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Review

Meta-analysis of the role of cardiac magnetic resonance in laminopathy

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ABSTRACT

Lamin A/C (*LMNA*) cardiomyopathy is an inherited form of dilated cardiomyopathy associated with high rates of arrhythmias, conduction disease and sudden cardiac death, often preceding overt heart failure. Although LMNA mutations account for a minority of dilated cardiomyopathy cases, they portend a particularly malignant course. Cardiac magnetic resonance (CMR) imaging, particularly the detection of late gadolinium enhancement, has emerged as a valuable tool for assessing myocardial fibrosis and risk stratification in laminopathy. This study aims to systematically evaluate the structural, functional and prognostic CMR features in LMNA mutation carriers, and to quantify the diagnostic and clinical implications of myocardial fibrosis. A comprehensive literature search was conducted through June 2025. Studies involving genetically confirmed LMNA mutation carriers with CMR data were included. Outcomes included ventricular variables (left ventricular ejection fraction, left ventricular end-diastolic volume index, left ventricular end-systolic volume index, left ventricular wall mass index), late gadolinium enhancement (LGE) presence and arrhythmic events. Between-group comparisons were made: LMNA cardiomyopathy versus healthy controls; laminopathy with versus without LGE; and LMNA-positive versus LMNA-negative cardiomyopathy. We identified 10 studies involving 847 individuals. The LGE risk ratio for patients with LMNA cardiomyopathy versus healthy controls was 14.39 ($P < 0.001$); the LGE risk ratio for patients with LMNA-positive versus LMNA-negative cardiomyopathy was 2.14 ($P < 0.001$). In patients with laminopathy, LGE was associated with an increased risk of atrioventricular block (risk ratio 6.94; $P = 0.004$) and a trend towards more ventricular tachyarrhythmia (risk ratio 3.32; $P = 0.056$). Despite these fibrotic changes, left ventricular volumes and wall mass did not differ significantly from controls. CMR imaging identifies a high burden of fibrosis in LMNA cardiomyopathy, even in early disease, with strong prognostic implications. LGE presence is a key risk marker for arrhythmia and conduction disease, supporting early imaging-based risk stratification and possible preventive implantable cardioverter-defibrillator implantation in mutation carriers.

1. Background

Lamin A/C (*LMNA*) cardiomyopathy is a genetically defined dilated cardiomyopathy (DCM) caused by heterozygous mutations in the *LMNA* gene, which encodes the nuclear envelope proteins lamins A and C [1]. These structural proteins are crucial for nuclear stability and gene regulation. Pathogenic variants in the *LMNA* gene result in a condition known as "laminopathy," which has multisystem effects. In the heart, *LMNA* mutations typically cause an aggressive autosomal-dominant cardiomyopathy characterized by left ventricular (LV) enlargement and systolic dysfunction, which is often preceded or accompanied by electrical disease [2]. Clinically, *LMNA*-related cardiomyopathy presents in early to mid-adulthood; patients frequently exhibit atrioventricular block (AVB), atrial fibrillation, ventricular tachyarrhythmia (VT) or sudden cardiac death as initial manifestations, sometimes even when the left ventricular ejection fraction (LVEF) is only mildly reduced or normal [3]. Indeed, clinical series report that nearly 90% of genotype-positive carriers eventually develop cardiac phenotypes by middle age [3,4]. Epidemiologically, *LMNA* mutations account for roughly 5–8% of familial non-ischaemic DCM cases [4], making laminopathy one of the

Abbreviations: AVB, atrioventricular block; CI, confidence interval; CMR, cardiac magnetic resonance; DCM, dilated cardiomyopathy; ICD, implantable cardioverter-defibrillator; LGE, late gadolinium enhancement; *LMNA*, lamin A/C; LV, left ventricular; LVEDVi, left ventricular end-diastolic volume index; LVEF, left ventricular ejection fraction; LVESVi, left ventricular end-systolic volume index; LVWMi, left ventricular wall mass index; MVA, malignant ventricular arrhythmia; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-analyses; VT, ventricular tachyarrhythmia.

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most common heritable causes of DCM. Importantly, laminopathies indicate a particularly severe prognosis; meta-analyses estimate that up to 46% of *LMNA* mutation carriers experience sudden cardiac death or malignant ventricular arrhythmias (MVAs), with many progressing to end-stage heart failure, resulting in high rates of cardiac transplantation or death [5,6]. *LMNA* cardiomyopathy is hallmarked by its electrical manifestations, which often precede significant LV dilation. Conduction system disease (including high-grade AVB) and atrial arrhythmias are seen in the majority of patients, whereas non-sustained and sustained VTs affect roughly one quarter to one half of carriers [4,7]. Heart failure typically develops later in the disease course, often after decades of electrical abnormalities [8]; when it does occur, it may be accompanied by diffuse myocardial remodelling and fibrosis. This fibrotic substrate often localizes to the basal to mid-interventricular septum in a mid-wall distribution [5]. Despite early arrhythmias, many patients with *LMNA* mutations maintain a relatively preserved LVEF for years [9]. The age-dependent incomplete penetrance and phenotypic overlap with other DCM subtypes mean that early diagnosis is challenging, especially before overt heart failure develops. Given the high risk of adverse events in *LMNA* mutation carriers, including sudden cardiac death, which can occur even with only moderate LVEF impairment, vigilant screening and risk assessment are crucial [10].

Risk stratification in *LMNA* cardiomyopathy is particularly demanding. Conventional predictors (such as LVEF or New York Heart Association class) are relatively insensitive in this context, because arrhythmic events often occur when LV function is still near to normal [3]. Individual prognosis remains difficult to predict, as even carriers with milder variants can experience sudden arrhythmic death. Recognizing these risks, contemporary guidelines have started to integrate genetic and imaging findings into patient management. Certain expert consensus recommendations and national standards now suggest that implantable cardioverter-defibrillator (ICD) therapy should be considered for *LMNA* mutation carriers who exhibit any high-risk features, such as non-sustained ventricular tachycardia or abnormal genetic results, even if their LVEF exceeds the typical 35% threshold [7,11]. In practice, many centres favour early ICD implantation or close monitoring in *LMNA* mutation carriers once conduction disease or fibrosis is detected.

Cardiac magnetic resonance (CMR) imaging has emerged as a key tool for the evaluation of laminopathy. CMR is uniquely capable of quantifying ventricular volumes and function with high accuracy, and of visualizing myocardial tissue characteristics [12]. Current cardiomyopathy guidelines accord CMR a central role in the initial diagnostic work-up of non-ischaemic DCM [11]. In *LMNA* cardiomyopathy, CMR offers several advantages: it can detect regional wall motion abnormalities, quantify both global and segmental dysfunction (including reductions in longitudinal strain) and, most importantly, identify myocardial fibrosis through late gadolinium enhancement (LGE) or T1 mapping. CMR can unmask subclinical myocardial involvement [13]. The prognostic information from CMR is particularly compelling in laminopathy. CMR not only refines diagnosis of laminopathy, but also may enable individualized risk stratification beyond clinical and genetic markers [14]. In light of these considerations, we undertook a comprehensive meta-analysis of published CMR studies in *LMNA* mutation carriers, to synthesize evidence on myocardial fibrosis prevalence, ventricular remodelling and arrhythmic risk. By consolidating data from various cohorts, we aimed to elucidate the diagnostic and prognostic significance of CMR variables, and to establish robust imaging benchmarks that can inform clinical decision-making and future research in laminopathy.

