ESC European Society of Cardiology

European Journal of Heart Failure (2026) **28**, 278–287
https://doi.org/10.1093/ejhf/xuaf030

RESEARCH ARTICLE

Clinical characteristics and outcomes of cardiomyopathies related to immune-mediated diseases

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Received 15 June 2025; revised 4 September 2025; accepted 12 November 2025; online publish-ahead-of-print 2 February 2026

Abstract

Aims Dilated cardiomyopathy (DCM) encompasses genetic and acquired aetiologies, yet the impact of immune-mediated mechanisms remains unclear. This study investigates the clinical characteristics and outcomes of immune-mediated DCM (ID-CMP).

Methods From the Maastricht Cardiomyopathy registry, 194 patients with ID-CMP were compared with 678 non-immune DCM controls over a median follow-up of 5.2 (3.7–10.7) years. ID-CMP was categorized into autoimmune-mediated (adaptive immunity dysfunction), autoinflammatory-driven (innate immunity dysfunction), and mixed-pattern (MHC Class I associations and autoinflammatory components). Patients with features of >1 category were classified as overlapping-CMP. Echocardiographic and genetic data were collected. Cox regression assessed major adverse cardiovascular events (MACE: cardiac mortality, heart failure hospitalization, life-threatening arrhythmias). Left ventricular ejection fraction (LVEF) trajectories were analysed using linear mixed-effects models. Findings were validated in an independent cohort of 201 ID-CMP patients.

Results ID-CMP was associated with a higher risk of MACE [HR: 1.68 (1.1–2.5), $P = .012$] after adjustment for age, sex, and baseline LVEF, confirmed in an external validation cohort [HR:2.40 (1.6–3.5), $P < .001$]. LVEF was lower in ID-CMP during the first year but converged with non-immune DCM thereafter ($P_{0–1year} = .018$; $P_{>1year}$ = ns). Outcomes did not differ among ID-CMP subtypes. Inflammation on EMB was related to worse clinical outcome [HR:2.0 (1.1–3.6), $P = .017$]. Pathogenic DCM gene variants were equally frequent in ID-CMP and non-ID-CMP patients (22% vs 20%, P = ns).

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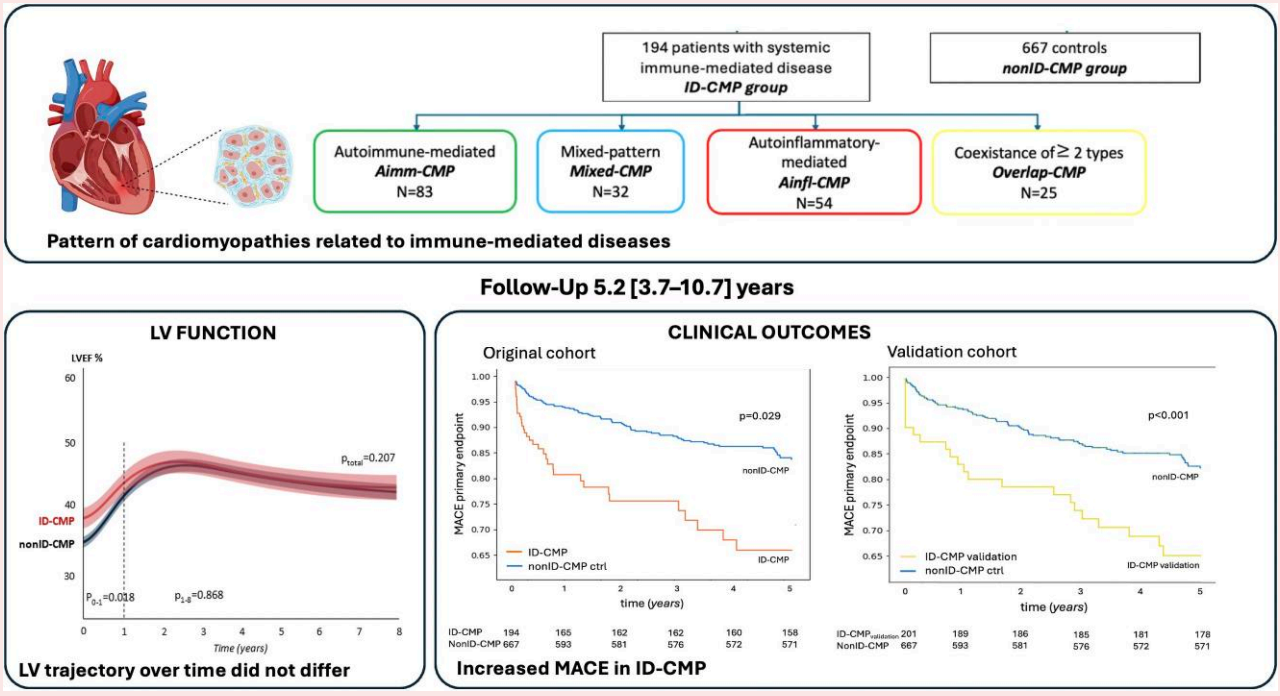
Conclusion ID-CMP patients have a higher risk of MACE despite similar LVEF trajectories, as confirmed in a validation cohort. Cardiac immune cell infiltration suggests an inflammatory substrate independent of genetics.

Graphical abstract



Above: From the Maastricht Cardiomyopathy registry, 194 patients with ID-CMP were compared with 678 non-immune DCM (nonID-CMP) controls over a median follow-up of 5.2 (3.7–10.7) years. The ID-CMP was further categorized into three groups: the autoimmune-mediated group (AImm-CMP, linked to adaptive immunity dysfunction), the autoinflammatory-driven group (AInfl-CMP, associated with innate immunity dysfunction), and the mixed-pattern group (Mixed-CMP, with MHC class I associations and autoinflammatory components). Patients exhibiting features of more than one category were classified separately as the overlapping-CMP (Overlap-CMP) group. Below: Left: ID-CMP patients had worse LVEF in the first year compared with nonID-CMP patients, but this difference resolved over time ($P_{0–1year}$ = .018; $P_{>1year}$ = ns). Below, middle and right: ID-CMP was associated with a higher risk of major cardiovascular adverse events, defined as a composite endpoint of cardiac mortality, heart failure hospitalization, life-threatening arrhythmias, after adjustment for age, sex, and baseline LVEF [log-rank P = .029, HR 1.68 (1.1–2.5), P = .012] (middle). This finding was confirmed in an external validation cohort [log-rank P < .001, HR 2.40 (1.6–3.5), P < .001] (right). DCM, dilated cardiomyopathy; HR, hazard ratio; ID-CMP, immune-mediated cardiomyopathy; LVEF, left ventricular ejection fraction.

