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ORIGINAL RESEARCH

Insights Into the Natural History of Recurrent Myocarditis, A Multicenter International Study (Re-Myo Study)

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BACKGROUND: Recurrence of acute myocarditis (AM) is challenging. The management and natural history of patients who experience a recurrence of AM (Re-AM) remain poorly characterized. The aim of this study is to investigate clinical characteristics and outcomes of patients with Re-AM.

METHODS: In this international multicenter study, 141 consecutive patients with biopsy-proven or cardiac magnetic resonance-proven Re-AM (35 [26–45] years, 77% male, median left ventricular ejection fraction 55%) were investigated and compared with 372 consecutive patients with single acute myocarditis (S-AM). The primary outcome was a composite of all-cause mortality, heart transplant and major ventricular arrhythmias.

RESULTS: Patients with Re-AM had more frequently a family history of cardiomyopathy (19% in Re-AM versus 2.8% in S-AM, $P<0.001$) and a diffuse late gadolinium enhancement compared with patients with S-AM (46% in Re-AM versus 34% in S-AM, $P=0.019$). The extent of late gadolinium enhancement also increased between the first and the second AM episode in patients with Re-AM ($P=0.001$). During a median follow-up of 33 months (interquartile range, 23–52) patients with Re-AM had a higher risk of primary outcome ($P=0.001$) compared with patients with S-AM, as well as a significantly elevated competing risk of major ventricular arrhythmias ($P<0.001$), which remained independently associated even after adjustment (hazard ratio, 2.15 [95% CI, 1.15–4.04], $P=0.017$). A family history of cardiomyopathy, autoimmune diseases, and ring-like late gadolinium enhancement was independently associated with a higher risk of recurrent AM.

CONCLUSIONS: Re-AM is a distinct clinical subgroup of AM associated with generally worse prognosis and a specific increased arrhythmic risk compared with S-AM.

Key Words: cardiac magnetic resonance ■ cardiomyopathy ■ myocarditis ■ prognosis ■ recurrent

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CLINICAL PERSPECTIVE

What Is New?

- Recurrent acute myocarditis defines a distinct, higher-risk phenotype of myocarditis, marked by a significantly greater incidence of major ventricular arrhythmias and progressive myocardial injury, compared with single-episode acute myocarditis, despite similar baseline clinical characteristics.
- Recurrence of myocarditis is independently predicted by specific cardiac magnetic resonance pattern and clinical factors ("red flags"), including diffuse or ring-like late gadolinium enhancement and family history of cardiomyopathy and autoimmune disease, highlighting a complex interplay between genetics, inflammation, and immune mechanisms.

What Are the Clinical Implications?

- Patients with recurrent acute myocarditis, especially if red flags are present, require closer long-term surveillance, including cardiac magnetic resonance-based risk stratification and ECG or device-based monitoring, to reduce arrhythmic risk and adverse outcome.

Nonstandard Abbreviations and Acronyms

AM	acute myocarditis
DSP	desmoplakin gene
EMB	endomyocardial biopsy
LGE	late gadolinium enhancement
MVA	major ventricular arrhythmia
Re-AM	recurrent acute myocarditis
S-AM	single-episode acute myocarditis
VUS	variant of uncertain significance

Acute myocarditis (AM) is a heterogeneous inflammatory disease of the myocardium.[1–3] Although most cases are self-limiting and resolve completely, some patients may experience further episodes of AM, called recurrent acute myocarditis (Re-AM).

Re-AM are poorly understood and their clinical course and natural history remain largely unknown, particularly compared with patients with a single-episode of acute myocarditis (S-AM).

Furthermore, emerging evidence suggests a potential overlap between myocarditis and genetically determined cardiomyopathies.[3–14] In this context, recurrent myocardial involvement—the so-called "hot phases," consisting of chest pain, release of myocardial enzymes, and ECG abnormalities in the presence of normal coronary arteries—has been frequently reported in patients with a specific genetic substate, such as *Desmoplakin* (*DSP*).[7–14] This raises the hypothesis that Re-AM may, in some cases, represent an early phenotypic manifestation of an underlying genetic cardiomyopathy, requiring focused investigation.

The aim of this study was to deeply characterize patients presenting with Re-AM, confirmed either by cardiac magnetic resonance (CMR) or endomyocardial biopsy (EMB), and assess their long-term evolution.

METHODS

This was an international, multicenter, retrospective, observational cohort study. Fourteen tertiary referral centers specialized in cardiomyopathies and myocarditis across Europe (Figure 1 and Table S1) participated in the study. Trieste University Hospital (Italy) acted as the coordinating center. The local regional institutional review board approved the study (identifier Cod. 263/2022H), and all participating centers obtained local institutional review board approvals, where necessary, for the collection of retrospective anonymized data. Patients provided informed consent according to institutional policy.

Data Availability

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

Study Design and Inclusion Criteria

Data were collected from patients with a diagnosis of AM confirmed by CMR, according to Lake Louise criteria,[15,16] or EMB in at least 2 episodes, between January 1, 2010 and December 31, 2021; they were defined as Re-AM.