Although several cohort studies and recent high-impact publications have established the association between *LMNA* cardiomyopathy, myocardial fibrosis on CMR and arrhythmic risk, the available evidence remains fragmented across relatively small populations. Individual studies differ substantially with respect to disease stage, clinical indication for imaging and comparator groups, limiting the generalizability of single-cohort findings. To date, no quantitative synthesis has systematically compared CMR phenotypes of *LMNA* mutation carriers across multiple clinically relevant contrasts, including healthy controls, non-*LMNA* cardiomyopathy and stratification by LGE status. Accordingly, the primary objective of this meta-analysis was not to propose novel mechanistic insights, but to consolidate and quantitatively synthesize existing observational data in order to assess the consistency and directionality of CMR-derived associations in *LMNA* cardiomyopathy. By pooling available evidence, we aimed to contextualize myocardial fibrosis within the broader structural and functional phenotype of laminopathy, and to clarify its prognostic relevance, while acknowledging the inherent limitations of observational data.

2. Methods

2.1. Search strategy

This systematic review and meta-analysis were conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Table A.1) [15]. A protocol for a meta-analysis was registered in the International Prospective Register of Systematic Reviews (PROSPERO), with the registration code "CRD420251080434". A comprehensive search was performed across multiple electronic databases, including PubMed and Web of Science, up to June 2025. The search strategy combined keywords and Medical Subject Headings (MeSH) terms related to "Cardiac Magnetic Resonance" and "Laminopathy.".

The detailed search strategy for PubMed was: ((((lamin[Title/Abstract]) OR (laminopathy[Title/Abstract])) OR (LMNA[Title/Abstract])) OR (lamins[Title/Abstract])) AND ((((((Cardiac-MRI[Title/Abstract]) OR (Cardiac magnetic resonance[Title/Abstract])) OR (Cardiovascular magnetic resonance[Title/Abstract])) OR (cardiovascular-MRI[Title/Abstract])) OR (CMR[Title/Abstract]))).

The detailed search strategy for Web of Science was: ((((TS = (lamin)) OR TS = (laminopathy)) OR TS = (LMNA)) OR TS = (lamins)) AND (((((TS = (Cardiac-MRI)) OR TS = (Cardiac magnetic resonance)) OR TS = (Cardiovascular magnetic resonance)) OR TS = (cardiovascular-MRI)) OR TS = (CMR)).

Reference lists of included studies and relevant systematic reviews were screened manually to identify additional eligible articles.

2.2. Eligibility criteria

Studies were included in this review if they met the following criteria: (1) patients with genetically confirmed laminopathy (*LMNA* mutation); (2) studies that used CMR to evaluate structural and/or functional cardiac changes (e.g. myocardial strain, tissue characterization, ventricular volumes) were considered, whereas studies relying solely on other imaging modalities or non-imaging biomarkers were excluded; (3) reporting of diagnostic accuracy (presence/extent of fibrosis) or prognostic outcomes (adverse cardiac events); and (4) study design: randomized controlled trials, cohort studies, case-control studies, cross-sectional studies and quasi-experimental studies.

Studies were excluded if they focused on unrelated conditions or interventions, did not include original data (including narrative reviews and case reports), did not have any extractable CMR data or were published in languages other than English.

2.3. Data extraction

Titles, abstracts and full-text articles were screened for eligibility. Extracted data included: study characteristics (authors, year, country, sample size and population age); CMR findings; and incidence of adverse cardiac events. When reported, LGE was extracted as a dichotomous variable (present/absent), because quantitative measures of fibrosis extent or standardized segmental distributions were not consistently

available across studies. Titles and abstracts were screened independently by the two reviewers; full texts of potentially eligible articles were then assessed against the inclusion criteria, and any disagreements were resolved through discussion.

2.4. Data synthesis and meta-analysis

A qualitative synthesis was conducted to summarize the characteristics and findings of the included studies. Meta-analysis was performed for specific outcomes (including LVEF, left ventricular end-diastolic volume index [LVEDVi], left ventricular end-systolic volume index [LVESVi], left ventricular wall mass index [LVWMi] and LGE) and adverse cardiac events (including AVB and VT). In some studies, instead of mean ± standard deviation for outcomes, median (interquartile range) was reported. Consistent with the previous study, these measures were converted to the equivalent mean ± standard deviation using the method of Wan et al. [16,17].

In our meta-analytical approach, we conducted three separate between-group comparisons to explore the spectrum of CMR findings in laminopathy: (1) *LMNA* cardiomyopathy versus healthy controls (we pooled data from studies of genetically confirmed *LMNA* mutation carriers and healthy volunteers to quantify the degree of myocardial alteration attributable to laminopathy); (2) patients with LGE-positive versus LGE-negative laminopathy (within the *LMNA* cohorts, we stratified patients by the presence or absence of LGE); and (3) *LMNA*-positive versus *LMNA*-negative cardiomyopathy (to assess disease-specific patterns, we compared *LMNA* mutation carriers with patients who had non-lamin genetic or idiopathic DCM).

Outcome data were pooled using both random-effects and fixed-effects models to account for heterogeneity across studies. Heterogeneity was assessed using the I^2 statistic. If heterogeneity was high ($I^2 > 50\%$) and statistically significant ($P < 0.1$), the random-effects model was considered appropriate. Conversely, if heterogeneity was low or moderate ($I^2 \leq 50\%$) and not statistically significant ($P \geq 0.1$), the common-effects model was applied.

2.5. Risk of bias assessment

The methodological quality of included studies was evaluated using the Newcastle-Ottawa Scale, which assigns up to nine stars across three domains [18]: selection (four stars); comparability (two stars); and outcome (three stars). Two independent reviewers evaluated each study, and disagreements were resolved through discussion.

3. Results

A total of 10 studies were included in this meta-analysis, selected from an initial pool of 161 records identified through database searches (Table 1) [19–28]. After removing duplicates and screening abstracts, 18 full-text articles were assessed for eligibility. Among them, eight studies were excluded because of insufficient data ($n = 2$) or study design ($n = 6$). This process is shown in the PRISMA flow diagram in Fig. 1. In total, the meta-analysis included 847 individuals. Finally, meta-analysis was performed for the following outcomes (Figs. 2–4): LVEF; LVEDVi; LVESVi; LVWMi; LGE presence; AVB; and VT. Fig. 5 shows the results of assessing bias. Based on the Newcastle-Ottawa Scale, five studies were rated as having a good overall quality, three studies were rated as fair and two studies were rated as poor. Most studies showed a low risk of bias in the selection and outcome domains, and comparability was the most variable domain across studies.

3.1. LGE-positive versus LGE-negative laminopathy comparisons (Fig. 2)

Patients with LGE had a significantly higher risk of AVB compared with those without LGE in three studies (risk ratio 6.94, 95% confidence interval [CI] 1.85 to 26.06; $P = 0.004$; $I^2 = 0\%$). There was a trend toward increased VT risk among LGE-positive patients based on four studies (risk ratio 3.32, 95% CI 0.97 to 11.39; $P = 0.056$; $I^2 = 54\%$). LGE-positive patients exhibited a lower LVEF according to the data from three studies (mean difference–5.03, 95% CI–9.50 to–0.56; $P = 0.027$; $I^2 = 0\%$). No significant difference in LVEDVi was observed (mean difference 3.57, 95% CI–4.50 to 11.65; $P = 0.386$; $I^2 = 0\%$), based on three studies.

