MAYO CLINIC

Electrocardiogram-Artificial Intelligence and Immune-Mediated Necrotizing Myopathy: Predicting Left Ventricular Dysfunction and Clinical Outcomes

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Abstract

Objective: To characterize the utility of an existing electrocardiogram (ECG)-artificial intelligence (AI) algorithm of left ventricular dysfunction (LVD) in immune-mediated necrotizing myopathy (IMNM).

Patients and Methods: A retrospective cohort observational study was conducted within our tertiary-care neuromuscular clinic for patients with IMNM meeting European Neuromuscular Centre diagnostic criteria (January 1, 2000, to December 31, 2020). A validated AI algorithm using 12-lead standard ECGs to detect LVD was applied. The output was presented as a percent probability of LVD. Electrocardiograms before and while on immunotherapy were reviewed. The LVD-predicted probability scores were compared with echocardiograms, immunotherapy treatment response, and mortality.

Results: The ECG-AI algorithm had acceptable accuracy in LVD prediction in 74% (68 of 89) of patients with IMNM with available echocardiograms (discrimination threshold, 0.74; 95% CI, 0.6-0.87). This translates into a sensitivity of 80.0% and specificity of 62.8% to detect LVD. Best cutoff probability prediction was 7 times more likely to have LVD (odds ratio, 6.75; 95% CI, 2.11-21.51; P=.001). Early detection occurred in 18% (16 of 89) of patients who initially had normal echocardiograms and were without cardiorespiratory symptoms, of which 6 subsequently advanced to LVD cardiorespiratory failure. The LVD probability scores improved for patients on immunotherapy (median slope, −3.96; $R = -0.12$; P=.002). Mortality risk was 7 times greater with abnormal LVD probability scores (hazard ratio, 7.33; 95% CI, 1.63-32.88; P=.009).

Conclusion: In IMNM, an AI-ECG algorithm assists detection of LVD, enhancing the decision to advance to echocardiogram testing, while also informing on mortality risk, which is important in the decision of immunotherapy escalation and monitoring.

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Cardiopulmonary involvement predicts mortality within idiopathic immune-mediated myopathies (IIM).[1,2] Left ventricular dysfunction (LVD) is the strongest predictor of mortality among these disorders (hazard ratio [HR], 4.6; 95% CI, 2.0-10.3; P>.0001).[3] Immune-mediated necrotizing myopathy (IMNM) is one form of IIM with the highest rates of LVD compared with dermatomyositis, polymyositis, and inclusion body myositis.[4-6] This disorder is often immune treatment-resistant, requiring escalating immunotherapy by steroids, intravenous immunoglobulins, and diverse steroid-sparing immunosuppressants.[7] The decision to escalate immunotherapy is complex but can be guided by the level of muscle breakdown creatine kinase (CK) enzyme, electromyographic findings (fibrillations and myotonia) and direct manual muscle testing.[8] Patients with cardiorespiratory involvement are likely to benefit from early and more aggressive immunotherapy given the risk of development of cardiac fibrosis, which is irreversible.[9,10]

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International guidelines have now recommended that all patients with IIM undergo electrocardiogram (ECG), with echocardiograms reserved for those with orthopnea, chest pain, or syncope.[9] Therefore, many patients with IMNM with asymptomatic LVD are likely go undiagnosed, especially when their extremity weakness limits cardiac challenge. Artificial intelligence (AI) convolutional neural network algorithms from standard ECGs are emerging within noninvasive testing workflows to detect diverse cardiac abnormalities.[11-15] One important aspect of these algorithms is their ability to detect cardiac abnormalities before symptoms appear. The detection of systolic LVD has been a special focus of the AI machine learning initiatives at our institution. Specifically, using 44,959 patients with 12-lead ECG and echocardiogram, an AI machine learning algorithm was generated.[16] This algorithm was used to test an independent set of 52,870 patients for LVD using standard 12-lead ECG alone compared with corresponding echocardiograms. The network model yielded values for detection of heart failure (ejection fractions $\leq$35%) with area under the curve (AUC, 0.93), sensitivity (86.3%), and specificity (85.7%). Based on this, the US Food and Drug Administration issued Emergency Use Authorization designation of the AI-ECG algorithm in COVID-19 on May 11, 2020. That experience demonstrated that the algorithm has the screening ability to detect cardiac dysfunction more broadly and specifically as related to a viral-induced inflammatory myocarditis.[17]

Herein, we assess the use of the existing AI-ECG algorithm to detect LVD in patients with IMNM and look at the implications of these results related to mortality and immunotherapy outcomes monitoring.