All CMR examinations had to be performed within a maximum of 30 days from the index admission. EMB was performed, when clinically indicated, according to international statements and clinical judgment.[1,3,17] Ischemic cause was systematically ruled out. As per protocol, patients with Re-AM are required to have normalization of troponin levels between the first episode of AM and the recurrence, to confirm resolution of the initial myocardial injury. Prespecified criteria for final inclusion were centrally revised (C.B.).

Data on genetic testing for cardiomyopathy screening (when performed) and on pharmacological and nonpharmacological therapy were also reported.

A multicenter (Trieste, Padua, Arezzo, and London) population of consecutive patients with CMR-proven

Figure 1. Fourteen international centers participated in the study.
Fourteen international centers participated in this multicenter study. Italian centers included University of Trieste – ASUGI (Trieste), Santa Maria della Misericordia Hospital (Udine), University Hospital of Padua (Padua), Niguarda Hospital (Milan), San Raffaele Hospital (Milan), San Donato Hospital (Arezzo), Ancona Hospital Ospedali Riuniti (Ancona), Careggi University Hospital (Florence), Sant'Andrea Hospital (Rome), and Casilino Hospital (Rome). From the United Kingdom, King's College Hospital and St Bartholomew's Hospital (London) contributed. Additional participating centers were Maastricht University Medical Center (Maastricht, Netherlands) and University Hospital Zurich (Zurich, Switzerland). ASUGI indicates Azienda Sanitaria Universitaria Giuliano Isontina.

or EMB-proven S-AM occurring during the same enrollment period (January 1, 2010 and December 31, 2021), was used for a comparison. Because all patients with Re-AM were discharged alive after their first episode, we restricted the single-episode group to patients who also survived to hospital discharge, in order to avoid bias related to survival time. If a nonfatal event (ie, major ventricular arrhythmias [MVAs]) occurred between the first AM episode and the recurrence, the patient was considered as S-AM.

The minimum follow-up duration was 12 months for all included patients.

CMR and EMB Assessment

CMR images were acquired in accordance with protocols recommended by the Society for Cardiovascular Magnetic Resonance.[18] The reference CMR criteria for the diagnosis of AM were the traditional Lake Louise criteria[15] in the period 2010 to 2018. From 2019 to 2020, the updated Lake Louise criteria[16] were adopted in those centers capable of measuring T1 and T2 mapping, with normal reference values derived from a local cohort of healthy subjects. Abnormal signals at T2-weighted short-Tau inversion recovery and the presence of late gadolinium enhancement (LGE) were analyzed using the American Heart Association 17-segments model for the left ventricle. LGE was visually assessed and categorized as localized (if its extension involved <2 left ventricle segments) or diffuse (if it involved >2 left ventricle segments).[19] Further characterization distinguished between subepicardial and midwall LGE distribution. Additionally, the presence of LGE with a circumferential pattern, defined as "ring like" by previous studies[20] (at least 3 contiguous

segments in the same short-axis slice), and septal nonischemic pattern was specifically requested to be reported by the centers. All participating centers had recognized experience in diagnosing and managing myocarditis.

EMB was performed following current guidelines,[17] according to case-by-case clinical decisions. AM was diagnosed using quantitative international established criteria.[21] According to the 2010 Task Force Criteria,[22] no patients met the criteria for a definite diagnosis of arrhythmogenic right ventricular cardiomyopathy.

Genetic Testing

Genetic analysis was performed and discussed with a specialized geneticist. Mutations in cardiomyopathy-associated genes were uniformly identified using next-generation sequencing. Genetic variants identified were evaluated based on the American College of Medical Genetics and Genomics and the Association for Molecular Pathology criteria.[23] Genetic testing was considered positive when variants were adjudicated as pathogenic or likely pathogenic. Variants of uncertain significance (VUS) were also reported for investigation purposes.

Outcome Measures

The primary outcome was defined as a composite of all-cause mortality, heart transplant and MVAs. The secondary outcome investigated terminal events such as all-cause mortality or heart transplant.

MVAs were defined as the first occurrence of aborted sudden cardiac death/ventricular fibrillation or sustained ventricular tachycardia or appropriate implantable cardioverter-defibrillator intervention.

Data were collected from the electronic database of each hospital and, when necessary and in accordance with local protocols, from patients' general practitioners or through telephone contacts with patients and their relatives.

Statistical Analysis

The results are reported following the Strengthening the Reporting of Observational Studies in Epidemiology guidelines[24]. Continuous variables were expressed as median with interquartile range (25–75), categorical variables were expressed as number (%). Baseline characteristics refer to clinical status at the time of the first AM episode for both Re-AM and S-AM. Within-patient comparisons between the first and second AM episodes in the group with Re-AM were performed using paired *t* test. Comparisons of baseline characteristics between the Re-AM and S-AM groups were performing using the chi-square for categorical variables and the ANOVA (or the *t* test for 2 groups) for continuous variables, as appropriate.

A logistic regression model was used to characterize predictors of recurrence in the Re-AM group.

Time-to-event Kaplan–Meier survival curves were performed on the composite end point and compared using the log-rank test. For secondary outcomes, cumulative incidence functions were estimated in the presence of competing risks and compared using the Fine and Gray test.[24] Uni- and multivariable Cox survival models were estimated to identify factors associated with outcomes (cause-specific models for the competing risks).