3.2. LMNA cardiomyopathy versus healthy control comparisons (Fig. 3)

Patients with laminopathy were significantly more likely to exhibit LGE, with a risk ratio of 14.39 (95% CI 2.97 to 69.82; $P < 0.001$). This result was consistent across all three contributing studies ($I^2 = 0\%$). LVEF was significantly lower in patients with laminopathy (mean difference–5.71, 95% CI–9.36 to–2.06; $P = 0.002$; $I^2 = 71\%$), based on four studies. No significant difference was found in LVEDVi between groups (mean difference 4.65, 95% CI–3.54 to 12.83; $P = 0.266$), across four studies ($I^2 = 56\%$). Based on two studies, LVESVi tended to be higher in patients with laminopathy, but the difference did not reach statistical significance (mean difference 7.26, 95% CI–1.68 to 16.20; $P = 0.112$), with considerable heterogeneity ($I^2 = 86\%$). No significant difference in LVWMi was observed between patients with laminopathy and controls (mean difference–4.40, 95% CI–9.99 to 1.18; $P = 0.122$; $I^2 = 0\%$), across two studies.

3.3. LMNA-positive versus LMNA-negative cardiomyopathy comparisons (Fig. 4)

LGE was significantly more prevalent among patients with *LMNA*-positive cardiomyopathy, with a risk ratio of 2.14 (95% CI 1.41 to 3.23; $P < 0.001$). This result was consistent across the two included studies, with no observed heterogeneity ($I^2 = 0\%$).

4. Discussion

Our meta-analysis highlights several key imaging features of cardiac laminopathy (*LMNA* mutation carriers) and their clinical implications. Compared with healthy individuals, *LMNA* mutation carriers show a dramatically higher prevalence of myocardial fibrosis (LGE): the pooled risk ratio for LGE in patients with *LMNA* laminopathy versus healthy controls was 14.39, reflecting the fact that most mutation carriers exhibit mid-wall fibrotic scarring on CMR. Unlike typical DCM, *LMNA*-related disease usually shows milder symptoms. In this condition, the LV may not expand as much, and many people still have nearly normal heart size, even though their heart function is reduced. We found that *LMNA* mutation carriers had only a slightly lower LVEF than healthy people, and there were no significant differences in LV volumes or mass index. Compared with non-lamin cardiomyopathy, the most significant difference was fibrosis; *LMNA* mutation carriers were much more likely to exhibit LGE than those with non-ischaemic cardiomyopathy (risk ratio 2.14); in contrast, differences in LVEF and LV volumes were less pronounced. These meta-analytic findings align well with known *LMNA* pathophysiology. Lamin A/C mutations cause a fibrotic arrhythmogenic DCM in which conduction disease and arrhythmias often precede overt pump failure [29]. Previous CMR studies have shown that LGE in *LMNA* cardiomyopathy typically appears in the basal and mid-ventricular septum with a linear mid-wall pattern [25]. For example, Holmström et al. found LGE in 88% of *LMNA* mutation carriers, almost exclusively in the basal/mid septum with a linear intramural pattern, and strongly associated with AVB [25]. Similarly, the study by Fontana et al., investigating 19 *LMNA* mutation carriers, found that LGE was far more common in those with LV dysfunction or with first-degree AVB [24]. Thus, our meta-analysis confirms that myocardial fibrosis (LGE) is nearly universal in laminopathy, and is far more prevalent than in healthy hearts

Table 1
Characteristics of included articles.

Study	Year	Country	Population	
			Groups (*n*)	Age (years)[a]
Topriceanu et al. [19]	2025	UK	HC: 47 Lamin + normal EF: 29 Lamin + low EF: 38 Wild-type lamin: 73	HC: 35 (30–63) Lamin + normal EF: 38 (29–41) Lamin + low EF: 47 (34–59) Wild-type lamin: 44 (33–59)
de Frutos et al. [20]	2023	Spain	Lamin: 14 Gene negative cardiomyopathy: 358	Lamin: 44.5 ± 11.9 Gene negative cardiomyopathy: 55.2 ± 13.5
Peretto et al. [21]	2020	Italy	MVA +: 8 MVA–: 33 LGE +: 25 LGE–: 16	MVA +: 32 ± 21 MVA–: 36 ± 16 LGE +: 37 ± 17 LGE–: 33 ± 16
Delhommeau et al. [22]	2020	France	LMNA +: 55 LMNA–: 35	N/A N/A
Hasselberg et al. [23]	2014	Norway	Ventricular arrythmia +: 21 Ventricular arrythmia–: 20	Ventricular arrythmia +: 36 ± 12 Ventricular arrythmia–: 32 ± 17
Fontana et al. [24]	2013	Italy	HC: 16 Lamin: 19	HC: 46 ± 18 Lamin: 45 ± 13
Holmström et al. [25]	2011	Finland	Lamin: 17	Lamin: 37.59 ± 13.33
Koikkalainen et al. [26]	2008	Finland	HC: 14 Lamin: 12	HC men: 45 ± 12 HC women: 28 ± 8 Lamin men: 28 ± 8 Lamin women: 36 ± 13
Raman et al. [27]	2007	USA	HC: 11 Lamin: 11	HC: 37.1 ± 9.3 Lamin: 33.1 ± 13.2
Smith et al. [28]	2006	UK	HC: 8 Lamin: 8	HC: 15.1 ± 11 Lamin: 18.5 ± 12

EF: ejection fraction; HC: healthy controls; LGE: late gadolinium enhancement; LMNA: lamin A/C mutation; MVA: malignant ventricular arrythmia.
[a] Data are expressed as median (interquartile range) or mean ± standard deviation.

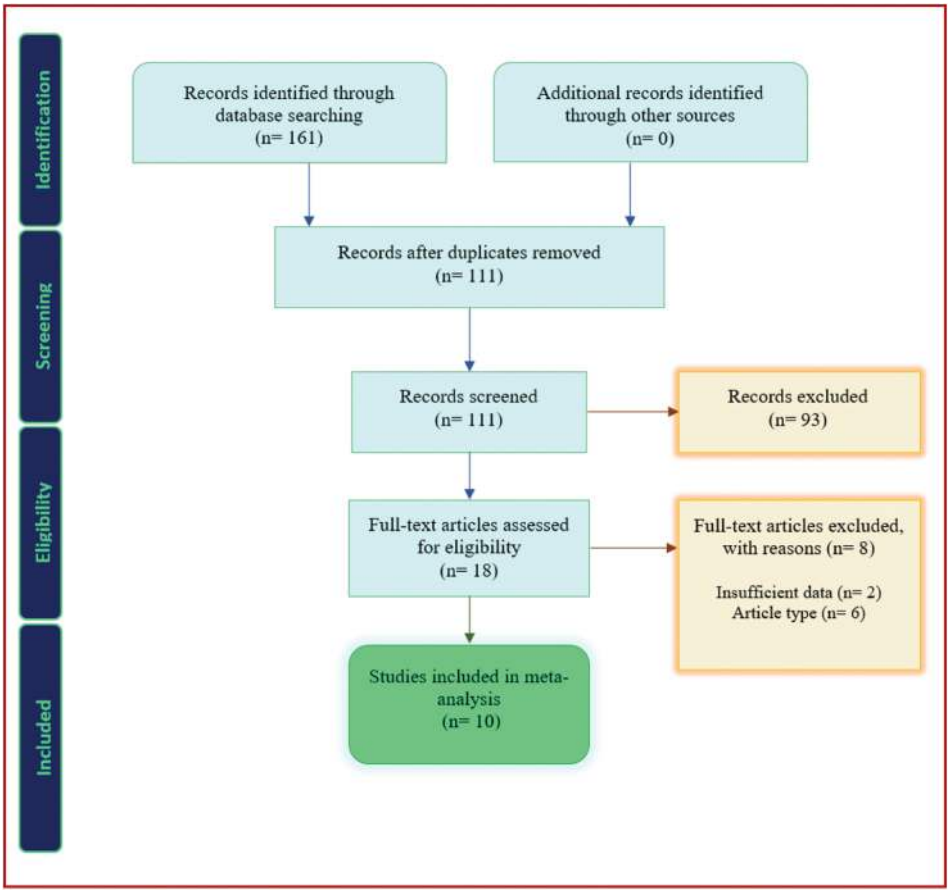


Fig. 1. Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) flow diagram.