Keywords Inflammatory cardiomyopathy • Heart failure • Autoimmune disease • Ejection fraction

Introduction

Dilated cardiomyopathy (DCM) represents a heterogeneous group of disorders with diverse aetiologies and varying degrees of myocardial dysfunction, often culminating in heart failure with a poor prognosis. The aetiologies include both genetic and acquired factors, with pathogenic variants in cardiomyopathy-associated genes and inflammatory processes being among the most common contributors.[1] The diverse underlying mechanisms that ultimately lead to reduced left ventricular ejection fraction (LVEF) may significantly contribute to the variability in treatment responses observed across clinical trials.[1] Traditionally, heart failure classification has been based on the extent of LVEF reduction, irrespective of aetiology. While this simplified approach has facilitated trial design and guided therapies targeting compensatory mechanisms of systolic dysfunction, there is growing recognition of the need for individualized treatment strategies that target the underlying aetiology.[1] Identifying specific patient subgroups could therefore offer valuable insights for optimizing clinical practice, refining trial design, and tailoring therapeutic approaches.

Emerging approaches in precision medicine include the identification of genetic predisposition and the evaluation of inflammatory contributions—either as primary drivers or in the context of systemic autoimmune disease. Recent advances in machine learning have identified inflammatory cardiomyopathies as distinct phenogroups with unique molecular signatures, emphasizing the importance of tailored management.[2] In particular, a distinct subgroup of patients with non-ischaemic DCM has been characterized by female predominance, the presence of systemic autoimmune diseases, lower body mass index (BMI), and impaired renal function.[2]

Immune-mediated diseases, classified as either autoimmune (driven by aberrant adaptive immune responses and autoantibodies) or autoinflammatory (due to primary innate immune dysfunction, typically presenting with

systemic inflammation), play a key role in the pathogenesis of DCM by affecting myocardial structure and function.[3] Cardiac involvement in these conditions often manifests as varying degrees of LVEF impairment.[1,3] Significant gaps remain in understanding and managing cardiac involvement in DCM associated with systemic immune-mediated diseases.

This study aims to investigate the clinical characteristics and outcomes of patients with immune-mediated diseases in presence of a cardiomyopathy (ID-CMP), focusing on patients with systemic autoimmune and/or autoinflammatory diseases according to the European Society of Cardiology (ESC) consensus paper classification, when compared with controls without immune-mediate disease (nonID-CMP).[3] Specifically, we will examine and compare: (i) long-term LVEF trajectories; (ii) differences in clinical outcomes; and (iii) disparities in clinical, histological, and genetic characteristics.

Methods

Population selection

The study included non-ischaemic, non-valvular DCM patients from the Maastricht Cardiomyopathy Registry (mCMP registry, NCT04976348), a prospective registry at MUMC + enrolling individuals with heart failure-like symptoms referred for cardiac/genetic testing (April 2004–April 2021). Details about patients' inclusion and exclusion criteria in the registry have been previously reported.[4] Approved by the institutional ethics committee, the study adhered to the Declaration of Helsinki.

Of 1036 registry patients, 912 underwent endomyocardial biopsy (EMB) within 90 days from inclusion were analysed. Forty patients were excluded due to relevant coronary artery disease (*Figure 1*). The final cohort (n = 872) was screened for immune-mediated or systemic autoinflammatory diseases. Patients meeting these criteria were classified as ID-CMP, while others formed the nonID-CMP control group. Among 872 patients, 194 (22%) were classified as ID-CMP and further categorized as defined in the ESC consensus statement[3]: autoimmune-mediated systemic disease (AImm-CMP, n = 83, 43%, i.e. non-organ-specific autoimmune systemic diseases linked to adaptive immunity dysfunction); mixed-pattern systemic disease (mixed-pattern-CMP, n = 32, 16%, i.e. diseases with MHC Class I associations and autoinflammatory components); autoinflammatory-mediated systemic disease (AInfl-CMP, n = 54, 29%, i.e. associated with innate immunity dysfunction), and Overlap-CMP (n = 25, 13%, i.e. overlapping features of autoimmune- and autoinflammatory-mediated disease). No cases of rare monogenic autoimmune or autoinflammatory diseases were identified (*Figure 1*).

The validation cohort included 201 patients with cardiomyopathies and systemic autoimmune/autoinflammatory diseases from registries in Trieste (Italy), Madrid (Spain), and Zurich (Switzerland), using similar inclusion/exclusion criteria. Of these, 21 (10%) had autoimmune-mediated disease, 5 (2%) had a mixed pattern, and 176 (88%) had autoinflammatory-mediated disease.

Echocardiographic data

All transthoracic echocardiography were reviewed for accuracy by expert staff blinded to group allocation after retrieval from the hospital system. Left ventricular ejection fraction measurements were obtained at baseline and subsequently on an annual basis. Measurements were retrieved from standard long-axis and apical views. Left ventricular ejection fraction was measured using the Simpson method, and when this was not possible, the Teichholz method was used.

Endomyocardial biopsy

Endomyocardial biopsy was obtained from the right ventricular septum via the internal jugular vein using a transcatheter bioptome (Cordis, Miami, FL,