PATIENTS AND METHODS

Informed written consent was obtained. The study was approved by the Mayo Institutional Research Board and follows STROBE reporting guidelines.

Study Population

We identified patients with IMNM seen at Mayo Clinic within our neuromuscular section from January 1, 2000, to December 31, 2020. European Neuromuscular Centre criteria were used, and serological status noted for IgG-antibodies against 3-hydroxy-3-methylglutaryl-CoA reductase or signal-recognition-particle-54.[7] All patients had 12-lead ECG within 12 months from symptom onset. Left ventricular dysfunction was determined against a gold standard of echocardiogram results. Left ventricular dysfunction was determined by all measures available from echocardiogram reports to indicate reduced functional left ventricular capacity, including systolic dysfunction (ejection fractions $\leq$35%), mildly abnormal LV systolic dysfunction, diastolic LV dysfunction, abnormal LV relaxation, filling diastolic distensibility, or diastolic stiffness.

Assessment of LVD Probability Using ECG-AI algorithm

We used our previously generated and validated convolutional neural network (CNN) model to determine its ability to identify LVD in our IMNM population.[16,18,19] The specifics of the model have been described in detail elsewhere.[16,18] The model used CNN with Keras with a Tensorflow (Google) with a dataset model generated and tested with individual echocardiograms paired with 12-lead ECGs that were obtained within a 2-week period.[16] That model was tuned using a validation set as outlined in the Introduction.

In the current study, this previously described algorithm was used without additional training or optimization. The patients used in the original training and validation sets were excluded. The only input in the model was a 12-lead standard ECG that was closest to the IMNM diagnosis, whereas the output represented LVD probability as a number between 0 and 1. This probability was reported as percent (%) probability of LVD. American College of Cardiology and American Heart Association 10-year atherosclerotic cardiovascular disease (ASCVD) risk algorithm in detecting high cardiovascular risk score was calculated for all patients in the initial data set and the data from our IMNM cohort. Other demographic characteristics related to cardiovascular risk factors and IMNM serology were compared against the model for significant associated outcomes.

