors. In our study, biphasic or inverted T waves in the inferior leads previously described in small, selected samples as a cardinal feature of bileaflet/arrhythmic MVP,[4] were present in only 17% of patients with ComVE, and in a similar proportion to those without ComVE. Hence, our data-driven machine learning approach provides novel ECG correlates of myocardial disease and arrhythmic risk beyond traditional ECG features of MVP/ComVE, in both mono and bileaflet MVP subtypes.

PREDICTION OF LGE ON CMR FROM 12-LEAD ECGs USING DEEP LEARNING.

In our cohort, LGE was present in the minority of MVPs with ComVE and available contrast CMR, as observed in prior studies.[16,17] LGE was more common in those MVPs with ComVE compared to without ComVE and was localized either in the papillary muscles or basal inferolateral wall. The sensitivity and NPV of our ECG-based deep-learning model for predicting LGE were excellent (100%), highlighting the potential usefulness of this screening tool in a clinical setting. We have shown both in living individuals and in postmortem samples that MVPs with ventricular arrhythmia or SCD do not consistently have replacement fibrosis.[17,20] In contrast, diffuse interstitial fibrosis is common, with and without significant MR. Diffuse fibrosis (either primary or MR-related) may cause ECG abnormalities even in the absence of LGE, thus reducing the specificity of our CNN.

ECG SEGMENTS CONTRIBUTING TO ECG PREDICTION OF LGE.

The ECG segments contributing most strongly to the LGE prediction were related to ventricular activity, possibly reflecting an underlying MVP-related myopathy. However, atrial activity also affected LGE prediction, likely reflecting the contribution of severe MR to development of LGE (Supplemental Table 4).[14] Interestingly, when we excluded patients with moderate-severe or greater MR, P-wave and PR-interval ECG segments ceased to be among the top 10 strongest ECG segment predictors of LGE, which instead were all QRS-related. Similar to our finding for ComVE, there may be ECG changes associated with a primary, MVP-related myopathy[17,31] that enable ECG-based prediction of LGE even in the absence of significant MR. Deep learning analysis of ECGs may provide a

more cost-effective way to select candidates for a CMR to detect fibrosis when traditional arrhythmic echocardiographic phenotypes such as bileaflet MVP or severe MR are absent.

STUDY LIMITATIONS.

The majority of our sample included non-Hispanic Whites, thus limiting the generalizability of our ECG-based machine-learning algorithm. Our definition of ComVE was based on the original literature highlighting high burden of PVCs with or without NSVT in MVP prior to SCA,[4] and on a recent consensus statement on arrhythmic MVP.[26] This definition has varied across other studies which have included only the most severe arrhythmic presentations in the ComVE definition.[7] We believe that studying ComVE as an intermediate stage of disease, before the development of sustained VT or ventricular fibrillation, may be equally, if not more important for the purpose of risk stratification. The majority of ComVE cases in our study had NSVT or pleomorphic PVCs, confirming an intermediate rather than a low-risk disease category.[4,21,32,33] For our examination of prediction of all-cause mortality and cardiac death, we acknowledge that we did not consider competing risks for these outcomes.

Because LGE was diagnosed with CMR, and CMR could not be obtained in our entire sample of 569 patients, the LGE cohort was small, thus reducing the generalizability of our LGE prediction model and immediate applicability to patient care. Moreover, we theorize that in some patients our LGE CNN algorithm may have detected ECG features related to interstitial/diffuse rather than focal fibrosis.[16,17,20,31] However, we could not confirm this observation, as T1 mapping was not available in all patients with a CMR.

While our ECG interpretability approach identified ECG features that drive predictions, these features may not necessarily be identical to those learned by the CNN. Our findings should be validated further in larger, multiethnic, multicenter studies with comprehensive Holter/event monitor and CMR assessment.

