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Laminopathies: natural history and risk prediction of heart failure

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Lamin A and C are proteins encoded by the *LMNA* gene that comprise the nuclear lamina, a structure that lies adjacent to the cell's nuclear membrane. The nuclear lamina provides structural support to the nucleus, and its proteins participate in various cellular functions, including chromatin organization, gene regulation, DNA damage repair, and cell motility, among many others that vary depending on the tissue type. Mutations in the *LMNA* gene have been shown to increase nuclear susceptibility to mechanical stress and induce defective mechanotransduction, resulting in increased cell death[1]. Mutations are inherited in an autosomal dominant fashion, with heterozygotes affected despite variable expression. Multiple mutations in the *LMNA* gene, a phenomenon known as allelic heterogeneity, may cause identical or markedly different phenotypes, making phenotypic expression difficult to predict in patients with confirmed laminopathies[2]. It is well established, however, that *LMNA* mutations can cause laminopathies that increase a patient's risk of developing ventricular arrhythmias and dilated cardiomyopathy (DCM), with phenotypic penetrance increasing over time[3]. Referred to as *LMNA* cardiomyopathy, electrical disturbances typically precede the structural changes of DCM, with myocardial fibrosis often developing before left ventricular dysfunction[4]. Although rare, the disease can progress rapidly to end-stage heart failure, with limited therapeutic options available, therefore leaving a need for better risk prediction models.

Current risk prediction models estimate the probability of clinical healthcare outcomes in patients with certain risk factors, such as those with genetic predispositions. A 2019 risk prediction tool estimates the risk of developing life-threatening ventricular tachyarrhythmia (VTA) in patients with *LMNA* cardiomyopathy[5]. This tool shows that there is increased risk of VTA with five variables including male sex, non-missense *LMNA* mutations, first-degree or higher atrioventricular block, nonsustained ventricular tachycardia and left ventricular ejection fraction (LVEF) as a continuous variable. This risk prediction model was externally validated by Rootwelt-Norberg *et al.* showing that independent risk factors were low ejection fraction and atrioventricular block but that male sex, non-missense

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LMNA mutations and nonsustained ventricular tachycardia were not[6]. It has been observed that there are higher rates of malignant tachyarrhythmias and end-stage heart failure in males with *LMNA* cardiomyopathy compared to females. This is potentially due to a difference in sex hormones and environmental modulators, though further investigation regarding this difference is needed[7].

As suggested above, the clinical manifestations of laminopathies can be influenced by the location of the mutation within the gene. Studies have shown that truncating variants in the *LMNA* gene are associated with higher rates of VTA compared with missense mutations in the tail and distal domains of the gene[8]. The biological reason for this is not fully understood. DCM and left ventricular dysfunction are hallmark characteristics of *LMNA* cardiomyopathy and may be associated with mutations in different regions of the gene. Interestingly, there has been no significant difference in the incidence of heart failure when comparing missense and truncating variants. However, missense mutations upstream of the nuclear localization signal have been associated with a higher incidence of cardiomyopathy and ventricular arrhythmias[9].

To date, there has been no risk prediction model that looks at the risk of heart failure major adverse cardiac events (HF-MACE) in patients with laminopathies. Most risk prediction models in this population have focused on the risk of developing sudden cardiac death (SCD), likely because electrical dysrhythmias tend to manifest earlier than HF-MACE outcomes in patients with laminopathies. SCD risk prediction also allows for immediate therapeutic intervention to prevent poor outcomes, such as the placement of an implantable cardioverter-defibrillator (ICD), whereas heart failure is progressive and not as easily treated. Additionally, the substantial phenotypic variability and incomplete penetrance among patients with *LMNA* mutations make it difficult to predict HF-MACE outcomes, as patients with the same genetic mutation may experience different clinical outcomes. Charron *et al.* set out to determine the probability of HF-MACE events occurring in patients with laminopathies by developing a risk prediction model in their recent paper "Laminopathies: natural history and risk prediction of heart failure"[10].