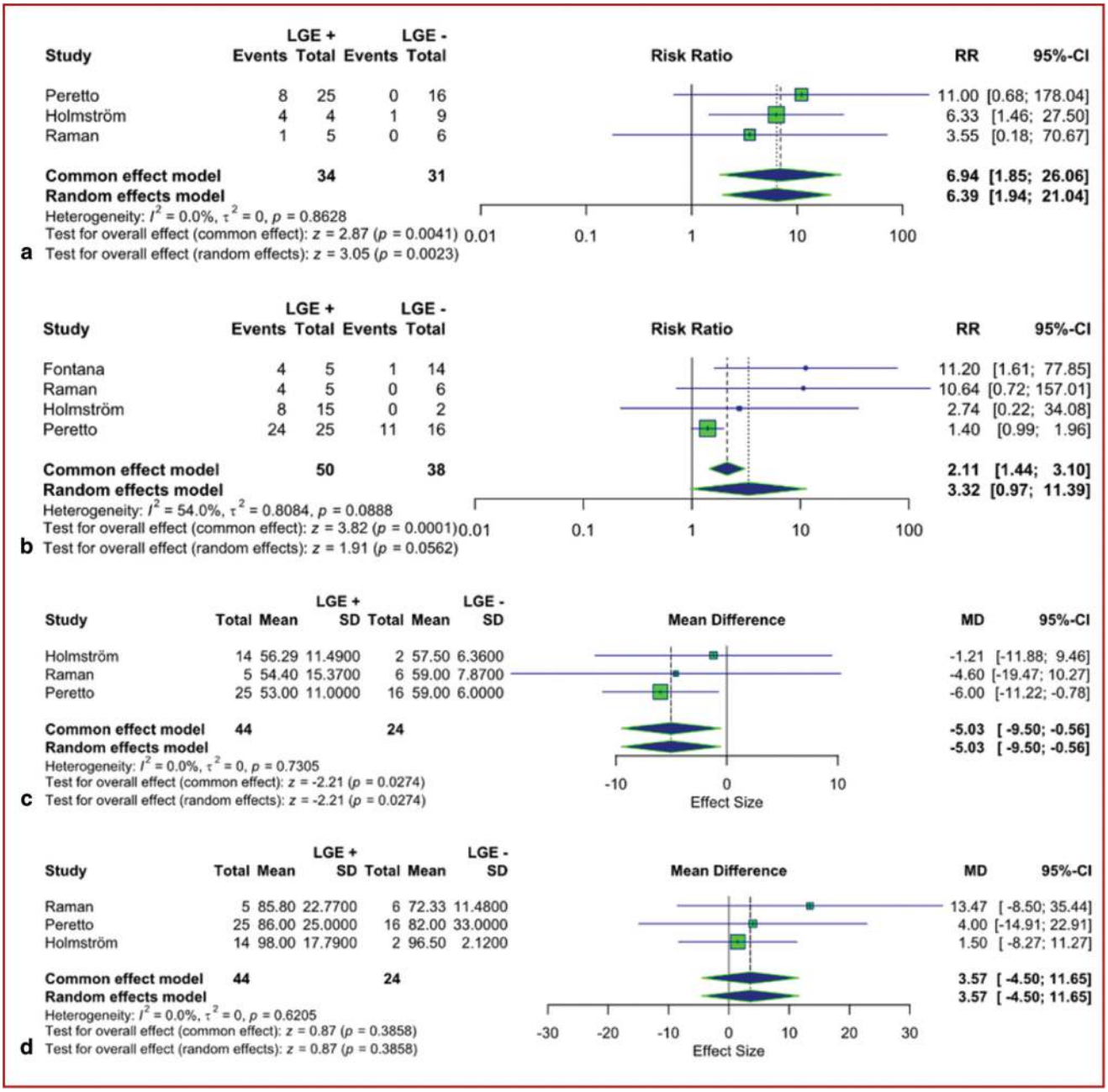


Fig. 2. Analysis of late gadolinium enhancement (LGE)-based laminopathy groups. A: atrioventricular block incidence. B: ventricular tachyarrhythmia incidence. C: left ventricular ejection fraction. D: left ventricular end-diastolic volume. CI: confidence interval; MD: mean difference; RR: risk ratio; SD: standard deviation.

or other DCMs, emphasizing its role as a disease hallmark. Interpretation of the present findings should take into account the substantial clinical and methodological heterogeneity of the included studies. The analysed cohorts ranged from asymptomatic mutation carriers undergoing screening to patients with overt DCM, with varying degrees of systolic dysfunction and differing clinical indications for CMR. Imaging protocols and LGE acquisition techniques also spanned nearly two decades of technological evolution. Consequently, although pooled analyses revealed consistent associations between *LMNA* cardiomyopathy, myocardial fibrosis and adverse electrical outcomes, the magnitude of pooled effect estimates should be interpreted with caution. Several risk ratios were associated with wide confidence intervals, and were derived from a limited number of studies. In this context, the direction and consistency of associations across studies are more robust and clinically informative than their precise quantitative values, and the present results should be viewed as hypothesis supporting rather than definitive effect-size estimates.

In practical terms, the presence of LGE in *LMNA* hearts sets them apart from normal hearts, and has important implications for prognosis. LGE-positive patients with laminopathy had significantly worse outcomes: they had a ~7-fold higher risk of complete AVB than LGE-negative patients (risk ratio 6.94; $P = 0.004$) and a trend toward more VT. Likewise, Peretto et al. reported that *LMNA* mutation carriers with LGE had significantly more MVA than those without; none of the LGE-negative group experienced VT or ventricular fibrillation during long-term follow-up [21]. Our pooled analysis echoes this; although the LGE-positive versus LGE-negative arrhythmia comparison narrowly missed conventional significance (risk ratio 3.32; $P = 0.056$), the effect size strongly suggests an elevated risk. In addition, LGE positivity marked worse LV function in laminopathy; LGE-positive carriers had an