A Markov illness-death model with all-cause mortality/heart transplant/MVA as an absorbing state and the risk of recurrence as an intermediate state was estimated. The model consists of 3 discrete health states (ie, alive without recurrence, alive with recurrence, dead or heart transplant or MVA) and a transition probability matrix is calculated between states. A multistate model fitting a Cox-type regression for each transition was used to estimate transition-specific hazard ratio (HR).

The follow-up for the Cox model began at the time of recruitment in the study (ie, the first episode for the S-AM and the first recurrence for the Re-AM). To align the baseline observation of the multistate models, the follow-up started at the time of the first episode of myocarditis in both groups.

We defined a P value <0.05 as statistically significant. All statistical analyses were performed using the R statistical software.

RESULTS

Study Population

A total of 141 consecutive patients with Re-AM meeting the baseline and follow-up study criteria were included. The population with S-AM comprised 372 patients. Baseline characteristics and the comparison between Re-AM and S-AM are summarized in Table 1 and Table S2. Overall, both groups had similar baseline characteristics. Patients with Re-AM were 35 (26–45) years old and 77% were male. Patients with S-AM were 37 (27–52) years old and 70% were male. The median left ventricular ejection fraction at presentation was similar in both groups with Re-AM and S-AM (55% for both groups, P=0.24). Of note, a family history for cardiomyopathies was more frequent in patients with Re-AM (19% in Re-AM versus 2.8% in S-AM, P<0.001). In addition, autoimmune diseases (including lupus erythematosus, rheumatoid arthritis, systemic sclerosis, Sjogren's syndrome, and

Table 1. Baseline Characteristics of the Population With Single Acute Myocarditis and the Population With Recurrent Acute Myocarditis at the First AM Episode

Variable	Overall N=513		Recurrent N=141		Single N=372		*P* value
	No. available		No. available		No. available		
Age, y	511	37 [27, 50]	141	35 [26, 45]	372	37 [27, 52]	0.068
Sex	511		141		372		0.082
Female		144 (28%)		32 (23%)		112 (30%)	
Male		367 (72%)		109 (77%)		258 (70%)	
Family history of cardiomyopathy	483	34 (7.0%)	126	24 (19%)	357	10 (2.8%)	<0.001
Hypertension	491	59 (12%)	134	9 (6.7%)	357	50 (14%)	0.034
Dyslipidemia	475	49 (10%)	131	17 (13%)	344	32 (9.3%)	0.243
Diabetes	492	21 (4.3%)	133	2 (1.5%)	357	19 (5.3%)	0.062
Chronic kidney disease	482	11 (2.2%)	125	1 (0.8%)	357	10 (2.8%)	0.303
Autoimmune disease	479	53 (11%)	136	19 (14%)	343	34 (9.9%)	0.179
Genetic testing	236	83 (35%)	141	68 (48%)	95	23 (24%)	<0.001
Genetic positive	91	41 (45%)	68	27 (40%)	23	14 (60%)	0.367
C-reactive protein at admission	430	15 [3, 50]	138	5 [1, 23]	317	22 [5, 65]	<0.001
LV end-diastolic volume at admission	390	109 [91134]	139	108 [95130]	306	110 [90, 135]	0.77
LV ejection fraction at admission	442	55 [47, 60]	141	55 [48, 60]	328	55 [46, 59]	0.242
Aspirin/NSAIDs	478	212 (44%)	122	73 (60%)	356	139 (39%)	<0.001
Beta blockers	486	248 (51%)	129	66 (51%)	357	182 (51%)	0.928
Mineralocorticoid receptor antagonists	486	57 (12%)	128	23 (18%)	358	34 (9.5%)	0.012
Renin-angiotensin-aldosterone system inhibitors	491	231 (47%)	130	65 (50%)	361	166 (46%)	0.433
Immunosuppression	480	84 (17%)	121	23 (19%)	359	61 (17%)	0.521
CMR findings	417		133		285		
LVEF at CMR	417	58 [53, 63]	133	58 [53, 63]	285	58 [53, 63]	0.749
Edema posterior/lateral	205	179 (87%)	117	97 (89%)	96	82 (85%)	0.344
Edema septal+posterior/lateral	186	15 (8%)	117	9 (9%)	86	6 (7%)	0.672
LGE extension							0.019
Diffuse	372	141 (38%)	117	54 (46%)	255	87 (34%)	
Localized	372	231 (62%)	117	63 (54%)	255	168 (66%)	
LGE type							<0.001
Midwall	389	78 (20%)	124	41 (33%)	256	37 (10%)	
Ring like	373	12 (3%)	117	7 (6%)	256	5 (1.3%)	
Subepicardial	389	298 (77%)	124	102(82%)	256	196(53%)	
LGE location							<0.001
Posterior/lateral	295	242 (82%)	132	98 (75%)	163	144(87%)	
Septal	295	54 (18%)	132	33 (25%)	163	21 (13%)	
Septal+posterior/lateral	295	40 (14%)	132	25 (19%)	163	15 (9%)	

Percentages are calculated based on the total number of patients evaluated for each variable. CMR data were available for 471 patients of the entire cohort and 133 patients with recurrent AM. AM indicates acute myocarditis; CMR, cardiac magnetic resonance imaging; LGE, late gadolinium enhancement; and LV, left ventricular.

polymyositis) were present in 19 patients with Re-AM (14%). At CMR assessment, the presence and pattern of edema was also similar in both groups, but the group with Re-AM had more diffuse LGE, with a ring-like pattern in 6% of the patients (versus 1.3% in the group with S-AM, $P<0.001$) and LGE involving both septum and posterolateral wall in 19% (versus 9% in the group with S-AM, $P<0.001$).