CONCLUSIONS

A CNN can detect MVP patients at risk for both ventricular arrhythmias and CMR-measured fibrosis from standard 12-lead ECGs and can identify novel ECG correlates of arrhythmic risk regardless of leaflet involvement or MR severity. The CNN also performs strongly to predict all-cause mortality and composite cardiac death. Deep learning-based analysis of ECGs may help identify within a large database of mostly benign MVP cases, those patients requiring closer follow-up and/or a CMR.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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ABBREVIATIONS AND ACRONYMS

CMR	cardiac magnetic resonance
CNN	convolutional neural network
ComVE	complex ventricular ectopy
ECG	electrocardiogram
LGE	late gadolinium enhancement
LV	left ventricular
MAD	mitral annular disjunction
MR	mitral regurgitation
MVP	mitral valve prolapse
NPV	negative predictive value
NSVT	nonsustained ventricular tachycardia
PPV	positive predictive value
PVC	premature ventricular contraction
SCA	sudden cardiac arrest
SCD	sudden cardiac death

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE:

Deep learning can identify MVP patients at risk for ventricular arrhythmias, death, and myocardial fibrosis from standard 12-lead ECGs, regardless of leaflet involvement or MR severity.

TRANSLATIONAL OUTLOOK:

Deep learning-based analysis of ECGs may help identify within a large database of mostly benign MVP cases, those at higher risk requiring more frequent ambulatory ECG monitoring and/or a CMR.

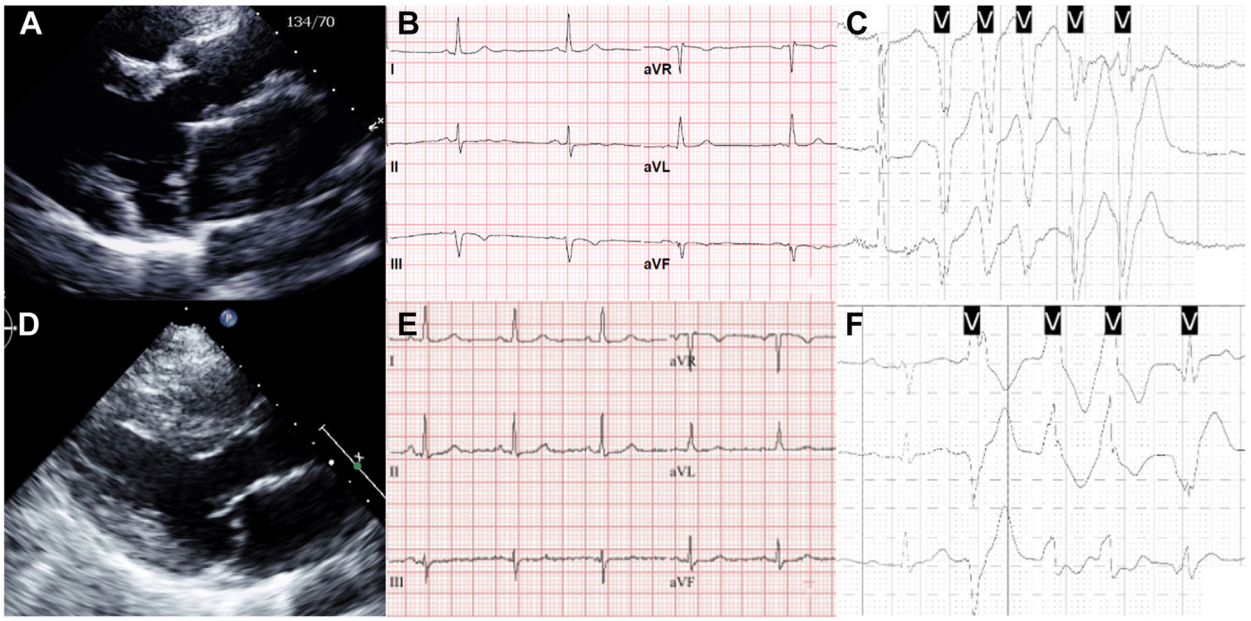


FIGURE 1. Echocardiographic and ECG Examples of MVP

Bileaflet MVP **(A)** and inverted T-wave inversions in the inferior ECG leads **(B)**. Posterior MVP **(D)** without repolarization abnormalities on ECG **(E)**. Both MVP cases had complex ventricular ectopy **(C and F)**. ECG = electrocardiogram; MVP = mitral valve prolapse.

