

Supplemental Material

Table S1. Center-specific enrollment of myocarditis patients.

Center Name	Patients with Re-AM (n)	Patients with S-AM (n)	Total (n)
Trieste Hospital	32	99	131
Niguarda Hospital	21		21
Maastricht Hospital	17		17
Padova Hospital	13	12	25
Barth's Hospital	13		13
San Raffaele Hospital	10		10
Udine Hospital	10		10
Ancona Hospital	6		6
Zurich Hospital	5		5
Sant'Andrea Hospital	3		3
Firenze Hospital	2		2
Casilino Hospital	2		2
Total (n)	141	372	513

Patients with recurrent myocarditis were enrolled across multiple centers, with detailed center-level data provided in Supplementary Table 4. Patients with single-episode myocarditis were available only from a subset of centers (Hospitals of Trieste, Padova, Arezzo, King's College), leading to an apparent imbalance in group size, which is discussed as a limitation.

Table S2. Additional baseline characteristics of the single acute myocarditis population and the recurrent acute myocarditis population at the first AM episode.

Variable	Overall N = 513	Recurrent N = 141	Single N = 372	p-value
Prodromal symptoms	265 (53%)	68 (52%)	197 (54%)	0.706
Smoker/ExSmoker	157 (33%)	42 (31%)	115 (33%)	0.677
Previous MI	6 (1.3%)	1 (0.7%)	5 (1.5%)	>0.999
Rhythm				0.344
sinus	446 (98%)	113 (97%)	333 (98%)	
atrial fibrillation	9 (2.0%)	2 (1.7%)	7 (2.1%)	
others	1 (0.2%)	1 (0.9%)	0 (0%)	
ST elevation	150 (34%)	37 (32%)	113 (35%)	0.669
QRS duration > 120 ms	27 (6.7%)	7 (6.1%)	20 (6.9%)	0.756
Colchicine	114 (23%)	29 (22%)	85 (24%)	0.772
Diuretics	50 (10%)	13 (10%)	37 (10%)	0.992
Antiarrhythmics	7 (1.7%)	4 (3.1%)	3 (1.1%)	0.213
MVAs				0.003
0	475 (93%)	123 (87%)	352 (95%)	
SVT	33 (6.5%)	17 (12%)	16 (4.3%)	
VF	2 (0.4%)	1 (0.7%)	1 (0.3%)	
Appropriate ICD intervention				0.08
0	266 (96%)	132 (94%)	134 (99%)	
yes on VT	10 (3.6%)	8 (5.7%)	2 (1.5%)	
yes on VF	1 (0.4%)	1 (0.7%)	0 (0%)	
Death	22 (4.3%)	8 (5.7%)	14 (3.8%)	0.34
Heart transplant	1 (0.2%)	1 (0.7%)	0 (0%)	0.275
Follow-up	50 [27, 82]	33 [23, 52]	61 [31, 87]	<0.001
Composite arrhythmia	55 (11%)	25 (18%)	30 (8.1%)	0.002

AM: acute myocarditis; ICD: implantable cardioverter defibrillator; MI: myocardial infarction; MVA: major ventricular arrhythmia; VF: ventricular fibrillation; SVT: sustained ventricular tachycardia.

Table S3a. Genetics in recurrent acute myocarditis group.