Comparison Between First AM Episode and Recurrence in Patients With Re-AM

AM recurrence occurred at a median time of 23 months from the first episode (interquartile range, [11–49] months), and 28 patients (20%) developed a further recurrent AM episode during follow-up. Total recurrences were, on average, 1.3 per patient (SD 0.62) and a maximum of 5 AM

episodes were observed in one patient. Genetic investigations for principal cardiomyopathy-associated genes were performed in 68 patients with Re-AM (48%).

Table 2 illustrates the evolution of the main clinical characteristics between the first and second episode of AM in patients with Re-AM. Both episodes had a similar prevalence of prodromal symptoms, a similar clinical presentation, which was most frequently chest pain (73% at first episode, 69% at recurrence) and comparable median left ventricular ejection fraction. However, after the recurrence, more patients were diagnosed with EMB (37% at recurrence versus 19% at the first AM, *P*=0.01), received beta blockers (64% at recurrence versus 51% at the first AM, *P*=0.03) and immunomodulatory therapy (34% at recurrence versus 19% at the first AM, *P*=0.01), including corticosteroids, methotrexate, and azathioprine.

Over time, patients with Re-AM had a significant increase in the extension of LGE (diffuse LGE in 67% of patients at second AM episode versus 46% in the first AM episode, *P*=0.001), in the prevalence of septal LGE (34% versus 25% in second versus first AM episode respectively, *P*=0.04) and ring-like LGE distribution (13% versus 6% in second versus first AM episode respectively, *P*=0.03).

Genetic Testing in the Population With Re-AM

Among the 68 patients with Re-AM genetically tested (68% male with a median age of 38 years, 25% with a family history for cardiomyopathy, Table S3a), 27 (40%) showed a positive test for pathogenic/likely pathogenic variants and 7 (10%) for VUS, whereas 34 (50%) were gene elusive.

The most frequently mutated genes were *DSP* (n=11/34, 32%: 10 pathogenic/likely pathogenic variants, 1 VUS) and *filamin C* (n=7/34, 21%: 6 pathogenic/likely pathogenic variants, 1 VUS). Other mutations involved *Titin*, *Lamin*, *Cardiac myosin binding protein C3, RNA binding motif protein 20*, and additional cardiomyopathy-related genes (see Table S3b for the complete list of all mutated genes).

Almost half of the patients carrying *DSP* (n=5, 45%) had a ring-like LGE pattern on CMR. Furthermore, an increased LGE extension between the first and second episode of AM was observed in 8 out of 11 (73%) patients with mutated *DSP* and 5 out of 7 (71%) patients with mutated *filamin C*.

Outcomes

During a median follow-up of 33 months (interquartile range, 23–52), the primary composite end point occurred in 55 patients, 25 (18%) in the group with Re-AM, and 30 (8.1%) in the group with S-AM (*P*<0.001, Figure 2, Figure S1).

Competing risk analysis revealed that the higher incidence of the primary outcome in Re-AM was predominantly driven by MVA events, which were significantly more frequent in Re-AM compared with S-AM (*P*<0.001, Figure 3).

After adjusting for age, family history of cardiomyopathy, autoimmune disease, complicated clinical presentation, and pattern of LGE (Table 3 and Table S4), Re-AM remained independently associated with the composite outcome (HR, 2.15 [95% CI, 1.15–4.04]; *P*=0.017). Additionally, family history of cardiomyopathy (HR, 2.23 [95% CI, 1.06–4.69]; *P*=0.034), autoimmune disease (HR, 2.1 [95% CI, 1.05–4.17]; *P*=0.035), and complicated clinical presentation (HR, 2.6 [95% CI, 1.41–4.77]; *P*=0.002) were also independently associated with the primary outcome. Among LGE patterns, only the ring-like pattern showed a significant association (HR, 4.14 [95% CI, 1.16–14.8]; *P*=0.029).

In a sensitivity analysis restricted to patients from centers contributing to both cohorts (Figure S2), the association between Re-AM and adverse outcomes remained consistent with the main analysis, although statistical power was reduced due to the smaller sample size.

In the multistate Markov illness-death model, patients with Re-AM had higher risk of transitioning to adverse outcomes, particularly related to arrhythmic events (Figure S3a–S3b). The results were also confirmed in a sensitivity analysis using a complete time scale from first observation (Figure S4) and using a time-varying Cox model (HR for recurrence, 5.40 [95% CI, 3.07–9.51]; *P*<0.001).

AM Recurrence Predictors

In the overall cohort, we analyzed all patients to identify predictors of AM recurrence. A positive family history of cardiomyopathy (odds ratio [OR], 5.32 [95% CI, 2.09–14.6], *P*<0.001), having an autoimmune disease (OR, 2.51 [95% CI, 1.04–6.35], *P*=0.048), and LGE on CMR (posterolateral versus absent: OR, 6.41 [95% CI, 3.59–11.8], *P*<0.001; septal versus absent: OR, 4.21 [95% CI, 1.30–12.6], *P*=0,012; ring-like versus absent: OR, 11.5 [95% CI, 2.61–54.7], *P*=0.001) were independently associated with an increased risk of recurrent AM episodes (Table 4).