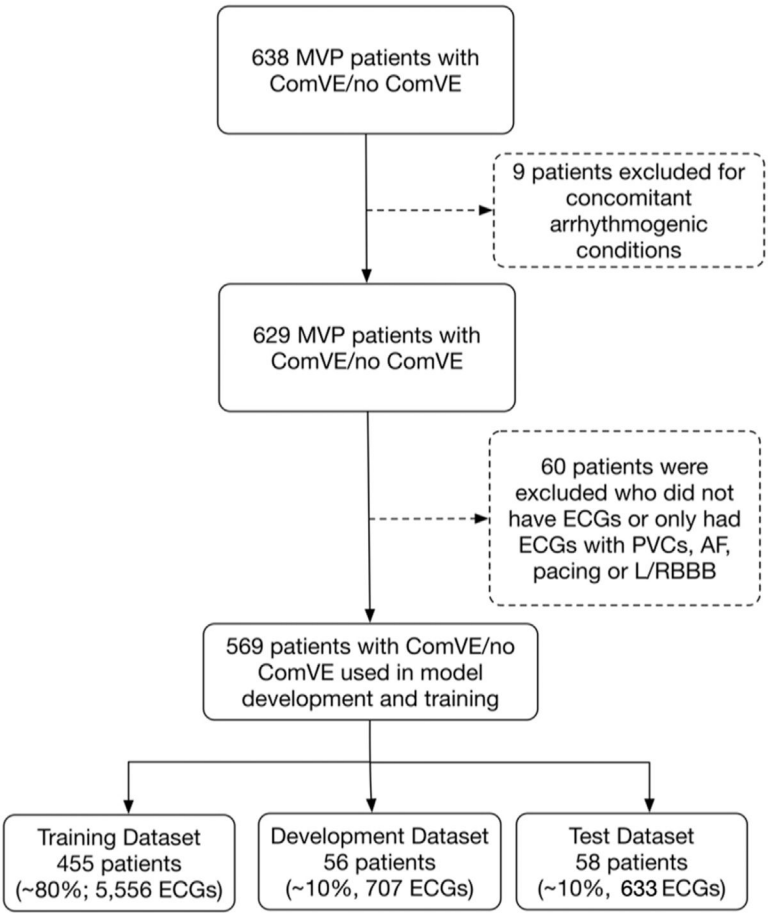


FIGURE 2. Diagram of Study Cohorts and Data Sets

MVP patients with and without complex ventricular ectopy (ComVE) were randomly split into training, development, and test data sets. AF = atrial fibrillation; ECG = electrocardiogram; L/RBBB = left/right bundle branch block; MVP = mitral valve prolapse; PVCs = premature ventricular contractions.