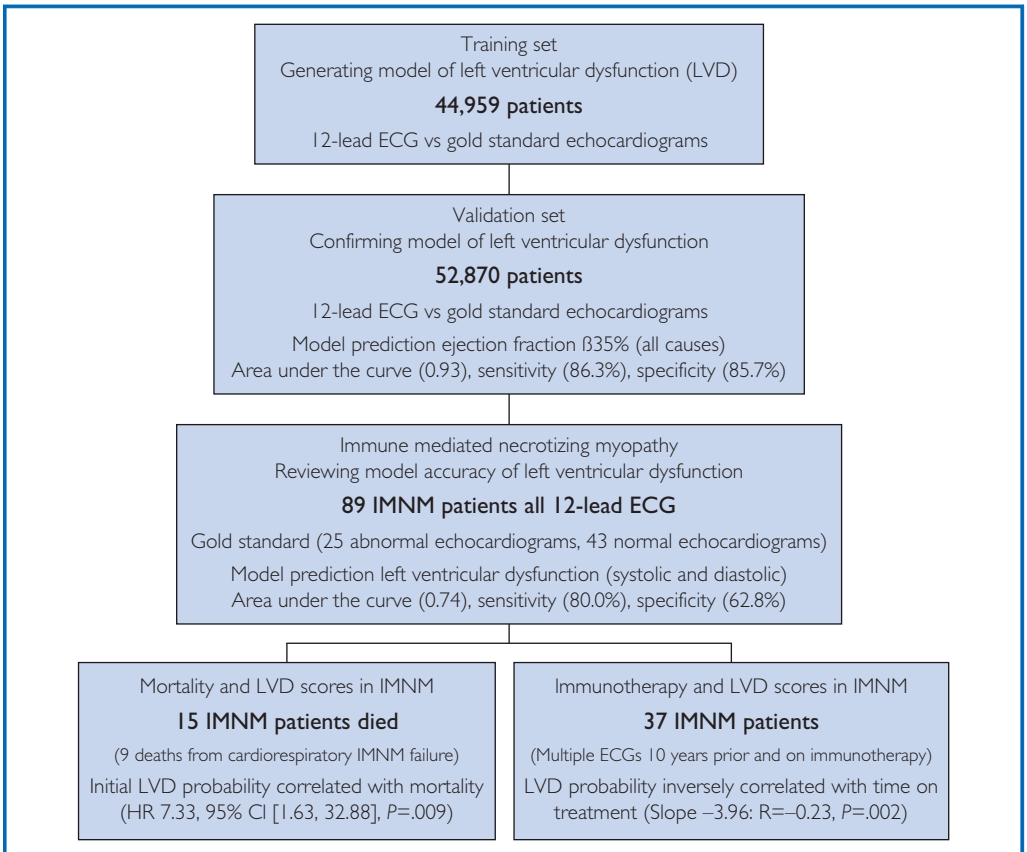

FIGURE 1. Model generation and current immune-mediated necrotizing myopathy (IMMN) study. Shown is the workflow utilized to generate the current model and the results of the model versus normal and abnormal echocardiogram in IMNM as well as mortality and treatment results versus LVD percentile score. ECG, electrocardiogram; LVD, left ventricular dysfunction.

Statistical Analysis

We used univariable and multivariable logistic regression models to evaluate the associations between AI-derived LVD probability and multiple demographic parameters related to heart disease. Our binary outcome of interest was cardiac LVD (yes or no) using the predictive model. Unpaired *t*-test was used to compare normally distributed continuous variables, a Mann-Whitney *U* test for nonnormally distributed variables, and a χ^2 test (or Fisher exact test) for categorical variables. Receiver operating characteristics analysis was performed to assess the optimal LVD probability cutoff within patients with IMNM. Kaplan-Meier methods were used to assess survival rates and LVD probability scores within 12 months of IMNM diagnosis. All statistical analyses were performed using JMP Pro software (SAS Institute, Inc).

RESULTS

Workflow and Model Results

A summary of the training sets used to generate the model and model performance results of this study of IMNM are summarized in Figure 1.

Baseline Demographic characteristics

We identified 89 patients with IMNM who had ECGs available within 12 months of symptom onset. None of the ECGs used were included in the training or validation set of the algorithm. The mean age was 62±13 years, and 46 (52%) were men. In

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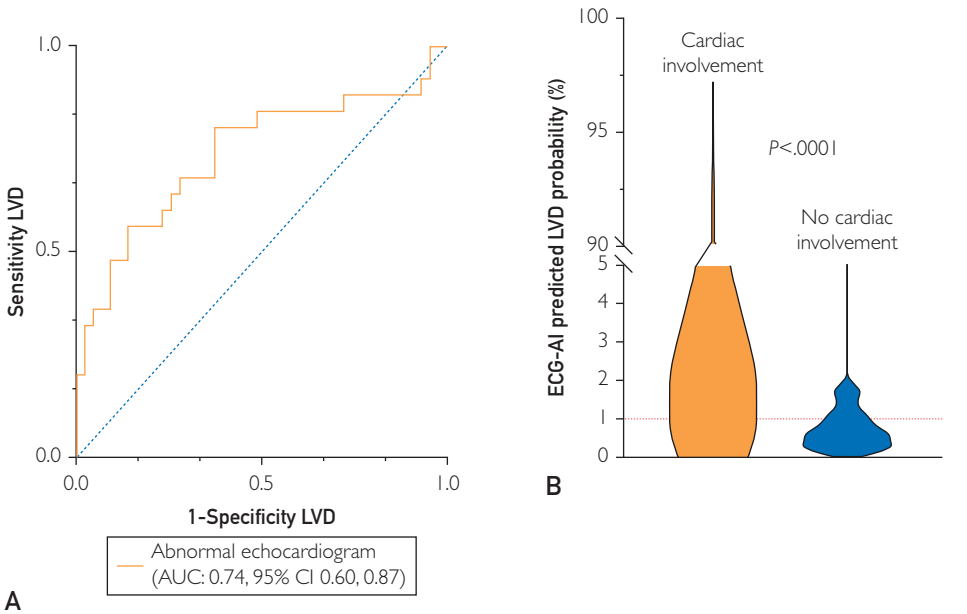