Characteristic	Positive Genetics	Negative Genetics	P value	DSP*	FLNC*	Other* genes
N patients (tested= 68; VUS=7)	27 (40%)	34 (50%)		11 (32%)	7 (11%)	16 (47%)
Age	35 [27;44]	42 [27;53]	0.334	34 [23;45]	38 [33;52]	41 [25;60]
Sex (male)	23 (85%)	26 (81%)	0.207	4 (36%)	7(100%)	12 (75%)
LVEF at admission	55 [48;56]	57 [43;62]	0.579	54 [48;59]	53 [45;64]	48 [33;61]
LV dysfunction at admission	9 (33%)	14 (41%)	0.070	2 (18%)	0	7 (44%)
RV dysfunction	2 (7%)	5 (15%)	0.057	0	1 (14%)	2 (13%)
Family history of CMP	11 (41%)	6 (18%)	0.098	5 (45%)	1 (14%)	5 (31%)
Presentation with arrhythmias	5 (19%)	7 (22%)	0.450	2 (18%)	1 (14%)	3 (19%)
Presentation with chest pain	20 (74%)	19 (49%)	0.039	9 (82%)	6 (86%)	10 (63%)
Presentation with HF	5 (19%)	13 (38%)	0.038	0	0	3 (19%)
Pericarditis	13 (48%)	10 (29%)	0.132	4 (36%)	4 (57%)	4 (25%)
ring-like LGE	7 (26%)	3 (9%)	0.076	5 (45%)	1 (11%)	1 (6%)
Diffuse LGE	16 (59%)	10 (29%)	0.172	8 (73%)	5 (71%)	6 (38%)
Septal LGE	12 (44%)	4 (12%)	0.036	4 (36%)	3 (43%)	7 (44%)
Immunosuppression	10 (27%)	20 (59%)	0.009	2 (18%)	1 (11%)	9 (56%)
More than 2 AM recurrences	7 (26%)	7 (22%)	0.750	6 (55%) *max 4 episodes	2 (29%) *max 1 episode	1 (6%)
More than 2 AM recurrences with immunosuppression	2 (7%)	3 (9%)	0.900	1 (9%)	0	1 (6%)
More than 2 AM recurrences without immunosuppression	5 (19%)	2 (29%)	0.801	3 (27%)	2 (29%)	0
MVA	13 (48%)	7 (21%)	0.034	6 (55%)	2 (29%)	6 (38%)
HTx	1 (3%)	0	0.328	0	0	1 (6%)
Death	2 (6%)	3 (9%)	0.592	0	0	2 (13%)

Abbreviations as in **Table 1**. DSP: Desmoplakin gene; FLNC: Filamin C gene; HF: heart failure; Htx: heart transplant; MVA: major ventricular arrhythmia; RV: right ventricle. *Considering P/LP and VUS variants: for DSP 10 P/LP and 1 VUS, for FLNC 6 P/LP and 1 VUS, for other genes 10 P/LP and 5 VUS.

Table S3b. Mutated genes in the Re-AM cohort.

Gene	n (%) of positive cases+VUS	Notes
Total (of 68 tested patients)	34 (50%)	27 (40%) LP/P variants 7 (10%) VUS
DSP	11 (32%)	10 LP/P variants 1 VUS
FLNC	7 (21%)	6 LP/P variants 1 VUS
LMNA	2 (6%)	1 LP/P variant 1 VUS
TTN	2 (6%)	2 LP/P variants
RBM20	2 (6%)	1 LP/P variant 1 VUS
MYBPC3	2 (6%)	2 LP/P variants
MYH7	1 (3%)	1 LP/P variant
DSC2	1 (3%)	1 LP/P variant
DSG2	1 (3%)	1 LP/P variant
VCL	1 (3%)	1 LP/P variant
ACTN2	1 (3%)	1 LP/P variant
RYR2	1 (3%)	1 VUS
DMD	1 (3%)	1 VUS
CTNNA3	1 (3%)	1 VUS