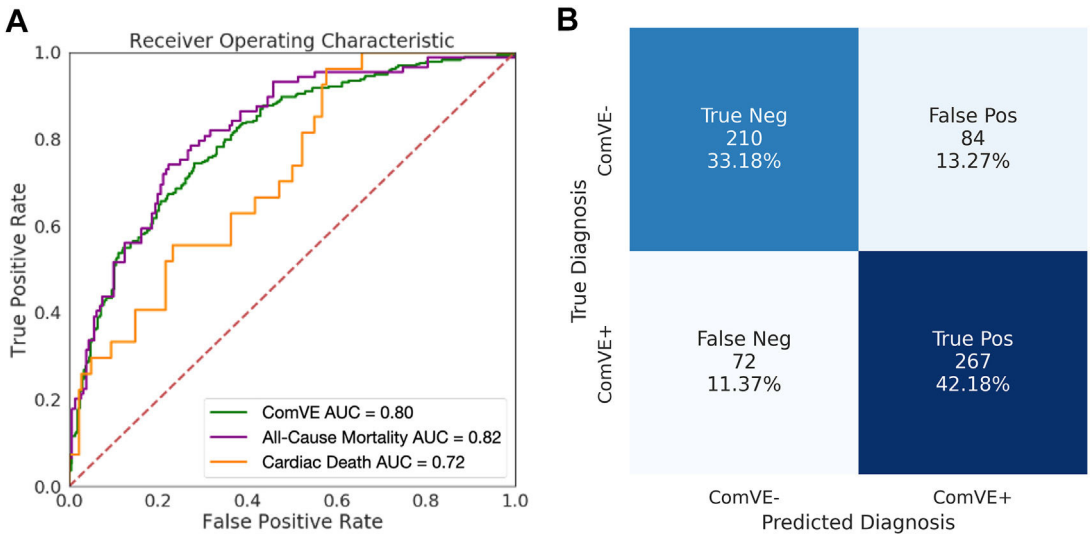


FIGURE 3. Performance of the Convolutional Neural Network

(A) Receiver operating characteristic curve for the CNN to predict ComVE **(green)**, all-cause mortality **(magenta)**, and composite cardiac death **(orange)**. **(B)** Confusion matrix demonstrating CNN performance to predict ComVE by ECG in the holdout test data set at the chosen score threshold of 0.39. AUC = area under the receiver operating characteristic curve; CNN = convolutional neural network; ComVE = complex ventricular ectopy.