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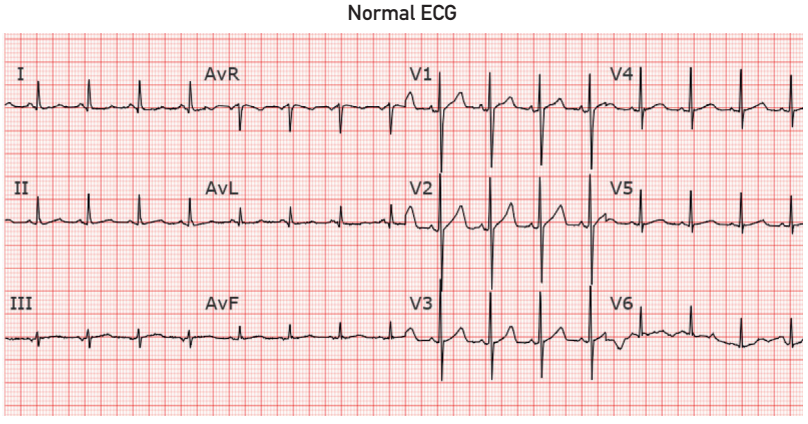

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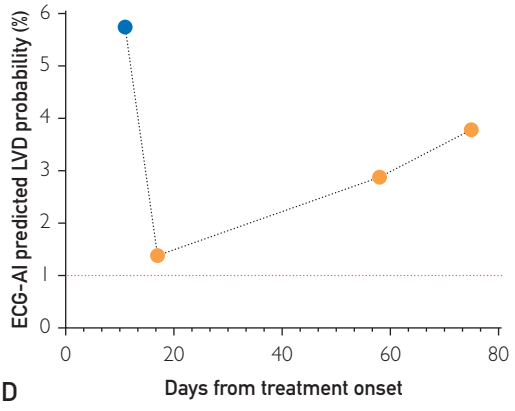

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FIGURE 2. Model performance for left ventricular dysfunction. (A) Area under the curve (AUC) shows high sensitivity and specificity to identify left ventricular dysfunction (LVD) using the ECG-AI model. (B) Patients with documented echocardiogram abnormalities had higher LVD probability compared with those without (2.94 interquartile range [1.02-26.69] vs. 0.72 interquartile range [0.34-1.57], *P*=.001).

total, 39 (44%) of patients had hypertension, 27 (30%) had diabetes, and the median ASCVD score was 12 (interquartile range [IQR], 4-24). Out of 75 patients with available serology data, 42 (56%) were anti-3-hydroxy-3-methylglutaryl-CoA reductase, 8 (11%) were anti-SRP, and 25 (33%) were seronegative (Table 1).

LV Abnormalities by Echocardiogram

A total of 68 patients had available echocardiograms within 1 year of symptom onset. The median time from symptom onset to echocardiogram was 4 months (IQR, 2.0-8.5). Cardiac abnormalities were common, with 37% (n=25/68) having abnormal echocardiograms. The most common abnormality on echocardiogram was isolated grade-1 LVD (diastolic) in 9 (13%), grade-1 LVD (systolic) in 5 (7%), left ventricular hypokinesis in 6 (9%), followed by regional ventricular wall motion abnormalities in 4 (7%). Only 1 patient had grade-2 diastolic dysfunction. Diaphragmatic respiratory involvement was present in 12% (n=10), studied by needle electromyographic and diaphragmatic ultrasound.[20] Of these 8 patients, 50% had restrictive pulmonary disease, all with abnormal LV function, as shown by echocardiogram.

Model Prediction of LVD in IMNM

The model performed well for the identification of LVD at a cutoff value of 1% (AUC, 0.74; 95% CI, 0.60-0.87), with a sensitivity of 80.0% and specificity of 62.8% in correlation with echocardiogram findings (Figure 2). Only abnormal echocardiogram, high-density-lipoprotein cholesterol, and respiratory involvement were found to be significantly associated with high LVD probability scores (Table 1). Seronegative patients were more likely to have documented LVD compared with seropositive patients (17 [68%] vs. 19 [38%], P=.01). Patients with confirmed LVD had higher probability scores (IQR, 2.94 [1.02-26.69] vs. IQR, 0.72 [0.34-1.57]; P=.001) and were 7 times more likely to have LVD probability >1% compared with those without (odds ratio, 6.75; 95%CI [2.11, 21.51]; P=.001) (Figure 2). This association remained significant after adjustment for positive serological status and ASCVD score in logistic regression models (OR, 4.26; 95% CI [1.97, 15.18]; P=.025). The model predicted cardiac dysfunction in 18% (n=16) of patients who had normal ECGs, as determined by visual inspection and an earlier basic screening algorithm, with 6 subsequently advancing to LVD cardiorespiratory failure and 3 dying within 5 years from complications of LVD. The algorithm did not label 6 patients with LVD echocardiographic abnormalities, only 1 who developed symptomatic cardiorespiratory dysfunction with eventual grade 2 diastolic dysfunction, and none with LVD mortality.