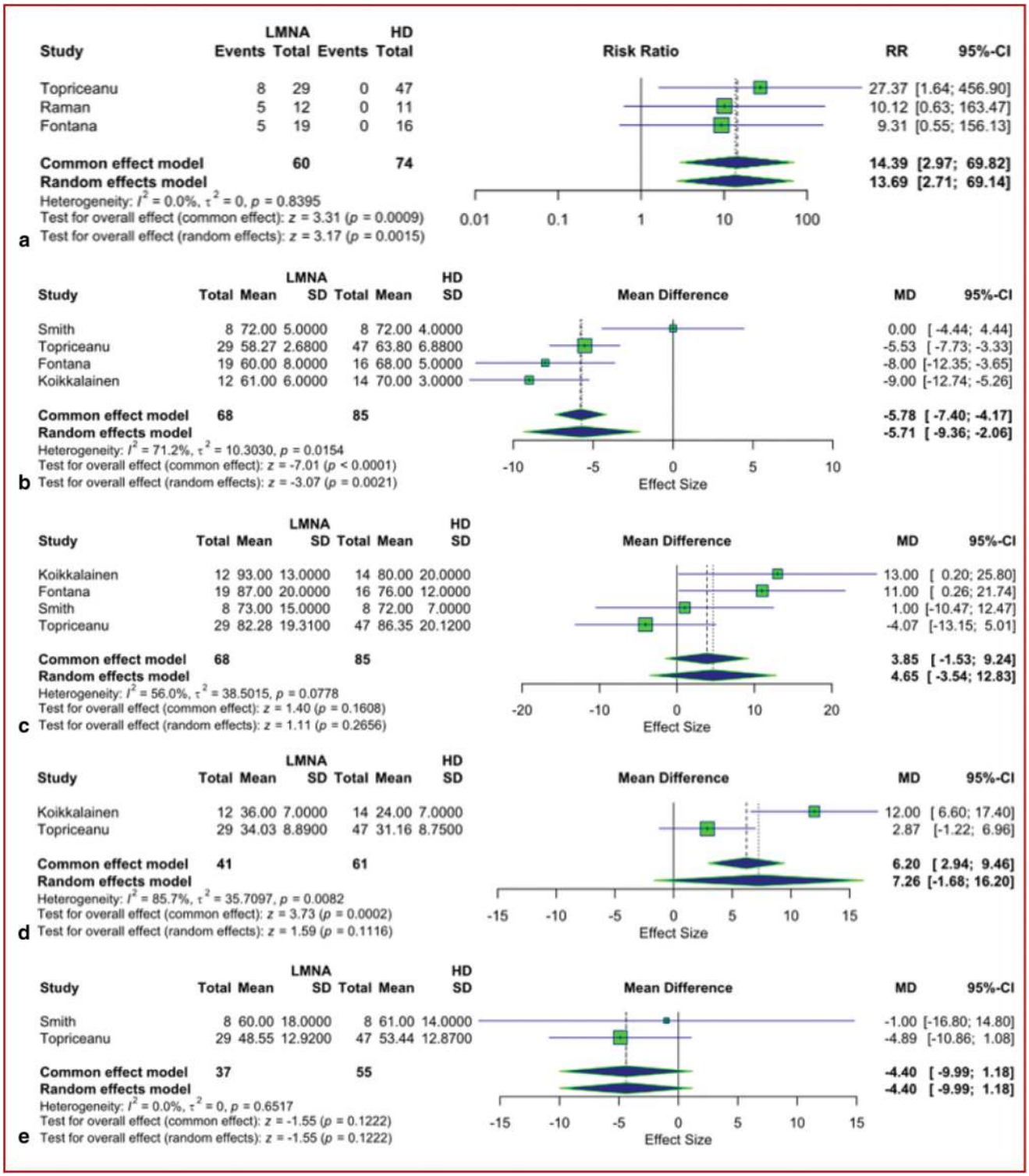


Fig. 3. Analysis of differences between patients with *LMNA* cardiomyopathy and healthy donors (HD). A: late gadolinium enhancement presence incidence. B: left ventricular ejection fraction. C: left ventricular end-diastolic volume. D: left ventricular end-systolic volume. E: left ventricular mass. CI: confidence interval; *LMNA*: lamin A/C; MD: mean difference; RR: risk ratio; SD: standard deviation.

LVEF that was about 5% lower than LGE-negative carriers ($P = 0.027$). Together, these findings highlight that fibrosis detected by CMR is a powerful indicator of electrical instability and pump dysfunction in *LMNA* disease, beyond what LVEF alone reveals. Our findings reinforce the role of CMR as an important component of risk assessment in *LMNA* cardiomyopathy, particularly through the identification of myocardial fibrosis. The presence of LGE was consistently associated with conduction abnormalities and adverse electrical outcomes across included studies. However, these associations should be interpreted within the context of multivariable risk stratification, rather than as isolated triggers for clinical decision-making. In this context, LGE represents one component of a broader multivariable risk-assessment framework. Although its presence may contribute incremental prognostic information, the observational data synthesized in this meta-analysis do not support

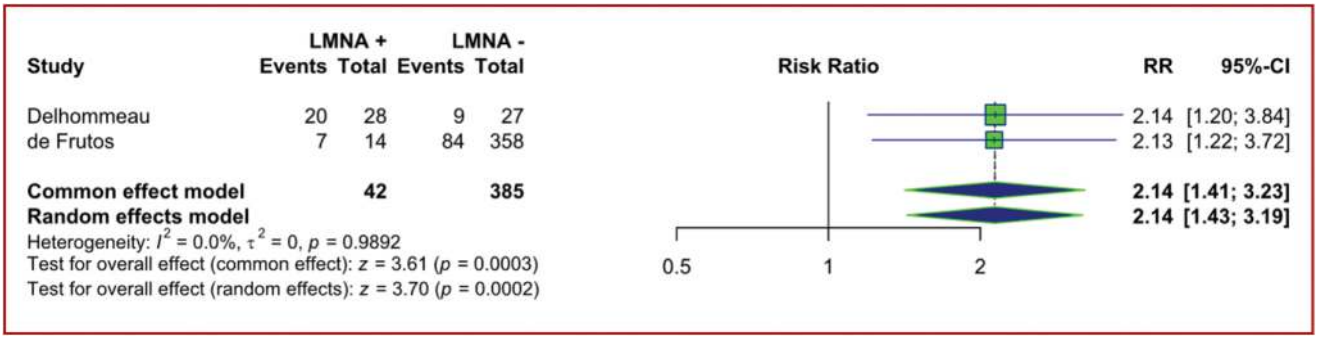


Fig. 4. Analysis of late gadolinium enhancement presence incidence in patients with *LMNA*-positive versus *LMNA*-negative cardiomyopathy. CI: confidence interval; *LMNA*: lamin A/C; RR: risk ratio.

the use of LGE alone as a criterion for preventive device therapy. Rather, CMR findings should complement established clinical and electrophysiological markers in guiding individualized management strategies.

LMNA cardiomyopathy is characterized by diffuse mid-wall fibrosis on CMR [25]. Our meta-analysis confirms a vastly higher LGE prevalence in patients with *LMNA* cardiomyopathy than healthy controls, reflecting that most *LMNA* mutation carriers develop scarring even before clinical symptoms. Significantly, LGE in laminopathy strongly correlates with conduction abnormalities. In our analysis LGE-positive carriers were ~7 times as likely to have AVB. Despite its severity, *LMNA* cardiomyopathy often shows mild ventricular remodelling. Our pooled data found no significant difference in LVEDVi between laminopathy and controls, and only a borderline trend towards higher LVESVi. We found that patients with laminopathy had an LVEF that was ~5–6% lower on average than controls, a statistically significant but clinically moderate reduction. This indicates that hearts with *LMNA* mutations experience contractile damage even before significant enlargement becomes apparent. We saw no significant differences in LVWMi between patients with *LMNA* cardiomyopathy and healthy controls; this supports the idea that laminopathy is a fibrotic process, not hypertrophic. Wall thickness is usually normal in these patients. In our "*LMNA*-positive versus *LMNA*-negative cardiomyopathy" analysis, the only substantial imaging difference was again fibrosis; *LMNA* mutation carriers had about double the risk of LGE compared with DCM controls. This finding implies a disease-specific phenotype. In other forms of non-ischaemic cardiomyopathy, LGE may be present, but tends to be less extensive. The uneven scarring observed in *LMNA* disease may account for its increased tendency to cause arrhythmias. Ventricular volumes and LVEF were not markedly different between two groups in the few studies available, reinforcing that fibrosis burden is a distinguishing imaging feature of laminopathy.