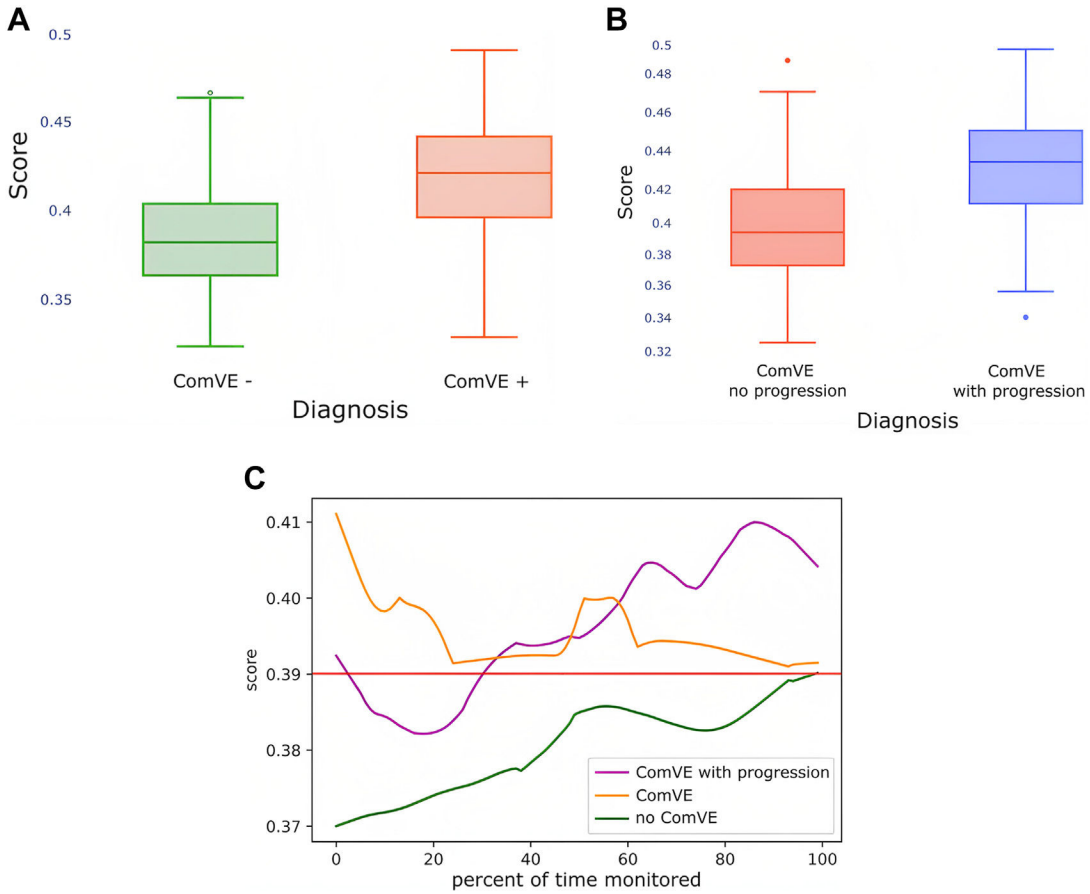


FIGURE 4. Distribution of ComVE CNN Scores by Strata in the Test Data Set

Box and whisker plots showing **(A)** distributions of ComVE CNN scores for mitral valve prolapse (MVP) patients with and without ComVE; **(B)** Distributions of ComVE CNN scores for ComVE patients with and without progression. **(C)** Averaged CNN scores (y-axis) by patient strata (ComVE, ComVE with progression, and no ComVE) plotted over time, as a percent of total follow-up time since ComVE diagnosis (x-axis). The red line indicates CNN score threshold used for binary classification of ComVE. CNN = convolutional neural network; ComVE = complex ventricular ectopy.

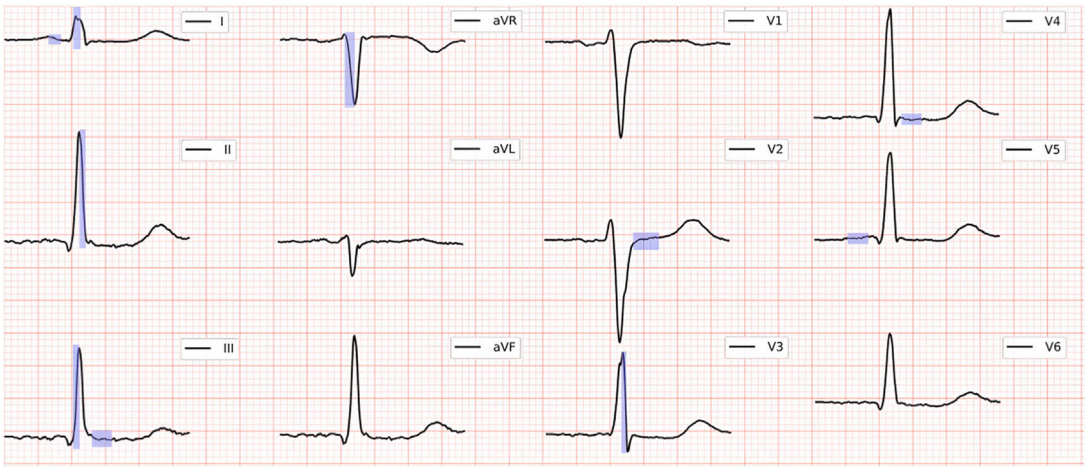


FIGURE 5. Importance of ECG Segments to the Prediction of ComVE

Highlighted ECG segments indicate the top 10 most important ECG segments for prediction of ComVE. ComVE = complex ventricular ectopy; ECG = electrocardiogram.