This study developed a risk prediction model using a derivation and validation cohort. The derivation cohort included 470 patients from the French Nationwide Registry with pathogenic/likely pathogenic *LMNA* variants dating back to 2000 when the genetic testing became regularly available. The derivation cohort included patients with an LVEF ≥ 30%. Patients with an LVEF < 30% were excluded from both the derivation and validation cohorts of the HF-MACE risk prediction model as these patients had a non-linear and much higher risk of developing HF-MACE, violating the proportional-hazards assumption. The validation cohort included 245 patients referred to multiple tertiary heart failure centers worldwide with adult-onset laminopathies and LVEF ≥ 30%. The primary endpoint was HF-MACE, defined as first hospitalization due to heart failure (HF), death due to HF, mechanical circulatory support, or heart transplantation. Results showed that over a median of 7.1 years, HF-MACE occurred in 65 patients, with a cumulative incidence of 9.7% at 5 years and 12.3% at 10 years. In the multivariate analysis, four variables were significantly associated with the occurrence of HF-MACE: male sex, LVEF < 50%, missense variants in head and rod domains, and complete left bundle branch block [Figure 1]. The Harrell Concordance index (C-index) of this model was 0.750, indicating a good discriminatory performance. In an auxiliary analysis of patients with LVEF < 30%, HF-MACE occurred in 50% at 1 year and 72.2% at 5 years, further highlighting the need for immediate intervention in this population.

There has been no risk prediction model to date that determines the risk of major HF events in patients with adult-onset laminopathies. This can make it difficult to optimize heart failure treatment in high-risk patients, and therefore these patients have worse outcomes. Current risk models in laminopathies that can predict increased risk of ventricular arrhythmias have led to better treatment and use of preventive therapies, including the use of ICDs[3]. This model may facilitate earlier identification of patients at increased risk of HF

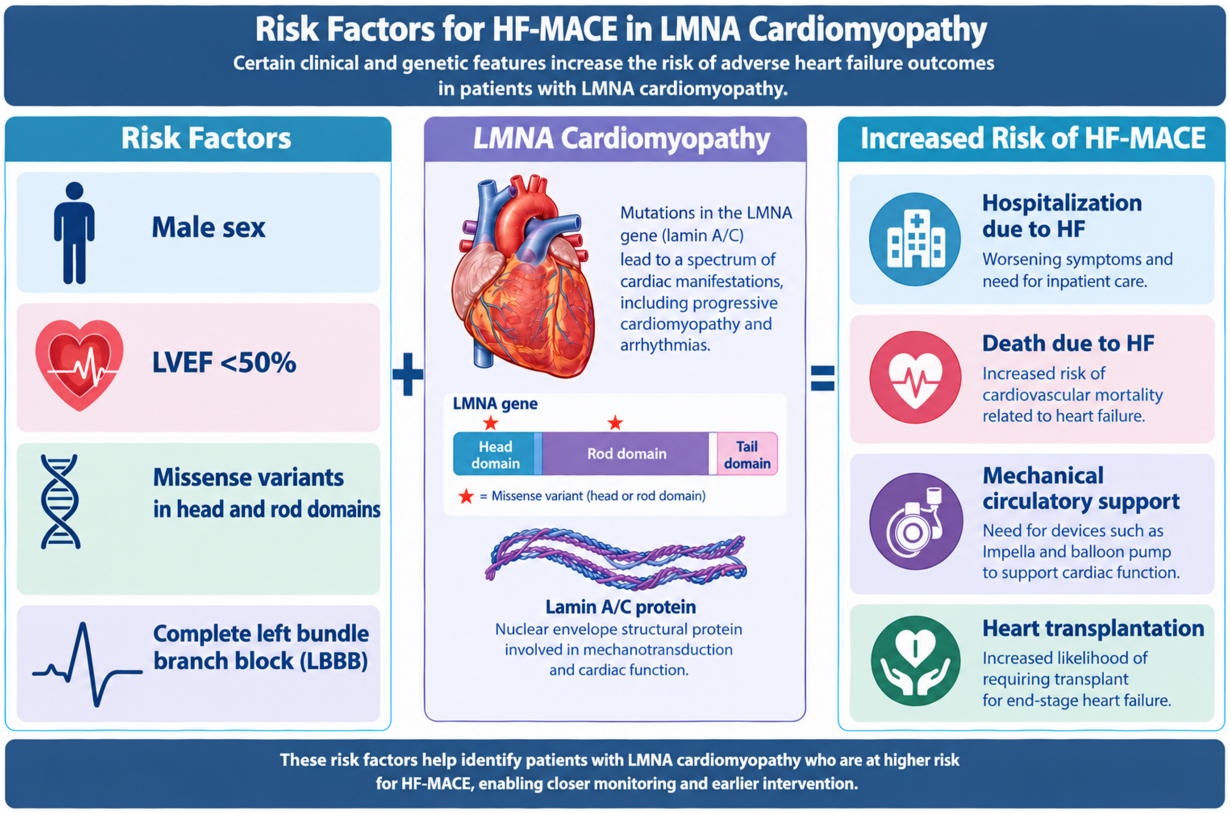


Figure 1. Risk factors reported in Charron *et al.*, 2026[10] that were identified to increase the risk of HF-MACE outcomes in patients with *LMNA* cardiomyopathies. HF: Heart failure; HF-MACE: heart failure major adverse cardiac events; LBBB: left bundle branch block; *LMNA*: lamin A/C gene; LVEF: left ventricular ejection fraction.