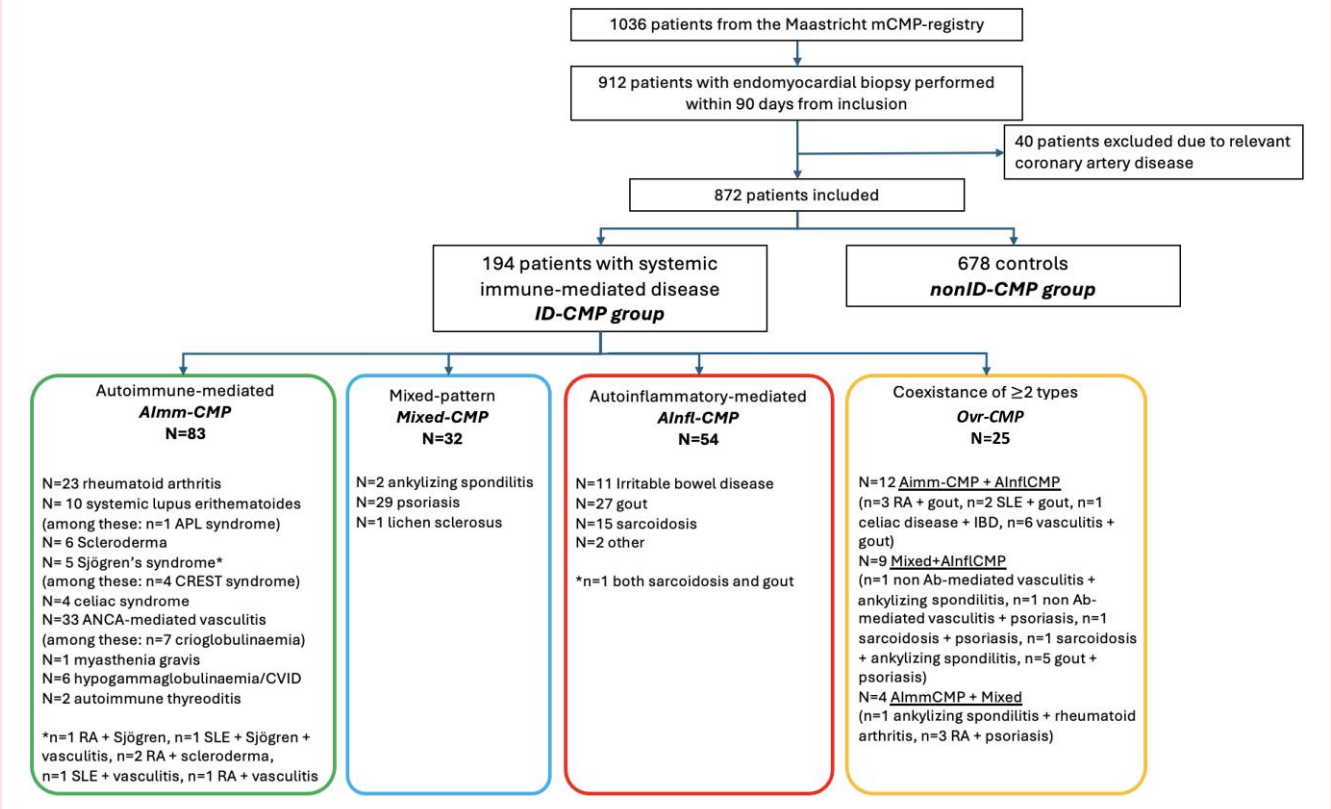


Figure 1 Flow chart of the population included in this study

USA) in the setting of a routine diagnostic procedure for DCM in all included patients. Three specimens were utilized for immunohistological analysis according to a pre-specified protocol, as previously described.[5] $CD3^+$, $CD4^+$, $CD8^+$, $CD45^+$, and $CD68^+$ were investigated. Inflammation was histologically defined as ≥14 leucocytes ($CD45^+$ positive cells) on EMB and/or ≥7 $CD3^+$ leucocytes.[6]

Outcome

As primary outcome a composite endpoint of cardiac mortality, hospitalization for heart failure, and life-threatening ventricular arrhythmia (defined as nonfatal ventricular arrhythmia leading to hospitalization, haemodynamic unstable sustained ventricular tachycardia, and/or sustained ventricular tachycardia with appropriate defibrillator-induced electrical shocks) was considered. As secondary outcome, the single endpoints of cardiac mortality, hospitalization for heart failure, and life-threatening ventricular arrhythmia were considered.

Genetic data

Genetic testing was performed by using targeted next-generation sequencing panels, including 48 cardiomyopathy-associated genes.[5] All genetic variants were classified according to the latest ACMG guidelines.[7]

Statistical analyses

Continuous variables are reported as mean ± standard deviation (SD) or median [interquartile range (IQR)] and compared using Student's *t*-test or Mann–Whitney *U* test. Categorical variables are presented as frequencies (%) and analysed using χ^2 or Fisher's exact test. Left ventricular ejection fraction trajectories were compared between ID-CMP and controls using linear mixed-effects analysis of variance (ANOVA) for repeated measurements, with between-group comparisons. Left ventricular ejection fraction variability over time was assessed via SD and IQR distribution. Survival analyses were conducted using Kaplan–Meier curves with log-rank tests. Cox regression, adjusted for age, gender, baseline LVEF, and New York Heart Association (NYHA) class, high-sensitivity troponin-T, and BMI, as appropriated, was performed. A two-way ANOVA with Tukey post hoc analysis tested for interactions. Statistical analyses were performed using SPSS (v28.0.1), Python (v3.9.7), and R Studio (v2023.12). A two-sided *P*-value <.05 was considered significant.

Model performance was assessed via C-statistic (area under the curve), with cohort comparisons using Hanley and McNeil's and DeLong's tests. Discrimination and reclassification were evaluated with Integrated Discrimination Improvement and Net Reclassification Improvement. Model fit was assessed using likelihood ratio test, Akaike Information Criterion, and Bayesian Information Criterion from Cox regression models.

Results

Population characteristics

Baseline characteristics of ID-CMP and nonID-CMP patients are summarized in *Table 1*. Age and gender were similar between groups. The ID-CMP patients had lower BMI but a higher prevalence of diabetes, while other cardiovascular risk factors did not differ. Heart failure therapy with beta-blockers and mineral-receptor antagonists was more common in nonID-CMP, whereas ID-CMP patients received more immunosuppressive therapy, as expected. Inflammatory markers [C-reactive protein (CRP)] were elevated, and haemoglobin was lower in ID-CMP, with no differences in N-terminal pro–B-type natriuretic peptide (NT-proBNP), high-sensitivity Troponin-T (hs-TnT), or creatinine clearance. Immunosuppressive therapy use varied significantly among ID-CMP subgroups, being highest in Overlap-CMP and Almm-CMP and lowest in mixed-pattern CMP ($P = .001$). Corticosteroid use also differed ($P = .002$, *Table 2*). Among the patients in the nonID-CMP group who received corticosteroid therapy ($n = 18$), 14 were treated due to myocardial inflammation confirmed by EMB, 2 for asthma, and 2 for nephrogenic systemic fibrosis.

Characteristics of the derivation and validation cohort are presented in Supplementary Table S1.