Our findings should be interpreted in the context of *LMNA* pathobiology. The nuclear lamina proteins, lamin A and C, are vital for maintaining the structural integrity of cardiomyocytes. Mutations in these proteins can lead to cell death, inflammation and fibrotic repair, particularly affecting the conduction system and myocardium [30]. As a result, the typical CMR imaging pattern is characterized by LGE in the septal and mid-wall areas, whereas the overall heart geometry remains relatively preserved. It is biologically plausible that patients with LGE experience a lower LVEF and a higher incidence of arrhythmias. Extensive fibrosis can disrupt the contractile function of the myocardium, leading to a reduced LVEF, and can also create a substrate for reentry circuits, which can trigger VT or cause AVB. Importantly, the fibrosis is often patchy, meaning that the global LVEF may not significantly decrease until the later stages of the disease. This helps to explain why many patients with *LMNA* mutations can experience sudden cardiac death or MVA, even when their LVEF is only mildly reduced [7].

Our results reinforce that CMR is a valuable tool in managing *LMNA* mutation carriers. Detection of mid-wall LGE should raise concern; LGE-positive patients in our analysis and others had significantly higher rates of AVB and VT. In practice, the finding of septal LGE in an asymptomatic *LMNA* mutation carrier might prompt closer rhythm monitoring, earlier consideration of an ICD or avoidance of atrioventricular blocker drugs, as per guideline recommendations. Indeed, current consensus documents already advise aggressive prophylaxis; for example, Hershberger and Jordan notes that in *LMNA*-related DCM one should "consider ICD implantation before the ejection fraction falls below 35%" because of the arrhythmic risk [2]. Similarly, all symptomatic patients with *LMNA* cardiomyopathy who need a pacemaker should receive a ICD instead of a simple pacemaker, given the high sudden cardiac death risk [2]. Our meta-analysis provides quantitative imaging evidence to support these strategies; we show that an LGE-negative patient with *LMNA* cardiomyopathy has a very low risk, whereas LGE presence corresponds to a markedly elevated risk of conduction disease and potential VT. In current clinical practice, management decisions in *LMNA* mutation carriers rely on the integration of multiple factors, including clinical presentation, electrocardiographic abnormalities, genetic features and longitudinal disease progression. Although the presence of LGE may contribute incremental prognostic information, the available observational data do not support its use as a stand-alone criterion for preventive device therapy. Rather, CMR findings should complement, rather than replace, established clinical and electrophysiological risk markers.

Our meta-analysis also has broader implications for understanding laminopathy. The relative preservation of LV mass and cavity size, despite progressive fibrosis and arrhythmic events, means that conventional criteria (e.g. LVEF < 35%) will miss high-risk patients. This justifies a phenotype-tailored approach–screening *LMNA* mutation carriers with CMR irrespective of LVEF, as recommended in expert consensus [2]. Additionally, the strong link between scarring and AVB in our results aligns with the clinical course of laminopathy; many patients present first with heart block or atrial arrhythmias in their 20s to 40s, sometimes years before heart failure develops [2,25]. Recognizing this sequence is important for timely intervention. For example, even an *LMNA* mutation carrier with a normal LVEF, but early LGE or conduction delay, might merit an ICD sooner than a similar patient with a non-*LMNA* DCM.

4.1. Study limitations

Several limitations should be noted. Only 10 studies were included in the analysis, highlighting the rarity of laminopathy. Some of the analyses showed moderate heterogeneity, probably as a result of small sample sizes and variations in patient selection or imaging protocols. Many of the studies were observational cohorts with differing definitions of outcomes. We addressed some data issues, such as converting medians to means, but residual imprecision may still exist. Additionally, most studies did not provide detailed CMR mapping or strain data, preventing us from conducting a meta-analysis of emerging variables. Publication bias is a concern; we excluded non-English reports, and negative or