DISCUSSION

In this study, investigating a large multicenter cohort of patients with recurrent episodes of AM, patients with Re-AM demonstrated a significantly higher risk of death, heart transplant, and major arrhythmias when compared with patients with a single episode of

Table 2. Characteristics of First and Second Acute Myocarditis Episode in The Population With Recurrent Acute Myocarditis

Variable	First episode, N=141	Recurrent episode, N=141	*P* value
Prodromal symptoms	68 (52%)	65 (47%)	0.431
Arrhythmic presentation	17 (12%)	18 (12%)	0.909
Heart failure presentation	23 (16%)	23 (16%)	1.000
Chest pain presentation	104 (73%)	100 (69%)	0.478
C-reactive protein level	5 (1–23)	3 (1–18)	0.354
Troponin peak	630 (41–2218)	667 (86–3633)	0.465
Sinus rhythm	113 (97%)	116 (93%)	0.353
ST elevation	37 (32%)	37 (30%)	0.633
CMR	133 (94%)	123 (87%)	0.108
Endomyocardial biopsy	28 (19%)	54 (37%)	0.001
Left ventricular end-diastolic volume admission	108 (95–130)	113 (95–135)	0.605
LVEF admission	55 (49–60)	55 (47–61)	0.881
LVEF discharge	58 (55–61)	58 (54–61)	0.668
Aspirin/NSAIDs	73 (60%)	70 (51%)	0.136
Colchicine	29 (22%)	33 (24%)	0.757
Beta blockers	66 (51%)	89 (64%)	0.027
Mineralocorticoid receptor antagonists	23 (18%)	20 (15%)	0.474
Renin-angiotensin-aldosterone system inhibitors	65 (50%)	76 (55%)	0.406
Diuretics	13 (10%)	18 (13%)	0.437
Antiarrhythmics	4 (3%)	7 (5%)	0.411
Immunosuppression	23 (19%)	46 (34%)	0.008
CMR findings			
LVEF at CMR	58 [53, 63]	58 [51, 62]	0.571
Edema septal	26 (25%)	34 (33%)	0.174
Edema posterior/lateral	97 (89%)	87 (84%)	0.256
Edema Ssptal+posterior/lateral	9 (8.7%)	17 (17%)	0.083
LGE extension			0.001
Diffuse	54 (46%)	80 (67%)	
Localized	63 (54%)	39 (33%)	
LGE type			
Midwall	41 (33%)	38 (31%)	0.969
Ring-like	7 (6%)	16 (13%)	0.028
Subepicardial	102 (82%)	106 (85%)	0.149
LGE location			
Septal	33 (25%)	53 (34%)	0.035
Posterior/lateral	98 (75%)	101 (66%)	0.752
Septal+posterior/lateral	25 (19%)	43 (28%)	0.015

Percentages are calculated based on the total number of patients evaluated for each variable. CMR indicates cardiac magnetic resonance; LGE, late gadolinium enhancement; and LVEF, left ventricular ejection fraction.

myocarditis. Patients with Re-AM showed specifically an increased risk of MVA, likely related to the increasing extent of myocardial fibrosis through AM episodes or a potentially arrhythmogenic genetic background. Finally, the presence of a family history for cardiomyopathy, autoimmune diseases, and LGE, especially the ring-like pattern, were independently associated with a higher risk of further recurrent AM episodes.

Natural History and Recurrence Risk in Acute Myocarditis

In our population with Re-AM, the first recurrence of AM occurred ~2 years from the first episode with 20% of patients experiencing at least a third recurrence. From a clinical perspective, it is important to understand the factors potentially contributing to a recurrent