Left ventricular ejection fraction trajectory

Baseline echocardiographic parameters were comparable between ID-CMP and nonID-CMP patients (*Table 1*). NonID-CMP patients had lower LVEF in the first year, but differences diminished over time ($P_{0–1year} = .018$; $P_{1–5years}$ and P_{total} = ns; *Figure 2*). To account for single variation over time among the groups, SD and IQR over years for both groups have been calculated: LVEF variation was similar between groups [ID-CMP: mean SD 7.7 (4.5–10.6), mean IQR 9.2 (4.5–12.5); nonID-CMP: mean SD 7.6 (4.2–10.7), mean IQR 9.3 (4–13)].

Outcome

The median follow-up duration was 5.2 years (3.7–10.7).[5] The primary clinical outcome (composite endpoint of cardiac mortality, hospitalization for heart failure, and life-threatening ventricular arrhythmia) occurred more frequently in ID-CMP than nonID-CMP (ID-CMP: 46 events, 24% vs nonID-CMP: 116 events, 17%, $P = .029$). ID-CMP was independently associated with adverse outcomes after adjusting for age, gender, baseline LVEF, and NYHA class [hazard ratio (HR) 1.78 (1.2–2.7), $P = .006$; *Figure 3A*]. No significant interactions were observed between ID-CMP and age, gender, LVEF, or NYHA class. The results remained significant after considering baseline differences in therapy such as RAAS blockade and beta-blocker [HR 1.56 (1.03–2.37), $P = .035$] and comorbidities such as diabetes, hypertension, and hypercholesterinaemia [HR 1.6 (1.1–2.32), $P = .013$; Supplementary Table S2].

The presence of myocardial inflammation on EMB was independently associated with the primary clinical composite outcome after adjusting for related cofounding factors such as age, gender, BMI, and high-sensitivity troponin [HR 2.0 (1.1–3.6), $P = .017$; *Figure 4*].

Secondary endpoints showed increased heart failure hospitalization in ID-CMP (13% vs 8%, $P = .047$), while cardiac mortality (14% vs 11%, $P = .590$) and life-threatening ventricular arrhythmias (7% vs 5%, $P = .255$) were similar. However, ID-CMP was not associated with any of the secondary endpoints individually in multivariate analysis.

In subgroup analyses, primary endpoint rates were similar across ID-CMP subtypes (Almm-CMP: 24%, Alnfl-CMP: 26%, mixed-pattern-CMP: 16%, overlap-CMP: 28%; $P > .1$; Supplementary Figure S1). Cardiac mortality and heart failure hospitalizations also showed no significant differences ($P > .7$).

Validation cohort

The validation cohort confirmed increased composite adverse outcomes in ID-CMP [major adverse cardiovascular event (MACE) $ID\text{-}CMP_{validation}$: 60 events, 30% vs nonID-CMP: 116 events, 17%, $P < .001$; *Figure 3B*]. As observed in the derivation cohort, this difference was primarily driven by a higher rate of heart failure hospitalizations in the $ID\text{-}CMP_{validation}$ group (44 events, 22%). ID-CMP remained independently associated with poor outcomes in the validation cohort [HR 2.40 (1.6–3.5), $P < .001$].

Endomyocardial biopsy

$CD3^+$ counts were available in $n = 801$, $CD45^+$ in 833, and $CD68^+$ in 778 patients. $CD3^+$ [4.7 (2.6–8.3) vs 4.2 (2.3–7.3), $P = .038$], $CD45^+$ [7.0 (4.3–12) vs 6.7 (4–11.2), $P = .018$], and $CD68^+$ [2.1 (1–5.6) vs 1.8 (0.8–3.8), $P = .003$] counts were higher in ID-CMP (*Table 3*). No differences were observed in $CD4^+$ or $CD8^+$. Counts of $CD3^+$, $CD45^+$,

Table 1 Baseline characteristics of the patients with nonID-CMP compared with patients with ID-CMP

	NonID-CMP controls $n = 667$	ID-CMP group $n = 194$	*P*-value
Age	56.6 (47–63)	58.1 (50–65)	.229
Body mass index	26 (23–30)	25.5 (23–29)	<.001
Female gender	240 (36)	70 (36)	1
Comorbidities			
Diabetes mellitus	76 (11)	36 (19)	.016
Hypertension	189 (28)	62 (32)	.372
Hypercholesteraemia	76 (11)	21 (11)	.898
COPD	76 (11)	18 (9)	.435
Supraventricular arrhythmia	120 (18)	42 (21)	.298
Clinical presentation			
NYHA class			.034
NYHA 1	291 (43)	63 (33)	
NYHA 2	247 (36)	79 (41)	
NYHA 3	81 (12)	29 (15)	
NYHA 4	7 (1)	6 (3)	
Hypervolaemia	62 (9)	28 (14)	.061
Palpitations	110 (16)	25 (13)	.215
Flu symptoms	23 (3)	10 (5)	.532
Medications			
Beta-blockers	460 (69)	112 (57)	.002
ACE inhibitors	355 (53)	92 (47)	.165
Sartans	109 (16)	32 (17)	.911
MRAs	234 (35)	47 (24)	.004
ARNIs	32 (5)	4 (2)	.105
Loop diuretics	296 (44)	81 (41)	.462
Thiazides	41 (6)	6 (3)	.147
Ca-antagonists	54 (8)	18 (9)	.556
SGLT2 inhibitors	17 (3)	2 (1)	.273
Colchicine	5 (1)	4 (2)	.107
Immunosuppression	22 (3)	48 (25)	<.001
Corticosteroids	18 (3)	38 (21)	<.001
Laboratory tests			
Haemoglobin, g/dl	8.7 (7.7–9.5)	8.1 (7–9.1)	.003
Thrombocytes, G/l	245 (198–308)	261 (187–321)	.700
Leucocytes, G/l	7.9 (7.7–9.5)	8 (6.4–10.1)	.829
Hs-TnT, ng/l	20.5 (9–58.3)	21.5 (6–86)	.563
C-reactive protein, mg/l	6 (3–19.5)	8.7 (4–26)	.044
NT-proBNP, ng/l	152 (54–451)	200 (55–750)	.300
eGFR, ml/min/1.73 m^2	66.5 (54.9–80.6)	64.2 (40.4–77)	.145
Echocardiography			
LVEF at inclusion	34.8 (25–43)	39.3 (26–45)	.015
EDVI, ml/m^2	82.9 (63.1–102.6)	74.7 (63.1–95.6)	.141
LVMI final	101.6 (83–124)	102.2 (81–122)	.08
LAVI, ml/m^2	39.2 (32–52)	39.1 (29–54)	.136
RA volume, ml	60 (42–82)	60 (42–78)	.193
PAP, mm Hg	21.2 (18–25)	21.2 (19–29)	.558
E/*e*′ average	9.5 (7–13)	8.6 (7–12)	.181
TAPSE, mm	19 (16–23)	18 (15–22)	.265
LV GLS	−12.2 (−15 to 9)	−11.3 (−16 to 8)	.661