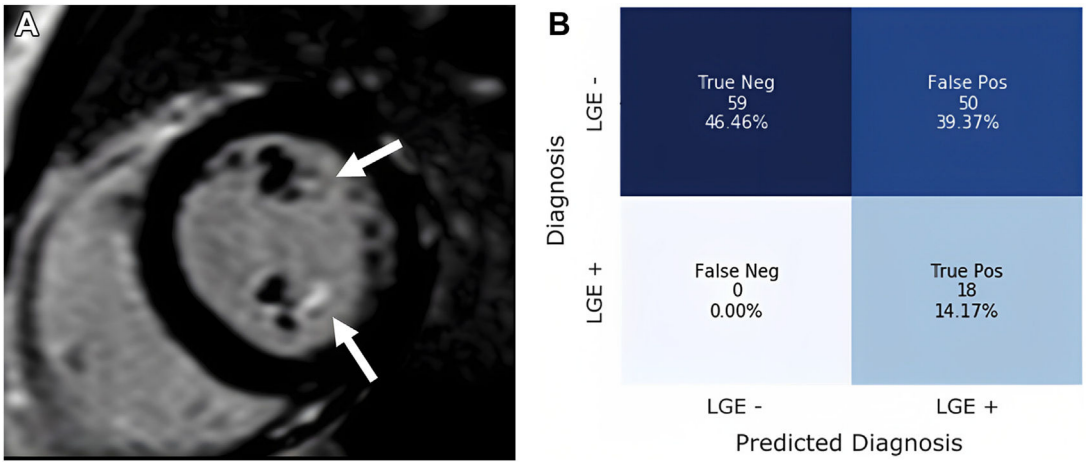
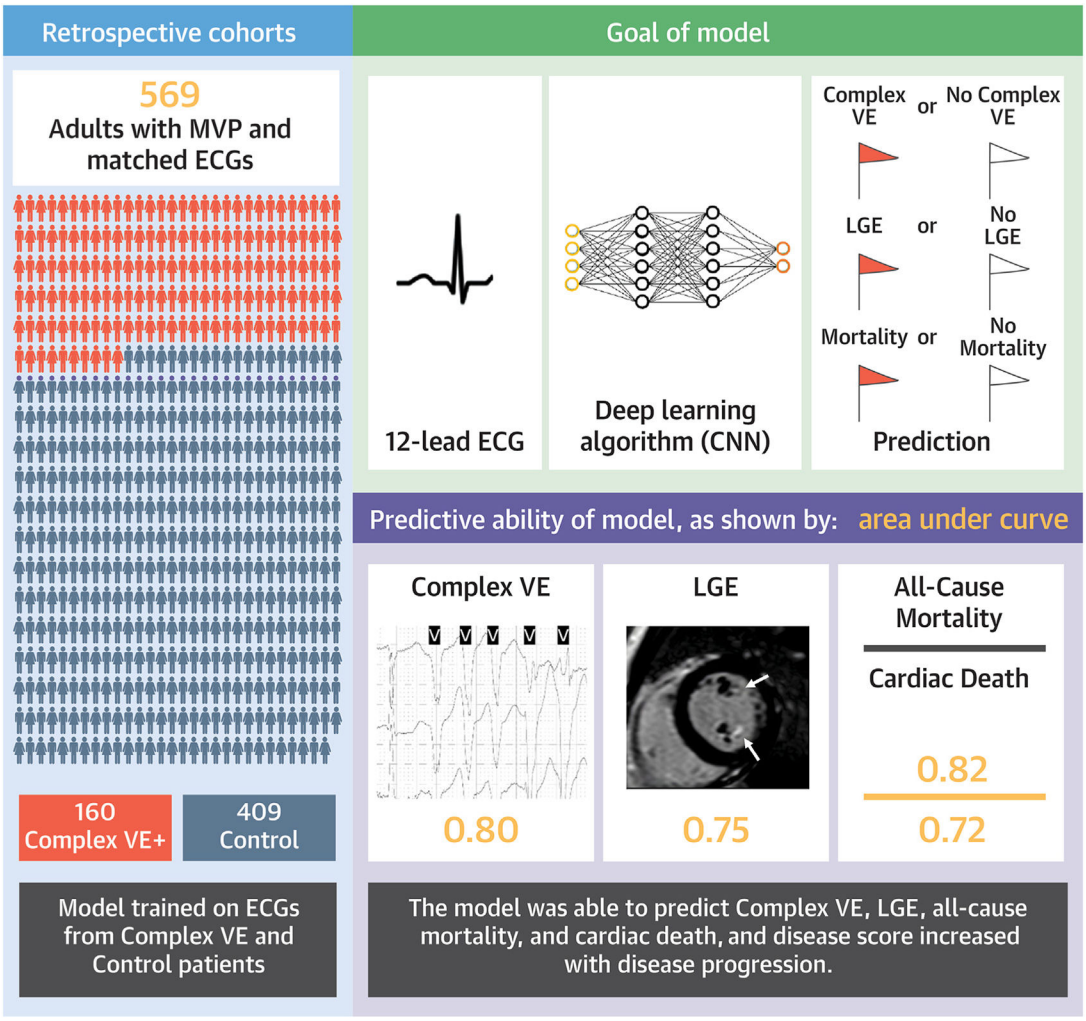