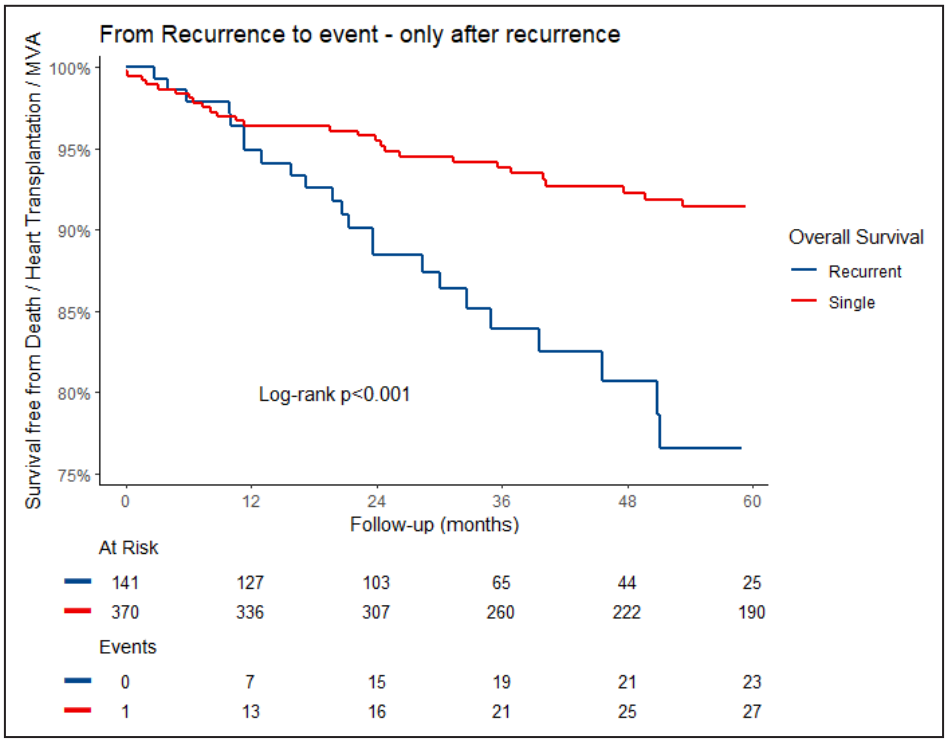

Figure 2. Comparison of primary outcome between the recurrent acute myocarditis and single acute myocarditis populations.
Kaplan–Meier curves showing survival free from the primary composite end point (death, heart transplantation, or MVA) in patients with Re-AM (blue line) vs single-episode acute myocarditis (red line). Patients in the group with Re-AM had a significantly higher incidence of the composite end point during follow-up (P<0.001, log-rank test). MVA indicates major ventricular arrhythmia; and Re-AM, recurrent acute myocarditis.

event, in order to guide the duration of follow-up after an apparently low-risk AM. Having LGE at CMR, especially when a ring-like pattern is present, was associated with a greater risk of Re-AM (OR up to 11.5) and was independently predictive of the primary end point (HR, 4.14 [95% CI, 1.16–14.8], P=0.029), suggesting that it may require careful monitoring over time.

In addition, the presence of autoimmune diseases and a positive family history of cardiomyopathy were independently associated with a higher risk of AM recurrence during follow-up. These findings underscore the potential contribution of underlying autoimmune mechanisms and genetic susceptibility to the pathogenesis of Re-AM, confirming a complex interplay between myocardial inflammation, autoimmunity, and genetic background.[25–29]

Importantly, the association between autoimmune diseases and recurrence is particularly striking considering that these patients are often already on immunosuppressive therapy—such as corticosteroids or disease-modifying agents—at the time of their AM episodes. Despite this, they still experience a higher number of adverse events and AM recurrences. Furthermore, the majority of genetically tested patients receiving immunosuppression were gene elusive (64%, see Table S2). This observation suggests that standard immunosuppression may be insufficient to fully control immune-mediated myocardial inflammation and raises the need for further investigation into tailored therapeutic strategies. These findings align with recent data in patients with *DSP*-related myocarditis, where immunosuppressive therapy may improve outcomes but does not appear to prevent recurrences, likely due to the genetically driven nature of the disease.[30]

Re-AM Evolution and Prognosis

Another further insight from this study is the progressive nature of Re-AM. Consistently with recent evidence,[31,32] the progression of LGE extension between the first and second episode of AM indicates continuous disease progression following inflammatory episodes.

Additionally, although chest pain remained the most frequently reported presentation, occurring in ~70% of patients during both the first and recurrent episodes, a notable proportion of patients presented with arrhythmic manifestations (~12% of cases at both AM episodes)