ACE, angiotensin-converting enzyme; ARNI, angiotensin receptor neprilysin inhibitors; COPD, chronic obstructive pulmonary disease; EDVI, end-diastolic volume indexed for body surface area; GLS, global longitudinal strain; LAVI, left atrial volume indexed for body surface area; LV, left ventricular; LVMI, left ventricular mass volume indexed for body surface area; MRA, mineral-receptor antagonists; PAP, pulmonary artery pressure; RA, right atrial; SGLT2, sodium-glucose cotransporter 2; TAPSE, tricuspid annular plane systolic excursion.

Table 2 Baseline characteristics of the patients with ID-CMP based on subgroups

	AImm-CMP $n = 83$	Mixed-pattern CMP $n = 32$	AInfl-CMP $n = 54$	Ovr-CMP $n = 25$	*P*-value
Age	57 (45–66)	56 (52–63)	56 (46–62)	58 (54.5–66)	.309
Body mass index	23.3 (21.4–27)	26.2 (24.8–31.2)	26.8 (24.4–30.4)	27.0 (24.2–29.1)	<.001
Female gender	36 (43)	9 (28)	16 (30)	8 (32)	.137
Comorbidities					
Diabetes mellitus	14 (16)	5 (14)	16 (24)	10 (40)	.482
Hypertension	24 (27)	11 (31)	26 (38)	13 (52)	.512
Hypercholesteraemia	8 (9)	2 (6)	11 (16)	5 (20)	.272
COPD	6 (7)	6 (17)	6 (9)	2 (8)	.353
Supraventricular arrhythmia	20 (23)	3 (8)	24 (36)	7 (28)	.016
Clinical presentation					
NYHA class					.212
NYHA 1	22 (25)	16 (44)	25 (36)	9 (38)	
NYHA 2	36 (41)	13 (36)	30 (44)	10 (42)	
NYHA 3	15 (17)	5 (14)	8 (12)	3 (13)	
NYHA 4	6 (7)	0	0	2 (8)	
Hypervolaemia	14 (16)	2 (6)	12 (17)	5 (21)	.273
Palpitations	7 (8)	7 (19)	11 (16)	3 (13)	.142
Flu symptoms	5 (6)	1 (3)	4 (6)	1 (4)	.716
Medications					
Beta-blockers	43 (52)	22 (69)	33 (61)	13 (57)	.240
ACE inhibitors	36 (43)	17 (53)	25 (46)	14 (61)	.634
Sartans	12 (15)	5 (16)	9 (17)	5 (22)	.952
MRAs	18 (22)	8 (25)	14 (26)	6 (26)	.960
ARNIs	2 (2)	2 (6)	0	0	.199
Loop diuretics	12 (15)	4 (13)	6 (11)	13 (57)	.434
Thiazides	3 (4)	1 (3)	0	2 (9)	.607
Ca-antagonists	8 (10)	5 (16)	3 (6)	1 (4)	.298
SGLT2 inihibitors	2 (2)	0	0	0	.428
Colchicine	2 (2)	0	0	2 (9)	.063
Immunosuppression	27 (33)	1 (3)	10 (19)	10 (43)	.001
Corticosteroids	22 (30)	1 (3)	6 (12)	9 (39)	.002
Laboratory tests					
Haemoglobin, g/dl	7.9 (6.9–8.9)	10 (8.2–9.7)	9.1 (8.1–9.7)	8.4 (7.85–9.03)	<.001
Thrombocytes, G/l	272 (205–331)	260 (193–300)	228 (175–280)	220 (182.5–271)	.015
Leucocytes, G/l	7.9 (6.5–10.1)	7.1 (6–8.8)	7.5 (5.7–9.7)	7.8 (6.65–10.45)	.561
Hs-TnT, ng/l	21.5 (6–72.5)	11 (7–18)	21 (7.8–44.5)	16.5 (0–74.5)	.606
C-reactive protein, mg/l	7 (2.7–23)	6.7 (3.2–20.3)	5.3 (3.7–13.5)	7.5 (4–23.75)	.917
NT-proBNP, ng/l	156 (28–820)	87 (29–193)	140 (47–361)	167 (55.2–300)	.525
eGFR, ml/min/1.73 m^2	61.8 (48.1–80.9)	77 (71.7–81.3)	64.2 (51.5–69.1)	46.5 (40.4–69.7)	.294
Echocardiography					
LVEF at inclusion	40.3 (28.1–46.2)	38.8 (35–40.9)	32.2 (22.6–43.8)	40.0 (30.0–48.0)	.022
EDVI, ml/m^2	114 (100–141)	140 (113–158)	132 (91–156)	84.6 (64.4–123.3)	.432
LVMI, g/m^2	99 (77–120)	110 (87–137)	102 (82–123)	107.2 (80.4–123.5)	.405
LAVI, ml/m^2	36.3 (29–47.1)	42 (29.9–47.7)	41.5 (29.1–65.7)	44.2 (28.2–64.3)	.374
RA volume, ml	55.5 (40.3–77)	62 (42–73)	65 (39–92)	60 (44.5–116.5)	.694
E/e′ average	7.7 (7–11.7)	8.3 (7.6–17.7)	8.2 (6.2–12.1)	9.3 (7.89–12.96)	.358
TAPSE, mm	20.5 (17.3–23)	17 (15–18.8)	17 (15–20.8)	16.0 (14.0–20.75)	.064
LV GLS	−12.6 (−16.8/−8.5)	−9.8 (−13.5/−6.9)	−11.4 (−14/−8.1)	−10.25 (16.05–6.83)	.554

Comparisons were made with the Kruskal-Wallis Test for independent samples or with the Pearson's Chi-square, as appropriate.
ACE, angiotensin-converting enzyme; ARNI, angiotensin receptor neprilysin inhibitors; COPD, chronic obstructive pulmonary disease; EDVI, end-diastolic volume indexed for body surface area; GLS, global longitudinal strain; LAVI, left atrial volume indexed for body surface area; LV, left ventricular; LVMI, left ventricular mass volume indexed for body surface area; MRA, mineral-receptor antagonists; PAP, pulmonary artery pressure; RA, right atrial; SGLT2, sodium-glucose cotransporter 2; TAPSE, tricuspid annular plane systolic excursion.