FIGURE 6. Performance of the ECG-Based CNN to Detect LGE by CMR in the Test Data Set
(A) CMR showing LGE in the papillary muscles **(arrows)**. **(B)** Confusion matrix demonstrating CNN performance to detect LGE with performance metrics shown in the chart **(lower)**. AUC = area under the receiver operating characteristic curve; CMR = cardiac magnetic resonance; CNN = convolutional neural network; ECG = electrocardiogram; LGE = late gadolinium enhancement; NPV = negative predictive value; PPV = positive predictive value.



CENTRAL ILLUSTRATION. Identifying Mitral Valve Prolapse at Risk for Ventricular Arrhythmias and Myocardial Fibrosis From 12-Lead Electrocardiograms Using Deep Learning
Tison GH, et al. JACC Adv. 2023;2(6):100446.

AUC = area under the receiver operating characteristic curve; CNN = convolutional neural network; ComVE = complex ventricular ectopy; dx = diagnosis; ECG = electrocardiogram; LGE = late gadolinium enhancement.

TABLE 1

Baseline Characteristics of MVP Patients in the Cohort According to the Presence or Absence of ComVE

	MVP ComVE (n = 160)	MVP Non-ComVE (n = 409)	*P* Value
Demographics			
Age, y	59 ± 16	59 ± 17	0.65
Male	92 (58)	204 (50)	0.10
Ethnicity			
Non-Hispanic Whites	143 (89)	348 (85)	0.16
Hispanic	3 (2)	18 (4)	0.15
Other	14 (9)	44 (11)	0.48
BMI, kg/m^2	24 ± 4	24 ± 4	0.85
Medical history			
Hypertension	59 (37)	167 (41)	0.40
Hyperlipidemia	42 (26)	109 (27)	0.94
Diabetes	12 (8)	35 (9)	0.70
Smoking history	58 (36)	144 (25)	0.80
Coronary artery disease	18 (11)	41 (10)	0.65
Atrial fibrillation or flutter	60 (38)	77 (19)	<0.0001
Sudden cardiac death	7(5)	0 (0)	N/A
Sudden cardiac arrest	13(9)	0 (0)	N/A
Inducible or spontaneous sustained VT	5	0 (0)	N/A
ICD	30 (19)	0 (0)	N/A
Radiofrequency catheter ablation	20 (13)	0 (0)	N/A
Family history of MVP	22 (14)	26 (6)	0.004
Family history of SCD or arrest	12 (8)	9 (2)	0.003
Medication use			
Anti-arrhythmic	30 (19)	36 (9)	0.001
Beta-blocker	82 (51)	130 (32)	<0.001
Calcium-channel blocker	16 (10)	49 (12)	0.51
Surgical history			
Mitral valve repair/replacement	8(5)	8 (2)	0.05