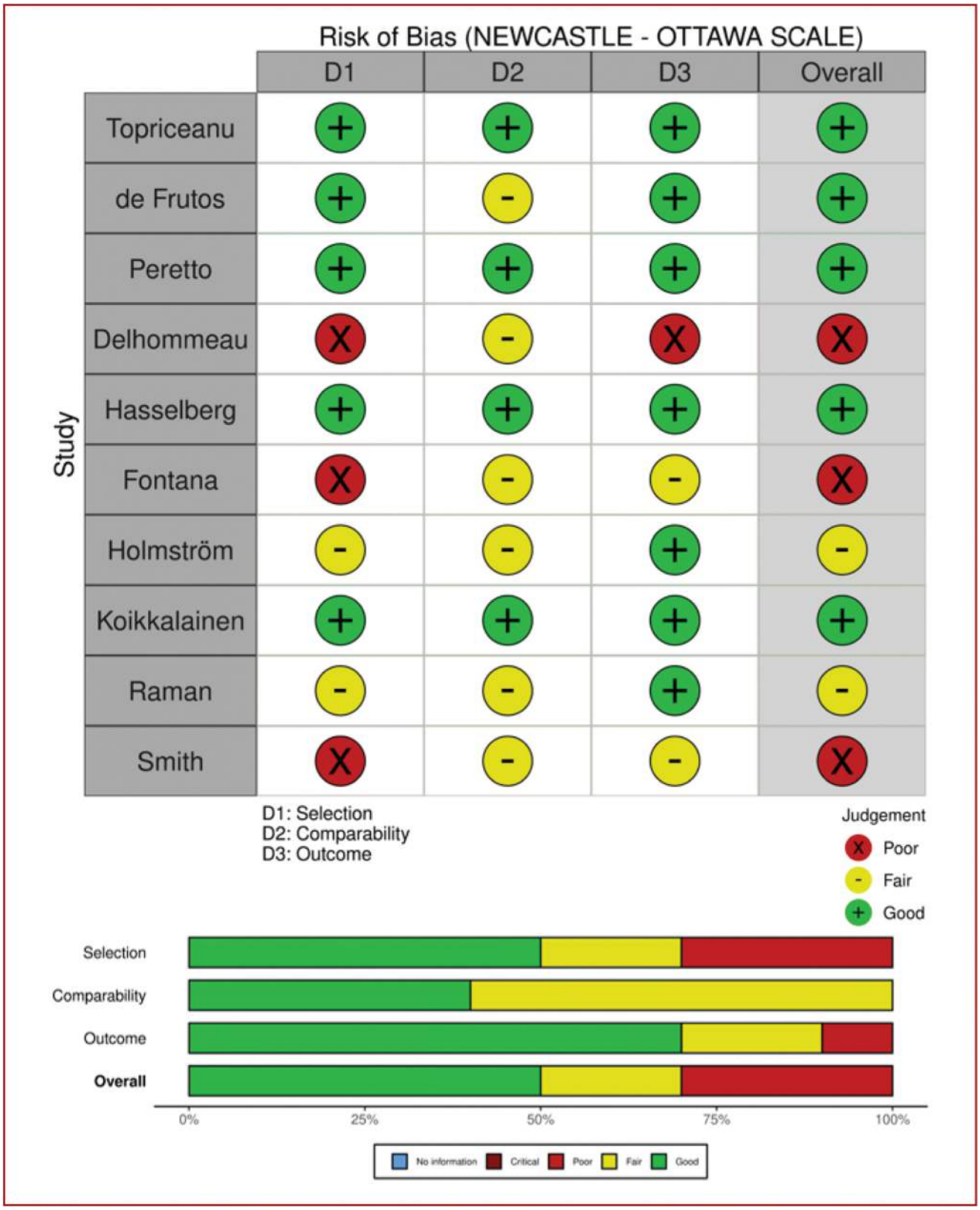


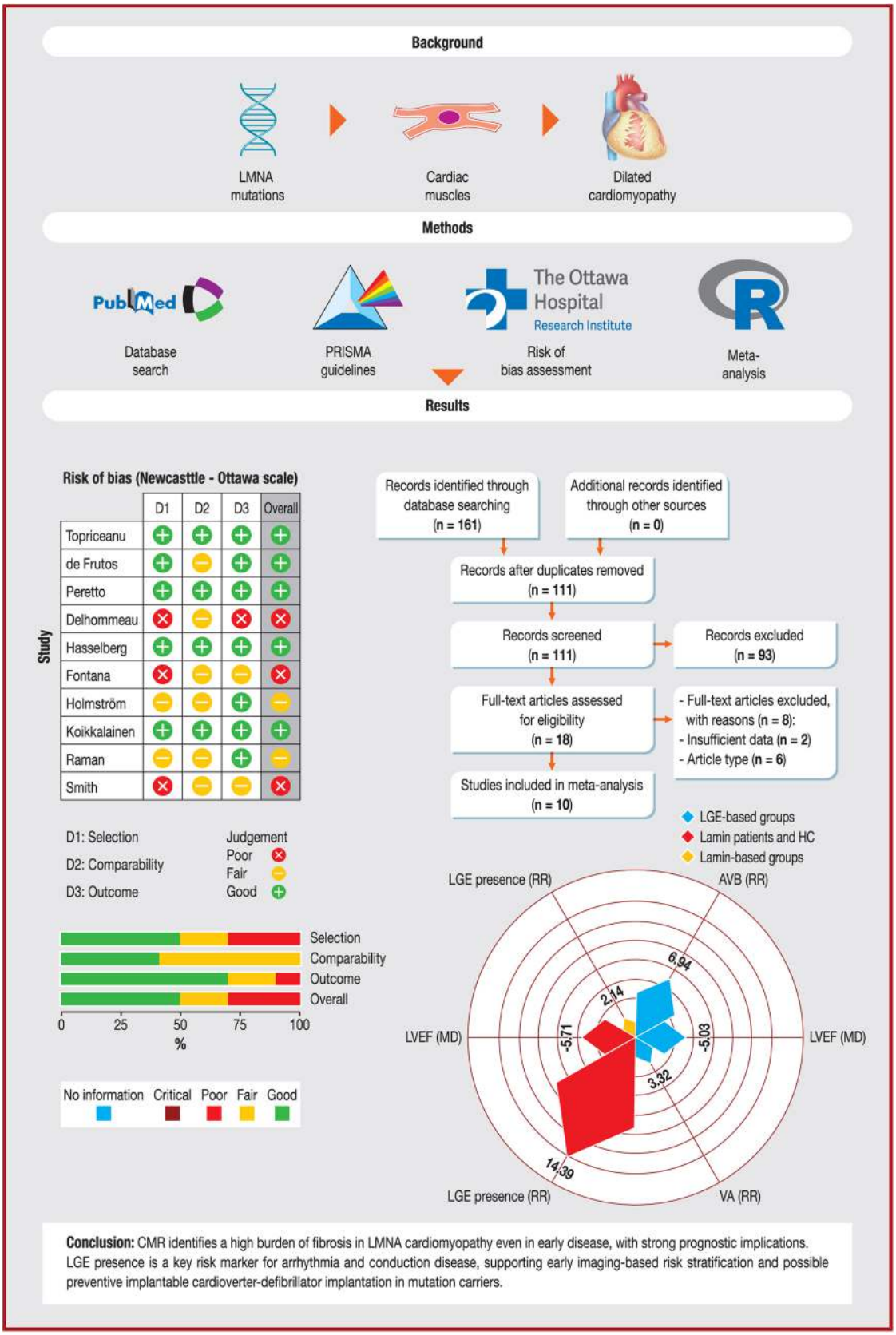
Fig. 5. Risk of bias assessment.

null studies may be under-represented. In addition, some pooled estimates are presented with relatively high numerical precision, despite being derived from small numbers of studies, and accompanied by wide confidence intervals. This level of precision should not be interpreted as reflecting robust or definitive effect sizes. Rather, the numerical values are reported for completeness, whereas the clinical interpretation should focus on the consistency and direction of associations across studies rather than on exact point estimates. Finally, our comparisons

with healthy controls and other DCMs depend on the limited cohorts in each study. Ideally, future research should involve large multicentre registries or prospective trials. An important methodological limitation of the present meta-analysis relates to how LGE was defined and analysed across included studies. For the purposes of quantitative pooling, LGE was treated as a binary variable (present versus absent), as most eligible studies did not provide sufficiently detailed or standardized data on fibrosis extent or spatial distribution. However, growing evidence suggests that fibrosis burden and pattern, particularly septal and mid-wall involvement, may carry incremental prognostic value in *LMNA* cardiomyopathy. Furthermore, LGE detection is highly dependent on postprocessing methodology and threshold selection, including visual assessment, signal intensity-based techniques (e.g. n-standard deviation methods) or full-width at half-maximum approaches. These methods likely varied substantially between centres and over time, particularly given the long study period encompassed by this review. This issue is especially relevant in *LMNA* cardiomyopathy, where fibrosis is often diffuse, mid-wall and of limited extent, rendering its detection sensitive to threshold definition. Consequently, misclassification of LGE status cannot be excluded, and may have reduced interstudy comparability and attenuated the depth of prognostic interpretation. These considerations highlight the need for future studies employing standardized LGE acquisition and quantitative fibrosis assessment. Another methodological limitation relates to the conversion of medians (interquartile ranges) to means $\pm$ standard deviations for quantitative pooling. Although established statistical methods were used for this purpose, such transformations introduce additional uncertainty, particularly in small cohorts or when data distributions are skewed. This may have affected the precision of some pooled estimates and contributed to residual heterogeneity. Accordingly, results derived from converted summary statistics should be interpreted with caution, and future studies reporting standardized parametric data would improve the robustness of meta-analytical synthesis in *LMNA* cardiomyopathy.

5. Conclusions

CMR reveals that *LMNA* cardiomyopathy is a fibrotic arrhythmogenic disease, even in mild stages. Our pooled results confirm that *LMNA* mutation carriers have significantly more mid-wall fibrosis (LGE) than healthy people or other patients with DCM, and that fibrosis predicts conduction block and lowers LVEF. By contrast, LV volumes and wall mass remain largely similar to normal. These findings highlight the importance of closely monitoring carriers of *LMNA* mutations using advanced imaging techniques. If LGE or other abnormalities are detected, it should lead to more rigorous risk assessment, such as conducting electrophysiology studies or considering early ICD implantation, even if the LVEF is only slightly reduced. However, given the observational nature of the available evidence of included cohorts, CMR findings should be interpreted in conjunction with clinical, genetic and electrophysiological variables. Also, CMR findings, including the presence of LGE, should be interpreted within the context of comprehensive multivariable risk stratification. Management decisions should integrate imaging results with clinical, genetic and electrophysiological factors, rather than rely on single imaging variables. Future prospective studies incorporating standardized imaging protocols and quantitative fibrosis assessment are needed to further refine the role of CMR in guiding individualized management strategies for *LMNA* cardiomyopathy. Future research should refine the role of CMR metrics (strain, T1/T2 mapping) in tracking disease progression and guiding therapy in laminopathy (Central illustration).



Central illustration. Meta-analysis of the role of cardiac magnetic resonance in laminopathy. AVB: atrioventricular block; HC: healthy controls; LGE: late gadolinium enhancement; LMNA: lamin A/C; LVEF: left ventricular ejection fraction; MD: mean difference; PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-analyses; RR: risk ratio; VA: ventricular arrhythmia. [VT (ventricular tachyarrhythmia) for consistency].