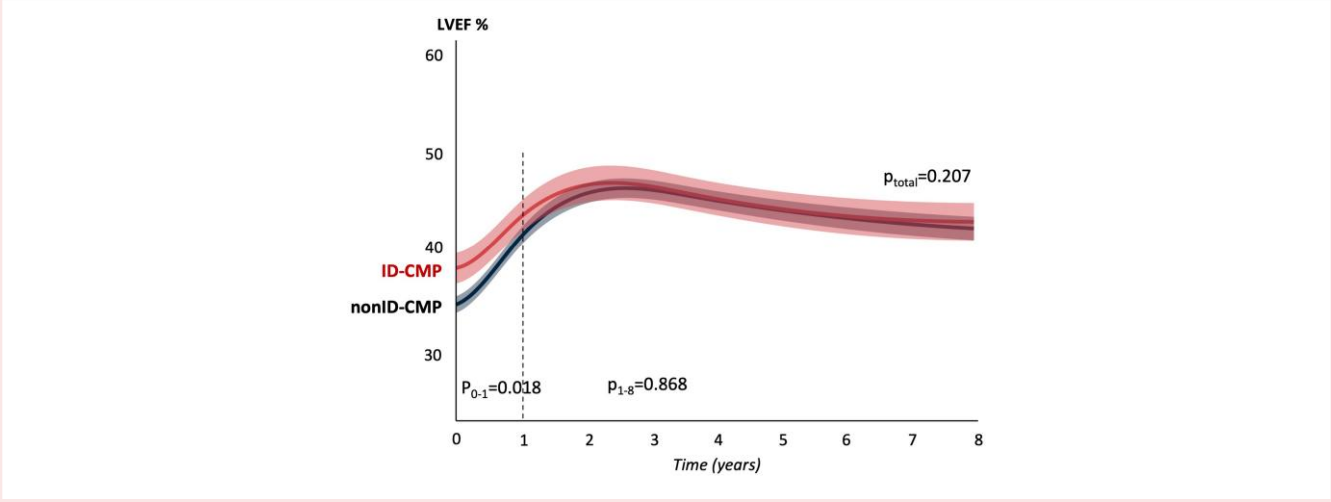


Figure 2 Long-term left ventricular ejection fraction trajectories in ID-CMP and nonID-CMP patients. Longitudinal left ventricular ejection fraction trajectories in patients with immune-mediated disease cardiomyopathy (ID-CMP, red) and nonID-CMP controls (black) over an 8-year follow-up period. Shaded areas represent 95% confidence intervals. During the first year, ID-CMP patients exhibited significantly lower left ventricular ejection fraction than controls ($P_{0–1year}$ = .018). However, this difference diminished over time, with no significant differences observed from Years 1 to 5 ($P_{1–8years}$ = .868) or overall (P_{total} = .207). Left ventricular ejection fraction variation over time was comparable between groups

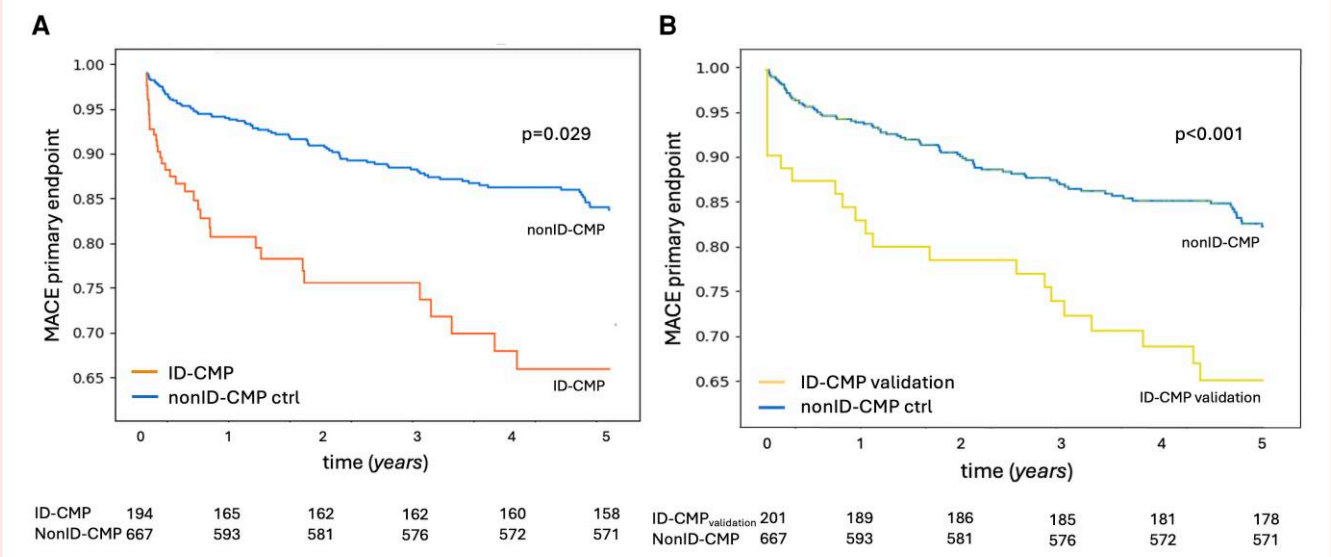


Figure 3 Survival analyses for the primary endpoints in patients with ID-CMP compared with patients in the nonID-CMP group in the derivation cohort (A) and in the validation cohort (B). (A) The primary composite endpoint (cardiac mortality, heart failure hospitalization, and life-threatening ventricular arrhythmia) occurred more frequently in the ID-CMP group than in nonID-CMP controls [24% (n = 47) vs 17% (n = 116), P = .029). Cox regression, adjusted for age, gender, left ventricular ejection fraction, and New York Heart Association class showed a significant association between ID-CMP and increased risk of adverse events [hazard ratio 1.78 (1.2–2.7), P = .006]. (B) The primary endpoint of major adverse cardiovascular event was more frequently reached in the validation cohort of ID-CMP patients compared with nonID-CMP controls [ID-CMP$_{validation}$: 30% (n = 60) vs nonID-CMP: 17% (n = 116), P < .001]. In Cox regression analyses, after adjustment for age, gender, and left ventricular ejection fraction at inclusion, the presence of ID-CMP remained significantly associated with an increased HR for the primary outcome [hazard ratio 2.40 (1.6–3.5), P < .001]

and CD68$^+$ were independently associated with ID-CMP after correction for age and LVEF [CD3$^+$: odds ratio (OR) = 1.003 (1–1.006), P = .024; CD45$^+$: OR = 1.004 (1.001–1.006), P = .004; CD68$^+$: OR = 1.009 (1.004–1.013), P < .001]. No differences were found in subgroup analyses (Supplementary Table S3).