progression and support closer surveillance, timely optimization of guideline-directed medical therapy (GDMT), and earlier referral for advanced heart failure therapies, such as transplant or left ventricular assist device, when appropriate. It should be noted that GDMT utilization in patients with laminopathies has not been well studied, likely due to the highly variable but often quick progression to end-stage heart failure[3]. Additionally, GDMT and other heart failure treatments in other forms of DCM have shown improvement in mortality and morbidity but again are limited in effect due to variable penetrance amongst genetic mutations that cause DCM, i.e., *TTN vs. DSP* truncations[11].

In suspected high-risk patients, myocardial injury could be more readily monitored with blood biomarkers, regular cardiac magnetic resonance imaging, and echocardiography, improving timing of receiving preventive treatment. Myocardial fibrosis has been identified in patients with laminopathies and may correlate with ventricular arrhythmias and subsequent mechanical impairment. Interstitial myocardial fibrosis, specifically, may serve as an early marker of mechanical impairment in *LMNA* cardiomyopathy; therefore, cardiac magnetic resonance imaging findings should be considered for incorporation into future risk prediction models[4]. It should be recognized, however, that prospective studies are required to determine whether such early risk-based interventions can improve clinical outcomes in patients with laminopathies as this study is purely a risk-stratification tool for development of HF outcomes.

The study had some limitations. The derivation cohort consisted of patients from one registry in France, limiting the generalizability of the findings. The findings were validated with an additional sample of patients at tertiary institutions around the world, but these patients were at baseline more clinically ill, and the cohort itself was much smaller (245 patients compared to 470). The benefit of a single registry, however, is that it

allows for uniform patient stratification and clinical characterization. These constant variables and criteria should continue to be applied to external validation cohorts. Additional external validation would be needed with a larger sample worldwide to apply this model generally to the adult laminopathy population. This could be achieved by utilizing not only patients who were referred to tertiary centers but by using larger, international multi-site registries such as the Sarcomeric Human Cardiomyopathy Registry (SHaRe)[12] which is able to provide retrospective data similar to the French derivation cohort but on a much larger scale. The model also did not account for ethnicity or shared genomic background, which may have introduced additional sources of variability. Genetic testing was also limited, with substantial changes in *LMNA* variant classification occurring between 2000 and 2017, which likely affected the identification of pathogenic/likely pathogenic variants included in this retrospective analysis. Other limitations include the potential for referral bias from tertiary centers, differences in treatment strategies over the long study period, and a lack of longitudinal imaging and biomarker data, which could significantly limit the generalizability of the study.

The development of a novel HF-MACE risk prediction model represents an important advance in the prognostic assessment of patients with adult-onset *LMNA* cardiomyopathy, complementing existing models focused on ventricular arrhythmias and sudden cardiac death. It successfully identified four independent variables associated with increased risk, including male sex, LVEF < 50%, missense variants in head and rod domains, and complete left bundle branch block. Future *LMNA* risk prediction models may improve individualized risk assessment by integrating genotype-specific information, such as mutation type and location, with imaging characteristics including myocardial fibrosis and ventricular dysfunction, as well as circulating biomarkers of myocardial injury and stress. While this current model is a large step forward for risk prediction in adult-onset laminopathies, there is still work to be done to determine the discriminatory power of this model in larger populations as risk prediction models can tend to overestimate the sensitivity of the model, leading to implementation of preventive management and treatment in patients who otherwise may not need it[6].

DECLARATIONS

Authors' contributions

Writing the manuscript, figure design, critical review: Newman SV
Conceptualization of the initial manuscript, critical revisions: Mestroni L

Availability of data and materials

Not applicable.

AI and AI-assisted tools statement

During the preparation of this manuscript, the AI tool ChatGPT (version 6, released 2026-09-03) was used to generate Figure 1 and assist with language editing. The tool did not influence the study design, data collection, analysis, interpretation, or the scientific content of the work. All authors take full responsibility for the accuracy, integrity, and final content of the manuscript.

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Conflicts of interest

Mestroni L is an advisor for Tenaya Therapeutics, Alexion, Rocket Pharmaceuticals, and BioBridge, and received grant funding from Greenstone Bioscience. Mestroni L is a Consulting Editor of *The Journal of Cardiovascular Aging*. Mestroni L was not involved in any steps of the editorial process, notably including reviewer selection, manuscript handling, and decision-making. Newman SV declares that there are no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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