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.acvd.2026.02.003.

Disclosure of interest

The authors declare that they have no competing interest.

References

[1] Goidescu CM. Dilated cardiomyopathy produced by lamin A/C gene mutations. Clujul Med 2013;86(4):309–12.
[2] Hershberger RE, Jordan E. LMNA-related dilated cardiomyopathy. Seattle (WA): University of Washington, Seattle; 2008. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1674/.
[3] Rosario KF, Karra R, Amos K, Landstrom AP, Lakdawala NK, Brezitski K, et al. LMNA cardiomyopathy: important considerations for the heart failure clinician. J Card Fail 2023;29(12):1657–66.
[4] Hasselberg NE, Haland TF, Saberniak J, Brekke PH, Berge KE, Leren TP, et al. Lamin A/C cardiomyopathy: young onset, high penetrance, and frequent need for heart transplantation. Eur Heart J 2018;39(10):853–60.
[5] Lau C, Gul U, Liu B, Captur G, Hothi SS. Cardiovascular magnetic resonance imaging in familial dilated cardiomyopathy. Medicina [Internet] 2023;59(3):439.
[6] Chen SN, Sbaizero O, Taylor MRG, Mestroni L. Lamin A/C cardiomyopathy: implications for treatment. Curr Cardiol Rep 2019;21(12):160.
[7] Nishiuchi S, Makiyama T, Aiba T, Nakajima K, Hirose S, Kohjitani H, et al. Gene-based risk stratification for cardiac disorders in *LMNA* mutation carriers. Circ Cardiovasc Genet 2017;10(6):e001603, http://dx.doi.org/10.1161/CIRCGENETICS.116.001603. PMID: 29237675.
[8] Wang X, Zabell A, Koh W, Tang WH. Lamin A/C cardiomyopathies: current understanding and novel treatment strategies. Curr Treat Options Cardiovasc Med 2017;19(3):21.
[9] Kumar S, Baldinger SH, Gandjbakhch E, Maury P, Sellal J-M, Androulakis AFA, et al. Long-term arrhythmic and nonarrhythmic outcomes of lamin A/C mutation carriers. J Am Coll Cardiol 2016;68(21):2299–307.
[10] van Berlo JH, de Voogt WG, van der Kooi AJ, van Tintelen JP, Bonne G, Yaou RB, et al. Meta-analysis of clinical characteristics of 299 carriers of LMNA gene mutations: do lamin A/C mutations portend a high risk of sudden death? J Mol Med (Berl) 2005;83(1):79–83.
[11] Groeneweg JA, van Dalen BM, Cox M, Heymans S, Braam RL, Michels M, et al. 2023 European Society of Cardiology guidelines on the management of cardiomyopathies: statement of endorsement by the NVVC. Neth Heart J 2025;33(5):148–56.
[12] Tetaj N, Segreti A, Ferro A, Ligorio V, Spagnolo A, Grigioni F. High-Risk Cardiomyopathy Genotypes and Arrhythmic Risk: LMNA, FLNC, RBM20, PLN and Desmosomal Genes in the ESC 2023. Era Genes 2026;17(4):370.
[13] Blaszczyk E, Gröschel J, Schulz-Menger J. Role of CMR imaging in diagnostics and evaluation of cardiac involvement in muscle dystrophies. Curr Heart Fail Rep 2021;18(4):211–24.
[14] Antonopoulos AS, Xintarakou A, Protonotarios A, Lazaros G, Miliou A, Tsioufis K, et al. Imagenetics for precision medicine in dilated cardiomyopathy. Circ Genom Prec Med 2024;17(2):e004301.
[15] Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. Bmj 2021;372:n71.
[16] Wan X, Wang W, Liu J, Tong T. Estimating the sample mean and standard deviation from the sample size, median, range and/or interquartile range. BMC Med Res Meth 2014;14(1):135.
[17] Shahshenas S, Yarmohammadi H, Soltanipur M, Sheikhi Z. Meta-analysis on effects of lymphatic drainage techniques in the management of carpal tunnel syndrome. J Orthop Surg Res 2025;20(1):491.
[18] Stang A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. Eur J Epidemiol 2010;25(9):603–5.
[19] Topriceanu CC, Al-Farih M, Joy G, Chan F, Webber M, Ilie-Ablachim DC, et al. The cardiovascular magnetic resonance phenotype of lamin heart disease. JACC Cardiovasc Imag 2025;18(6):644–60.
[20] de Frutos F, Ochoa JP, Fernández AI, Gallego-Delgado M, Navarro-Peñalver M, Casas G, et al. Late gadolinium enhancement distribution patterns in non-ischaemic dilated cardiomyopathy: genotype-phenotype correlation. Eur Heart J Cardiovasc Imaging 2023;25(1):75–85.
[21] Peretto G, Barison A, Forleo C, Di Resta C, Esposito A, Aquaro GD, et al. Late gadolinium enhancement role in arrhythmic risk stratification of patients with *LMNA* cardiomyopathy: results from a long-term follow-up multicentre study. Europace 2020;22(12):1864–72.
[22] Delhommeau P, Marleau L, Kyndt F, Beaufils A, Fresse KW, Serfaly JM, et al. The added value of contrast-enhanced cardiac magnetic resonance to predict positive genetic testing in clinically suspected Lamin A/C cardiomyopathy. Eur Heart J 2020;41:2044–50.
[23] Hasselberg NE, Edvardsen T, Petri H, Berge KE, Leren TP, Bundgaard H, et al. Risk prediction of ventricular arrhythmias and myocardial function in Lamin A/C mutation positive subjects. Europace 2014;16(4):563–71.
[24] Fontana M, Barison A, Botto N, Panchetti L, Ricci G, Milanesi M, et al. CMR-verified interstitial myocardial fibrosis as a marker of subclinical cardiac involvement in *LMNA* mutation carriers. JACC Cardiovasc Imaging 2013;6(1):124–6.
[25] Holmström M, Kivistö S, Heliö T, Jurkko R, Kaartinen M, Antila M, et al. Late gadolinium enhanced cardiovascular magnetic resonance of lamin A/C gene mutation related dilated cardiomyopathy. J Cardiovasc Magn Reson 2011;13(1):30.
[26] Koikkalainen JR, Antila M, Lötjönen JMP, Heliö T, Lauerma K, Kivistö SM, et al. Early familial dilated cardiomyopathy: identification with determination of disease state parameter from cine MR image data. Radiology 2008;249(1):88–96.
[27] Raman SV, Sparks EA, Baker PM, McCarthy B, Wooley CF. Mid-myocardial fibrosis by cardiac magnetic resonance in patients with lamin A/C cardiomyopathy: possible substrate for diastolic dysfunction. J Cardiovasc Magn Reson 2007;9(6):907–13.
[28] Smith GC, Kinali M, Prasad SK, Bonne G, Muntoni F, Pennell DJ, et al. Primary myocardial dysfunction in autosomal dominant EDMD. A tissue doppler and cardiovascular magnetic resonance study. J Cardiovasc Magn Reson 2006;8(5):723–30.
[29] Peretto G, Sala S, Benedetti S, Di Resta C, Gigli L, Ferrari M, et al. Updated clinical overview on cardiac laminopathies: an electrical and mechanical disease. Nucleus 2018;9(1):380–91.
[30] Lukas Laws J, Lancaster MC, Ben Shoemaker M, Stevenson WG, Hung RR, Wells Q, et al. Arrhythmias as presentation of genetic cardiomyopathy. Circ Res 2022;130(11):1698–722.