The presence of myocardial inflammation on EMB was related to the diagnosis of autoimmune systemic disease [CD3$^+$: r = 0.076 (0.01–0.14), P = .032; CD45$^+$: r = 0.03, (0.02–0.15), P = .016] as well as to elevated high-sensitivity troponin T [both CD3$^+$: r = 0.38 (0.29–0.46), P < .001, and CD45$^+$: r = 0.49 (0.42–0.56), P < .001].

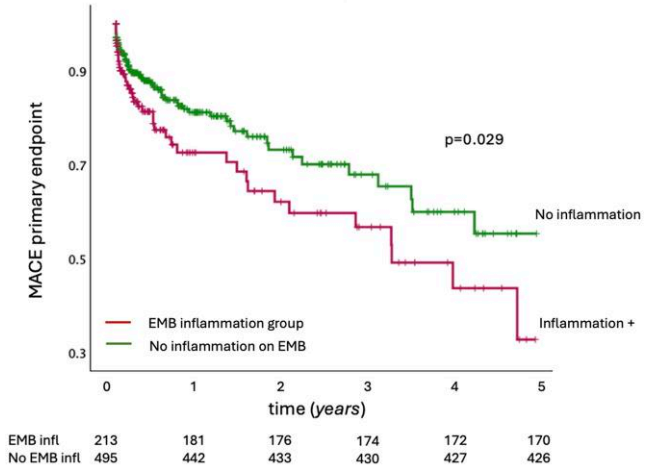


Figure 4 The composite primary endpoint occurred in 21% ($n = 44$) of patients presenting with inflammation on endomyocardial biopsy and in 14% ($n = 70$) of patients without inflammation on endomyocardial biopsy, Log-rank $P = .029$

Table 3 Endomyocardial biopsies immunohistochemistry findings in ID-CMP versus non-ID-CMP patients

	NonID-CMP controls $n = 641$	ID-CMP group $n = 183$	*P*-value
$CD3^+$ ($n = 631/170$)	4.2 (2.3–7.2)	4.7 (2.6–8.3)	.038
$CD4^+$ ($n = 603/173$)	2 (1–3.9)	2.2 (0.97–4.6)	.329
$CD8^+$ ($n = 651/176$)	2.2 (1.1–4.1)	2.3 (1.1–4.9)	.653
$CD45^+$ ($n = 653/179$)	6.9 (3.9–11.1)	7.0 (4.3–12)	.018
$CD68^+$ ($n = 608/169$)	1.8 (0.8–3.8)	2.1 (1–5.6)	.003

Immunohistochemical analysis of inflammatory cell markers in endomyocardial biopsy samples from patients with ID-CMP and nonID-DCM controls. The number of biopsies analysed for each marker is indicated in parentheses. Values are presented as medians with interquartile ranges (IQR).
ID-CMP, immune-mediated dilated cardiomyopathy.

Genetic testing

Genetic testing was conducted in 60% of ID-CMP patients and 57% of nonID-CMP controls. Pathogenic or likely pathogenic variants were found in 22% of ID-CMP, with truncating *TTN* variants (TTNtv) as the most common (29%), and in 20% of nonID-CMP (of which 50% was TTNtv).

Discussion

Our study shows that patients with ID-CMP have a higher risk for MACE compared with nonID-CMP, irrespective of age, gender and baseline LVEF, therapy, or comorbidities. Similarly, the presence of myocardial inflammation on EMB was related to adverse clinical outcome after correction for cofounding factors. Although ID-CMP patients have a steeper increase of LVEF in the first year after treatment, the dynamic trajectory of LVEF over time is comparable. There are significant higher numbers of $CD3^+$, $CD45^+$, and $CD68^+$ cells in the hearts of ID-CMP patients, and the genetic yield of (likely) pathogenic DCM-associated genes is comparable between ID-CMP and nonID-CMP patients.

Left ventricular ejection fraction trajectory and outcomes of ID-CMP

Systemic immune-mediated diseases represent a heterogeneous spectrum of immune disorders characterized by either systemic inflammation or mainly driven by innate immunity derangements. These diseases are often accompanied by varying degrees of myocardial involvement, even among asymptomatic individuals.[3] Despite the absence of studies advocating for systematic cardiac screening, myocardial involvement is frequently associated with a poorer prognosis in patients with systemic immune-mediated diseases.[3]

This is the first study to systematically investigate clinical outcomes in patients with systemic immune-mediated diseases and coexisting cardiomyopathy (ID-CMP). Our findings demonstrate that despite similar long-term LVEF trajectories between ID-CMP and nonID-CMP patients, those with ID-CMP experience significantly worse long-term cardiovascular outcomes. Previous studies have primarily focused on acute myocarditis or short-term outcomes in patients with systemic immune-mediated diseases, leaving a gap in understanding their long-term cardiac prognosis.[8] Our study addresses this gap by showing that the presence of an immune-mediated disease in patients with cardiomyopathy is associated with an increased risk of adverse events, independent of LVEF recovery. These findings align with prior research demonstrating that myocardial involvement in systemic immune-mediated diseases is linked to increased mortality, even when LVEF is preserved. For instance, in patients with systemic sclerosis, myocardial involvement has been associated with worse outcomes, independent of LVEF.[9] Similarly, cardiac involvement is a leading cause of mortality in systemic lupus erythematosus, highlighting the significant impact of immune-mediated cardiac disease beyond conventional markers of systolic function.[10] A previous study focused on patients with acute myocarditis, identifying an underlying autoimmune or autoinflammatory disorder in 7% of cases. Although some presented with severely reduced LVEF, mid-term outcomes (16 months) were favourable following immunosuppressive therapy, with LVEF differences resolving over

time.[11] In contrast, our study investigates patients with chronic systemic immune-mediated diseases rather than acute presentations, providing insights into long-term outcomes. Despite similar LVEF trajectories over time, ID-CMP patients exhibit a worse prognosis compared with nonID-CMP patients. These findings could suggest that persistent myocardial inflammation, rather than transient systolic dysfunction, plays a key role in myocardial disease progression.