Model Comparison Before and While on Immunotherapy

A total of 37 patients had multiple ECGs available both before and after receiving immunotherapy. The analysis of all ECGs 10 years before and while on treatment for LVD showed that the probability score was inversely correlated with time on treatment (slope, −3.96; R = −0.23; P=.002) (Figure 3).

Higher Mortality Risk was Detected by the Model

Median (IQR) follow-up duration after baseline ECG was 31 (15−70) months. A total of 15 (17%) patients with IMNM died during follow-up. Median age of death in patients with IMNM was 72 (48−87) years. The causes of death were related to immune-mediated myopathy cardiorespiratory LVD failure in 8, infection in 2, malignancy in 2, and

(C, D) Example 64-year-old woman with immune-mediated necrotizing myopathy having normal routine ECG and no ventricular abnormalities on initial echocardiogram despite marked abnormal AI prediction (blue bubble) with marked proximal weakness and creatinine kinase 14,667 U/L not responding to high dose methylprednisolone (days 1-10) but with introduction of intravenous Immunoglobulin had marked improved AI LVD prediction score by day 18 and improved creatinine kinase 4,764 U/L and overall strength. She became immune treatment-resistant, with increasing LVD probability scores correlating with clinical declines. ECG, electrocardiogram; AI, Artificial intelligence.

Mayo Clin Proc Inn Qual Out ■ October 2022;6(5):450-457 ■ https://doi.org/10.1016/j.mayocpiqo.2022.08.003
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TABLE 1. Characteristics of Patients with Immune-Mediated Necrotizing Myopathy Determined to be High-Risk Using the Model

		ECG- derived LVD algorithm output		
	Total (n=89)	**Model predicts no cardiac involvement (n=42)**	**Model predicts cardiac involvement (n=47)**	*P* value
Abnormal echocardiogram (n=68)	25/89 (37%)	5/42 (16%)	20/47 (56%)	***.001***
Age (y), mean ± SD	62±13	62±12	62±13	.91
Male, n (%)	46 (52%)	21 (50%)	25 (53%)	.76
Hypertension, n (%)	39 (44%)	15 (36%)	24 (51%)	.15
Diabetes mellitus, n (%)	27 (30%)	12 (29%)	15 (32%)	.73
HDL-C (mg/dL)	49±11	52±12	46±10	**.01**
ASCVD score, per unit	12.0 (4.0, 23.6)	9.3 (4.5,22.1)	13.0 (3.0, 25.8)	.78
Statins, n (%)	62 (69%)	31 (74%)	31 (66%)	.42
Serology, n (%) 75				
Seronegative	25 (33%)	9 (24%)	16 (43%)	.07
Anti-HMGCR Ab^+	42 (56%)	25 (66%)	17 (46%)	.08
Anti-SRP Ab^+	8 (11%)	4(11%)	4 (11%)	>.99
Respiratory muscle involvement, n (%)	10 (12%)	1 (2%)	9 (20%)	**.02**
Restrictive pulmonary disease, n (%)	5 (6%)	1 (2%)	4 (9%)	.36

ASCVD, atherosclerotic cardiovascular disease; Anti-HMGCR Ab^+, anti-3-hydroxy-3-methylglutaryl coenzyme A reductase autoantibody positive; anti-SRP Ab^+, anti-signal-recognition-particle antibody positive; ECG, electrocardiogram; HDL-C, high-density-lipoprotein cholesterol; LVD, left ventricular dysfunction.

undetermined in 3. Using Cox proportional modeling, there was a high risk of mortality among those with high LVD probability scores (HR, 7.33; 95% CI [1.63, 32.88]; *P*=.009), which remained significant after adjustment for potential confounders of age (HR, 6.85; 95% CI [1.52, 30.92]; *P*=.01) and ASCVD score (HR, 5.94; 95% CI [1.29, 27.39]; *P*=.02). Likewise, in a Kaplan-Meier analysis, >1% of patients were more likely to experience mortality during follow-up (log-rank *P*=.002), Figure 3.