	MVP ComVE (n = 160)	MVP Non-ComVE (n = 409)	*P* Value
ECG			
Inverted or biphasic T waves inferior leads	27 (17)	57 (14)	0.18
QRS duration, msec	101 ± 23	98 ± 21	0.07
QTc, ms	444 ± 37	439 ± 35	0.18
Ambulatory ECG			
Frequent PVCs (>5%) (isolated or as bigeminy)	106 (66)	0 (0)	<0.0001
NSVT	94 (59)	0 (0)	<0.0001
Echocardiography			
Prolapsing leaflet			
Bileaflet	81 (51)	169 (41)	0.04
Flail	14 (8)	33 (8)	0.78
Mitral annular disjunction	74 (46)	140 (34)	0.007
Degree of mitral regurgitation			
Trace or mild	68 (43)	205 (50)	0.11
Mild-moderate or moderate	48 (30)	98 (24)	0.14
Moderate-severe or severe	19 (12)	48 (12)	0.96
Chamber measurements			
LV mass index (g/m^2)	93 ± 27	83 ± 26	0.0002
LVEDVI (mL/m^2)	59 ± 21	53 ± 18	0.002
LVESVI (mL/m^2)	26 ± 11	22 ± 10	0.0004
LVEF (%)	61 ± 9	62 ± 8	0.09
LA volume index (mL/m^2)	42 ± 22	40 ± 35	0.39
RV dilatation	16 (1)	61 (1)	0.11
RV systolic dysfunction	12(7)	30 (7)	0.97
CMR			
Contrast CMR performed	49 (30)	38 (9)	<0.0001
Positive LGE (among those with contrast)	16 (32)	5(13)	0.03
LV papillary muscles	5	1	
Basal or mid inferolateral LV	9	3	
Inferolateral LV and papillary muscles	2	1	

Values are n (%) or mean ± SD.

BMI = body mass index; CMR = cardiac magnetic resonance; ComVE = complex ventricular ectopy; ECG = electrocardiogram; ICD = implantable cardiac defibrillator; LA = left atrial; LGE = late gadolinium enhancement; LV = left ventricular; LVEDVI = left ventricular end-diastolic volume index; LVEF = left ventricular ejection fraction; LVESVI = left ventricular end-systolic volume index; MVP = mitral valve prolapse; NSVT = nonsustained ventricular tachycardia; PVC = premature ventricular contraction; RV = right ventricular; SCD = sudden cardiac death.

TABLE 2

Performance of the Convolutional Neural Network to Predict Complex Ventricular Ectopy, All-Cause Mortality, and Composite Cardiac Death

	AUC	Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value	F1 Score
ComVE	0.80 (0.77–0.83)	0.79 (0.74–0.83)	0.71 (0.66–0.76)	0.79 (0.75–0.83)	0.74 (0.70–0.80)	0.77 (0.74–0.81)
AU-cause mortality	0.82 (0.77–0.87)	0.93 (0.88–0.98)	0.49 (0.43–0.57)	0.50 (0.42–0.59)	0.93 (0.86–0.98)	0.65 (0.59–0.73)
Composite cardiac death	0.72 (0.62–0.80)	0.96 (0.88–1.00)	0.38 (0.32–0.44)	0.16 (0.10–0.21)	0.99 (0.96–1.00)	0.27 (0.19–0.35)

Values are respective point estimates (95% CI).

AUC = area under the receiver operating characteristic curve; ComVE = complex ventricular ectopy.

TABLE 3

Performance of the Convolutional Neural Network on Sensitivity Analysis Cohorts With Specified Exclusions

	AUC	Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value	F1 Score
Excluded MV repair replacement	0.81 (0.79–0.84)	0.64 (0.57–0.76)	0.87 (0.79–0.95)	0.67 (0.57–0.78)	0.85 (0.78–0.92)	0.65 (0.58–0.72)
Excluded Moderate-severe MR	0.80 (0.77–0.83)	0.83 (0.71–0.95)	0.55 (0.43–0.67)	0.59 (0.44–0.74)	0.81 (0.74–0.88)	0.70 (0.65–0.75)
Excluded Bileaflet MVP	0.81 (0.76–0.85)	0.87 (0.81–0.93)	0.60 (0.51–0.69)	0.76 (0.67–0.85)	0.75 (0.67–0.83)	0.81 (0.73–0.89)

Values are respective point estimates (95% CI).

AUC = area under the receiver operating characteristic curve; MR = mitral regurgitation; MV = mitral valve; MVP = mitral valve prolapse.