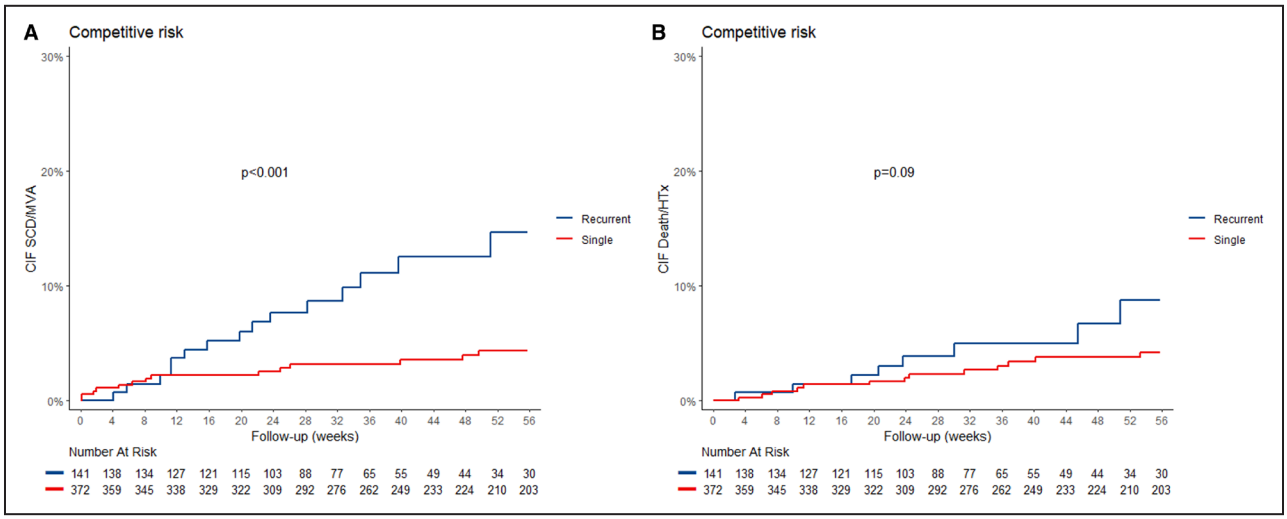

Figure 3. Competing risk analysis for SCD and MVA (A) and for all-cause death and heart transplantation (B) between the recurrent acute myocarditis and single acute myocarditis populations.
A, The curves represent the competing risk analysis of SCD and (MVAs in the population with Re-AM (blue line) vs S-AM (red line). The higher incidence of the primary outcome in the group with Re-AM was predominantly driven by MVA events (P<0.001). **B**, The curves represent the competing risk analysis of death or heart transplantation (HTx) in the population with Re-AM (blue line) vs the population with S-AM (red line). No statistically significant difference was observed between groups for these events (P=0.09). CIF, cumulative incidence function; HTx, heart transplant; MVA, major ventricular arrhythmia; Re-AM, recurrent acute myocarditis; S-AM, single-episode acute myocarditis; and SCD, sudden cardiac death.

and with heart failure (16% of cases at both AM episodes). These findings suggest that Re-AM encompasses a broad and potentially severe clinical spectrum, underlining the importance of systematic assessment. The significantly increased use of EMB at recurrence (37% versus 19% at first AM, P=0.01) reflects the growing diagnostic complexity, especially in differentiating true inflammatory recurrence from postinflammatory remodeling or underlying genetic cardiomyopathies. It is important to emphasize that our diagnostic approach required troponin normalization and new CMR or EMB-confirmed myocarditis at each episode, to differentiate recurrences from complications of the initial event—an essential step to avoid misclassification, especially in patients presenting with arrhythmias.

Interestingly, this study highlights the clinical significance of a recurrent episode of myocarditis independently by other known clinical parameters, including a complicated presentation or the presence of LGE.[33,34]

In this regard, somewhat unexpectedly, the presence of septal LGE alone was not independently associated with adverse outcomes, despite its known prognostic value in myocarditis.[33,34] A possible explanation is that a modest proportion of patients with Re-AM carry *DSP* mutations, which often presented with posterolateral or extensive ring-like LGE patterns, rather than septal LGE alone.[9]

Despite the confirmed prognostic value of a complicated presentation, in our population, left ventricular ejection fraction was largely preserved (median 55%). Therefore, recurrent myocarditis may represent an additional prognostic marker in otherwise low-risk patients with myocarditis, highlighting the need for close follow-up even in the presence of normal systolic function.

In fact, despite the similar baseline characteristics compared with the group with S-AM, patients with Re-AM emerged as a distinct and high-risk group with an increased risk of adverse events, mostly due to MVA, which occurred in nearly 1 in 5 patients with Re-AM within 3 years of the recurrence.

These results point out that the population with Re-AM deserves special attention in clinical practice, including a long-term follow-up, as a probable disease progression through recurrent myocardial inflammatory episodes confers a worse prognosis and a possible increased electrical instability. Although there is a lack of randomized data on treatment, our patients with Re-AM had intensification of medical antineurohormonal and immunosuppressive treatments over time. Whether these patients will benefit from a more aggressive and comprehensive management since the first episode remains unknown and warrants investigation in future studies.

Genetics in Re-AM

Although limited in a subgroup of patients, our findings in the genetically tested population with Re-AM revealed a notable prevalence of mutations in *DSP* (32%)

Table 3. Multivariate Analysis of Factors Associated With the Occurrence of the Primary End Point

Characteristic	HR	95% CI	*P* value
Age	1.02	1.00–1.04	0.03
Family history of cardiomyopathy	2.23	1.06–4.69	0.034
Autoimmune disease	2.1	1.05–4.17	0.035
Complicated presentation	2.6	1.41–4.77	0.002
Late gadolinium enhancement position			
None	—	—	
Posterior/lateral	1.64	0.83–3.25	0.2
Ring like	4.14	1.16–14.8	0.029
Septal	1.14	0.38–3.45	0.8
Recurrent acute myocarditis (vs single episode)	2.15	1.15–4.04	0.017

HR indicates hazard ratio.

and *filamin C* (20%), which may be particularly relevant for understanding the arrhythmic risk and disease progression in this cohort. These results align with previous studies[8–14,35–40] suggesting that mutations in desmosomal and cytoskeletal genes contribute to recurrent myocardial injury, increased arrhythmic risk, and a more severe disease course. Notably, our patients with *DSP* mutations frequently exhibited a characteristic ring-like LGE pattern on CMR, and both *DSP* and *filamin C* mutation carriers demonstrated a progressively increased LGE burden between AM episodes, supporting a genotype–phenotype correlation linked to progressive myocardial injury. This underscores the complex overlap between recurrent myocarditis and inherited cardiomyopathies, making it challenging to classify some cases as Re-AM versus arrhythmogenic cardiomyopathy or nondilated left ventricular cardiomyopathy. Re-AM may represent an early or incomplete phenotypic expression of an underlying genetic cardiomyopathy (arrhythmogenic cardiomyopathy/nondilated left ventricular cardiomyopathy) rather than a purely inflammatory process, warranting focused investigation, as recently stressed by Gasperetti et al in *Circulation*.[14]

On the other hand, approximately half of the genetically tested patients with Re-AM had no identifiable mutations, underscoring the current limitations of panel-based genetic approaches. This gap in genetic findings suggests a potential pathogenic role for unidentified genetic variants, polygenic interactions, and additional contributing factors, emphasizing the need for more comprehensive genomic and environmental research to better understand the multifactorial nature of recurrent myocarditis.