DISCUSSION

Our results demonstrate that an existing AI-ECG algorithm assists in the ascertainment of LVD in IMNM. The algorithm frequently predicted presymptomatic LVD cardiac disease, with 18% initially having normal ECGs without cardiorespiratory symptoms and 6 subsequently advancing to LVD cardiorespiratory failure. The algorithm assisted in the detection of both systolic and diastolic dysfunction, when LVD probability scores more than 1% were used as the best cutoff value from AUC prediction vs echocardiogram abnormalities corrected for positive serological status and ASCVD score. Although the overall AUC of 0.74 is less than that described when the LVD percent abnormality was compared with ejection fractions ≥35% (AUC, 0.94),[16] this experience supports the utility of the model to predict LVD in both systolic and diastolic dysfunction. This finding would be consistent with the algorithm's ability to detect wider LVD, as shown with an earlier experience in COVID-19 patients[17] and emerging literature suggesting diastolic dysfunction that is common in patients with acute myocarditis.[21,22] Only abnormal echocardiogram, high-density-lipoprotein cholesterol, and respiratory involvement were found to be significantly associated with high LVD probability scores. Cutoff probabilities of >1% were 7 times more likely to have LVD (Figure 2). Among the infrequent persons with abnormal echocardiograms and normal LVD probability scores, only 1 developed symptomatic cardiorespiratory involvement. The data support the utility of this AI-ECG algorithm to assist

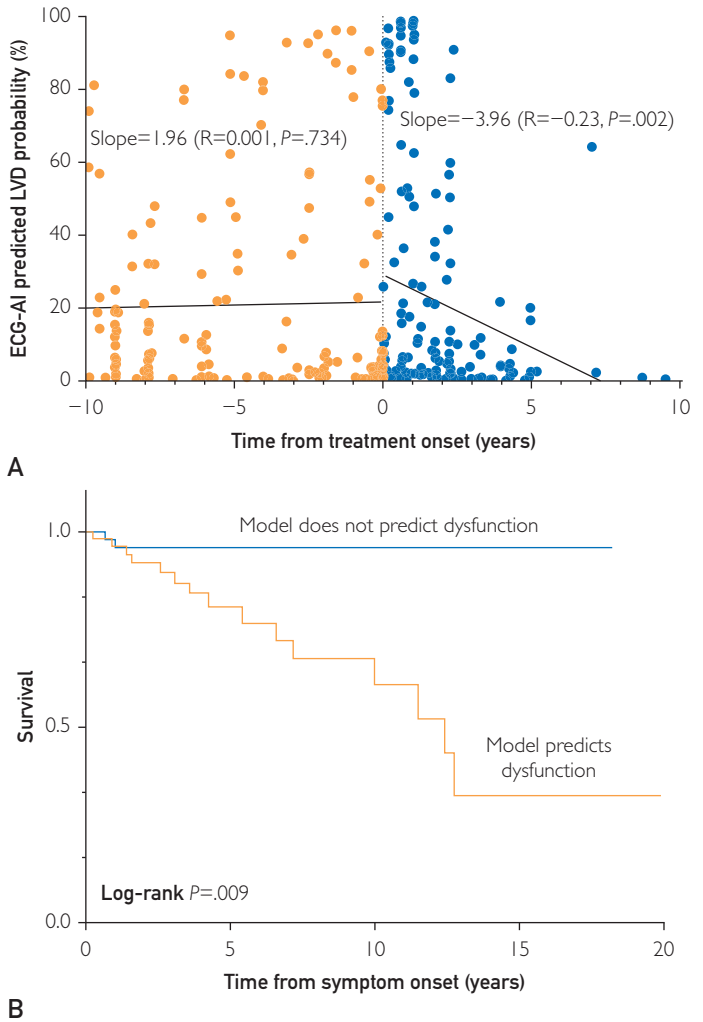

FIGURE 3. Outcomes of left ventricular dysfunction with treatment and mortality. (A) Scatter plot of all immune-mediated necrotizing myopathy patients who had ECG performed before and after treatment, many with multiple ECGs. Continuous lines represent the mean of all probabilities in each group. Shown is the overall improvement in left ventricular dysfunction (LVD) while on immunotherapy (blue) compared with before (red) immunotherapy. (B) Kaplan-Meier survival curves for all-cause mortality comparing patients with high LVD probability (>1%) to low LVD probability. Patients with high LVD probability had higher rates of mortality. ECG, electrocardiogram; AI, Artificial intelligence.