Our findings on long-term outcomes were confirmed in an external, multicentric validation cohort, despite a higher proportion of patients with autoinflammatory systemic diseases in this cohort—conditions primarily driven by innate immune dysfunction. This validation is particularly relevant, as it suggests that the adverse prognosis in ID-CMP extends beyond adaptive immunity-related diseases and may be influenced by innate immune mechanisms, further supporting the role of persistent myocardial inflammation in disease progression.

Role of inflammation

Our study exclusively included patients who underwent EMB, allowing for a detailed histopathological assessment of myocardial inflammation. Elevated CRP levels, but mainly increased $CD3^+$, $CD45^+$, and $CD68^+$ immune cell counts in ID-CMP patients, provide evidence of persistent myocardial inflammation. Additionally, higher endomyocardial lymphocyte counts were independently associated with an ID-CMP diagnosis after adjusting for confounders, reinforcing the presence of a distinct inflammatory substrate. These findings align with prior research demonstrating that myocardial inflammation, characterized by increased $CD3^+$ and $CD68^+$ counts, is a common feature in DCM and is associated with a threefold increased risk of cardiac death or heart transplantation.[12] Machine-learning-based patient clustering has further shown that ID-CMP is distinguished by the activation of cardiac pro-inflammatory pathways compared with other DCM phenotypes.[2] Prolonged myocardial inflammation in response to injury is a recognized maladaptive mechanism, contributing to myocardial fibrosis, ventricular remodelling, and adverse cardiac outcomes, even in idiopathic DCM.[13,14] We found that increased inflammation on EMB at time of diagnosis was related to adverse clinical outcome.

Genetic background

In this study, the prevalence of pathogenic or likely pathogenic genetic variants was similar in ID-CMP and nonID-CMP patients, suggesting that there is a shared genetic background in line with our previous research.[15] Truncating *TTN* variants (TTNtv) were the most frequently observed mutations, consistent with previous studies reporting a high prevalence of TTNtv in patients with lymphocytic myocarditis, along with pathogenic mutations linked to arrhythmogenic cardiomyopathies such as *DSP* and *FLNC*.[16,17] Prior research has also shown that up to 18% of patients with DCM and cardiac inflammation carry a pathogenic or likely pathogenic variant in a DCM-associated gene, with inflammation being associated with earlier disease onset and thus a potential trigger for disease.[5,18] The similar genetic burden in both groups could suggest that the pathophysiological mechanisms associated with immune-mediated diseases (such as inflammation) can be a trigger in patients that unveil the DCM phenotype in those that are genetically susceptible.[19] Additionally, there is increasing evidence that genetic defects are associated with increased inflammation in the heart, of which *DSP* variants are a clear example.[20] Therefore, there might be an intrinsic interaction between inflammation and genetic susceptibility in those patients with a systemic immune-mediated disease that develop a DCM.

Clinical characteristics and outcomes in ID-CMP subgroups

Subgroup analyses showed no outcome differences between autoimmune (adaptive immunity-driven) and autoinflammatory diseases, despite the latter presenting with worse biventricular function. This reinforces the validity of our findings in the validation cohort, where a higher prevalence of autoinflammatory diseases suggests a role for innate immune mechanisms in ID-CMP progression. Histological analyses confirmed increased $CD3^+$, $CD45^+$, and $CD68^+$ immune cell infiltration in ID-CMP, independently associated with the ID diagnosis. The absence of differences in $CD4^+$, $CD8^+$, and $CD20^+$ counts suggests a broader inflammatory response rather than a specific T- or B-cell-driven process. Previous studies linked immune-mediated diseases to increased cardiovascular risk but did not distinguish between immune pathways.[21,22] Our findings indicate that both innate and adaptive immunity may contribute to myocardial involvement, with persistent inflammation playing a key role. Higher $CD3^+$ counts in ID-CMP align with reports of lymphocytic myocarditis in up to 10% of adaptive immunity disorders.[23,24] However, the lack of outcome differences between subgroups suggests additional mechanisms beyond T-cell-driven inflammation influence prognosis.

Limitations

This retrospective study includes prospectively enrolled patients, with potential inherent limitations. The classification of systemic immune-mediated diseases follows the ESC position statement but remains somewhat arbitrary, as it does not fully account for the potential continuum between different disease groups. EMB, performed per ESC recommendations, may have led to underestimating myocardial inflammation in milder ID-CMP cases. Despite a higher prevalence of autoinflammatory diseases in the validation cohort, consistent primary outcome results reinforce the study's robustness. Subgroup analyses showed no significant outcome differences between autoimmune and autoinflammatory conditions, supporting their collective consideration in ID-CMP, though underlying differences warrant further investigation. Due to the relatively small sample sizes within the ID-CMP, comparisons of the primary outcome within this subgroup should be interpreted with caution, as limited statistical power may affect the robustness of the findings.

Conclusions

This study systematically investigates long-term outcomes in ID-CMP, showing worse prognosis despite similar LVEF trajectories compared with nonID-CMP. The findings were confirmed in an external validation cohort, reinforcing the adverse prognosis in ID-CMP. These findings highlight the need for enhanced cardiovascular surveillance, including closer follow-up and tailored clinical management, and suggest that factors beyond left ventricular function contribute to disease progression.

Acknowledgements

The authors thank the support from A. Ferravante, mathematician, for helping with Python coding for implementing analyses.

Supplementary data

Supplementary data are available at *European Journal of Heart Failure* online.

Declarations

Disclosure of Interest

All authors declare no disclosure of interest for this contribution.

Data Availability

The data that support the findings of this study are available from the corresponding author upon reasonable request. Due to privacy and

ethical restrictions, individual-level patient data cannot be made publicly available.

Funding

This study was supported by the Rutishauser Travel grant from the Swiss Heart Foundation (Schweizerische Herzstiftung).

Ethical Approval

The study was approved by the institutional ethics committee of the Maastricht University Medical Centre.

Pre-registered Clinical Trial Number

NCT04976348.

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