Clinical Implications

Recurrent episodes of myocarditis should potentially raise awareness in clinical practice. Patients with Re-AM require an integrated and individualized approach in order to achieve a correct diagnosis and ensure adequate management. A comprehensive investigation is needed since the first episode of AM, including a detailed family and immunologic history investigation, advanced imaging study and potentially genetic testing. However, a considerable number of patients with Re-AM remain genetically negative despite extensive testing, suggesting that monogenic causes alone may not explain the full spectrum of disease. In such cases, emerging tools like polygenic risk scores and broader multigene panels could improve risk stratification and shed light on subtler genetic predispositions.

In selected cases with red flags for underlying cardiomyopathy—such as extensive or ring-like LGE, a strong family history, or significant arrhythmic presentation—EMB should be considered in the management of Re-AM, aiding in differentiating postinflammatory remodeling from ongoing inflammation or underlying cardiomyopathic processes (arrhythmogenic cardiomyopathy/nondilated left ventricular cardiomyopathy), as recently suggested.[14,41] This clarification may support individualized and precision-guided therapeutic strategies, including the use of immunomodulatory treatments, which currently remain debated and under investigation.

Finally, identifying a Re-AM after the first episode remains challenging. Especially those patients with AM and autoimmune disease, diffuse LGE (particularly if ring-like pattern is present), or family history of cardiomyopathy should undergo close follow-up for at least 2 years after their first myocarditis presentation, as these features may help uncover individuals at higher risk of recurrence and complications.

Study Limitations

Some limitations must be acknowledged. The retrospective nature of the study introduces inherent limitations in terms of data consistency, potential missing variables, and unmeasured confounding factors. Clinical decision-making was not standardized across centers, which may have affected outcome interpretations. Systematic virological or bacterial serology were not consistently performed across all sites, because this was outside the primary scope of the study and because of their well-recognized limitations in establishing causality in myocarditis. Given the nature of the study, it is not possible to exclude entirely a potential referral bias, attributed to the participation of tertiary referral centers. We acknowledge that patients with S-AM were contributed by a limited number of centers. However, in our opinion, this did not alter the main presented findings. Although the multivariable model included a minimal degree of overfitting, this modeling choice was made to retain all variables that showed statistical significance in univariate analysis

Table 4. Multivariate Analysis of Factors Associated With the Recurrence of AM

Characteristic	OR	95% CI	*P* value
Family history of cardiomyopathy	5.32	2.09–14.6	<0.001
Hypertension	0.24	0.08–0.62	0.006
Diabetes	0.54	0.05–3.17	0.6
Chronic kidney disease	0.78	0.04–6.31	0.8
Autoimmune disease	2.51	1.04–6.35	0.048
Complicated presentation	1.13	0.53–2.36	0.7
Aspirin/NSAIDs	2.20	1.27–3.86	0.005
Beta blockers	0.67	0.35–1.25	0.2
Mineralocorticoid receptor antagonists	1.59	0.50–5.19	0.4
Diuretics	0.68	0.17–2.36	0.6
Immunosuppression	1.02	0.43–2.37	>0.9
Renin-angiotensin-aldosterone system inhibitors	1.79	0.94–3.46	0.079
Late gadolinium enhancement type			
None	–	–	–
Posterior/lateral	6.41	3.59–11.8	<0.001
Ring like	11.5	2.61–54.7	0.001
Septal	4.21	1.30–12.6	0.012
Septal+posterior/lateral	13.5	5.17–36.8	<0.001

OR indicates odds ratio.

and were considered clinically relevant. Moreover, the relatively small number of outcome events resulted in wide CIs for some estimates. Given that multiple testing was not accounted for, associations that are close to the conventional 0.05 significance threshold may be false positives. Therefore, further studies in larger populations are needed to confirm these results.

Regarding genetic testing, it was not systematically performed and was available for only a subset of patients in populations with Re-AM, reflecting the lack of recommendations for its investigation among patients with myocarditis.[42] Moreover, given the potential gene–inflammation interaction in the specific context of Re-AM, we considered it reasonable to describe the distribution of the VUS.

In the absence of guidelines, the management strategies of patients with Re-AM, particularly the use of immunosuppressive therapy and implantable cardioverter-defibrillators, were left to clinical judgment. Finally, the heterogeneous and relatively short follow-up period did not allow us to assess the possible occurrence of a Re-AM in the group with S-AM, although at least 1-year follow-up was mandatory to be included in the study and the median follow-up of patients with S-AM was 61 months (interquartile range, 31–87).

CONCLUSIONS

In this large, longitudinal study, Re-AM was associated with a progressive increase in myocardial scarring, leading to a poorer prognosis and heightened electrical instability. Consequently, patients with Re-AM require careful monitoring and a comprehensive management approach in clinical practice. Larger prospective studies are required to confirm these findings and improve the comprehensive tailored management of patients with Re-AM.

ARTICLE INFORMATION

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Supplemental Material

Tables S1–S4
Figures S1–S4

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