screening methods in immune-mediated myopathies at risk for LVD. Our findings will complement the current recommendation that all patients with IIM should undergo ECG.[9] The AI-ECG algorithm will enhance decisions of who should obtain traditional echocardiograms and possibly more expensive MRI heart and invasive cardiac biopsy testing when uncertainty remains.

Determining who needs more aggressive immunotherapy in IMNM is challenging.[7] This AI-ECG algorithm may provide a potential new tool to assist monitoring beyond CK values, direct manual strength, and electromyographic testing.[8] Specifically, we note a significant improvement of AI-ECG-predicted LVD probability scores in patients while on immunotherapy. However, our study has limitations to address this point given the lack of uniform follow-up with echocardiograms in all patients. This will be important as current standard approaches in immune treatment monitoring do not assess cardiac function and serial echocardiograms seem costly and impractical in most patients. More aggressive immunotherapy may be warranted in patients with cardiac involvement as heart function has been seen to improve in patients while on immunotherapy.[4] It is reasonable to surmise that early recognition of cardiac involvement with proper immunotherapy escalation could reduce the risk of interstitial myocardial fibrosis, as inflammation is treatable, whereas fibrosis is irreversible.[9]

This study also substantiates the value of an AI-ECG algorithm by aiding prognostication of mortality. Higher LVD probability scores strongly correlated with mortality, and a 7-fold greater mortality risk occurred with abnormal probability scores. This is important as we note both here and in the earlier literature that mortality in IMNM patients most commonly relates to advancing cardiomyopathy versus other causes of death.[1-3] Knowing which patients at first visit are inclined to have more serious mortality risk is essential in proper counsel about the seriousness of their illness and need for treatment escalation with medications that themselves have risk. Previously, it has been shown that nearly 50% of patients with cardiac involvement had no cardiac history before IMNM diagnosis,[4] suggesting the importance of reviewing earlier ECGs for LVD AI predicted abnormalities in considering common coexisting cardiac dysfunction.

CONCLUSION

Expanding the analysis of ECG by machine learning ECG-AI algorithm should assist in

Mayo Clin Proc Inn Qual Out ■ October 2022;6(5):450-457 ■ https://doi.org/10.1016/j.mayocpiqo.2022.08.003
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noninvasive inexpensive workflow assessment of ventricular dysfunction assessment in IMNM and advancing appropriate patients to echocardiogram and other more invasive cardiac testing. Although our AUC of 0.74 is considered an acceptable cutoff value in a screening laboratory test, increasing the evaluation of more IMNM patients will be important in understanding the model's performance in this rare disorder. Prospective immunotherapy trials should incorporate this algorithm in the assessment of treatment outcomes measured against standard approaches of CK elevation, direct manual muscle testing, and uniform echocardiogram testing in all patients.

Abbreviations and Acronyms: **AI,** artificial intelligence; **ASCVD,** atherosclerotic cardiovascular disease; **AUC,** area under the curve; **CK,** creatine kinase; **CNN,** convolutional neural network; **ECG,** electrocardiogram; **IIM,** idiopathic immune-mediated myopathy; **IMNM,** immune-mediated necrotizing myopathy; **LVD,** left ventricular dysfunction; **MRI,** magnetic resonance imaging; **OR,** odds ratio

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Grant Support: This work was funded by Mayo Clinic Foundation and the Department of Neurology and Cardiovascular Medicine and Mayo Cardio-vascular Research Center with no industry support.

Potential Competing Interests: Drs Klein, Ozcan, Cohen-Shelly, Lerman, Medina-Inojosa, Milone have no industry sponsored monies and are without potential conflict of interest. Drs. Zachi, Lopez-Jimenez, Friedman, have licensure interest in the ECG-AI algorithm utilized, specifically the utilized algorithm is license to Mayo Clinic by Anumana, Eko health, and AliveCor, and Mayo Clinic.

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