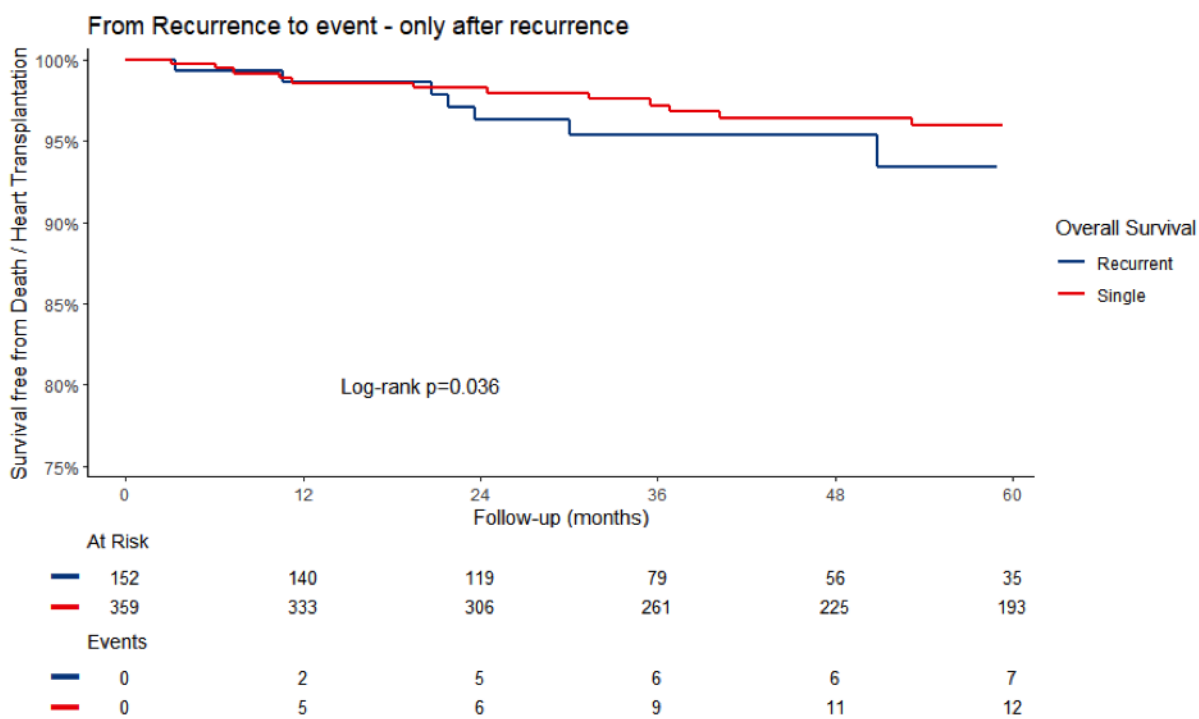
ACTN: Actinin Alpha 2 gene; CTNNA3: *Catenin alpha-3 gene*; DMD: *Dystrophin gene*; DSC2: *Desmocollin-2 gene*; DSG2: *Desmoglein-2 gene*; DSP: *Desmoplakin gene*; FLNC: *Filamin C gene*; LMNA: *Lamin gene*; LP/P: likely pathogenic/pathogenic; MYH7: *Myosin heavy chain 7 gene*; MYBPC3: *Cardiac myosin binding protein C3 gene*; RBM20: *RNA binding motif protein 20 gene*; RYR2: *Ryanodine receptor 2*; TTN: *Titin gene*; VCL: *Vinculin gene*; VUS: variant of uncertain significance.

Table S4. Univariate analysis of factors associated with the occurrence of the primary endpoint.

Characteristic	HR	95% CI	p-value
Age	1.03	1.01, 1.04	<0.001
Sex (Male)	0.72	0.42, 1.25	0.24
Family history of CMP	4.42	2.28, 8.59	<0.001
Smoker/ExSmoker	1.42	0.83, 2.42	0.2
CKD	0.81	0.11, 5.87	0.84
Previous MI	3.61	0.88, 14.8	0.075
Autoimmune disease	2.14	1.10, 4.14	0.024
CRP level	1	0.99, 1.00	0.12
Troponin peak	1	1.00, 1.00	0.46
BNP level	1	1.00, 1.00	0.56
NT-ProBNP level	1	1.00, 1.00	0.39
Rhythm	2.34	0.98, 5.60	0.057
QRS duration	1.88	0.80, 4.44	0.15
Complicated presentation	2.25	1.11, 4.45	0.021
LVEDV at admission	1.01	1.00, 1.01	0.054
LVEF at discharge	0.99	0.97, 1.02	0.59
LVEF at CMR	0.98	0.96, 1.01	0.17
LVEF Reduced	1.97	0.98, 3.93	0.056
Edema Septal	1.28	0.53, 3.06	0.59
Edema PostLat	1.12	0.33, 3.74	0.85
Edema Septal+PostLat	1.54	0.36, 6.58	0.56
LGE extension			
Diffuse	1.29	0.67, 2.47	0.44
Localized	1.16	0.58, 2.32	0.68
LGE type			
Midwall	2.23	1.18, 4.20	0.013
Ring-like	4.49	1.30, 15.6	0.018
Subepicardial	1.07	0.58, 1.99	0.82
LGE location			
PostLat	1.89	1.03, 3.48	0.041
Septal	1.84	0.64, 5.28	0.26
Septal+PostLat	3.67	1.65, 8.17	0.001
Group2			
Recurrent (Re-AM)	—	—	
Single (S-AM)	0.36	0.21, 0.61	<0.001

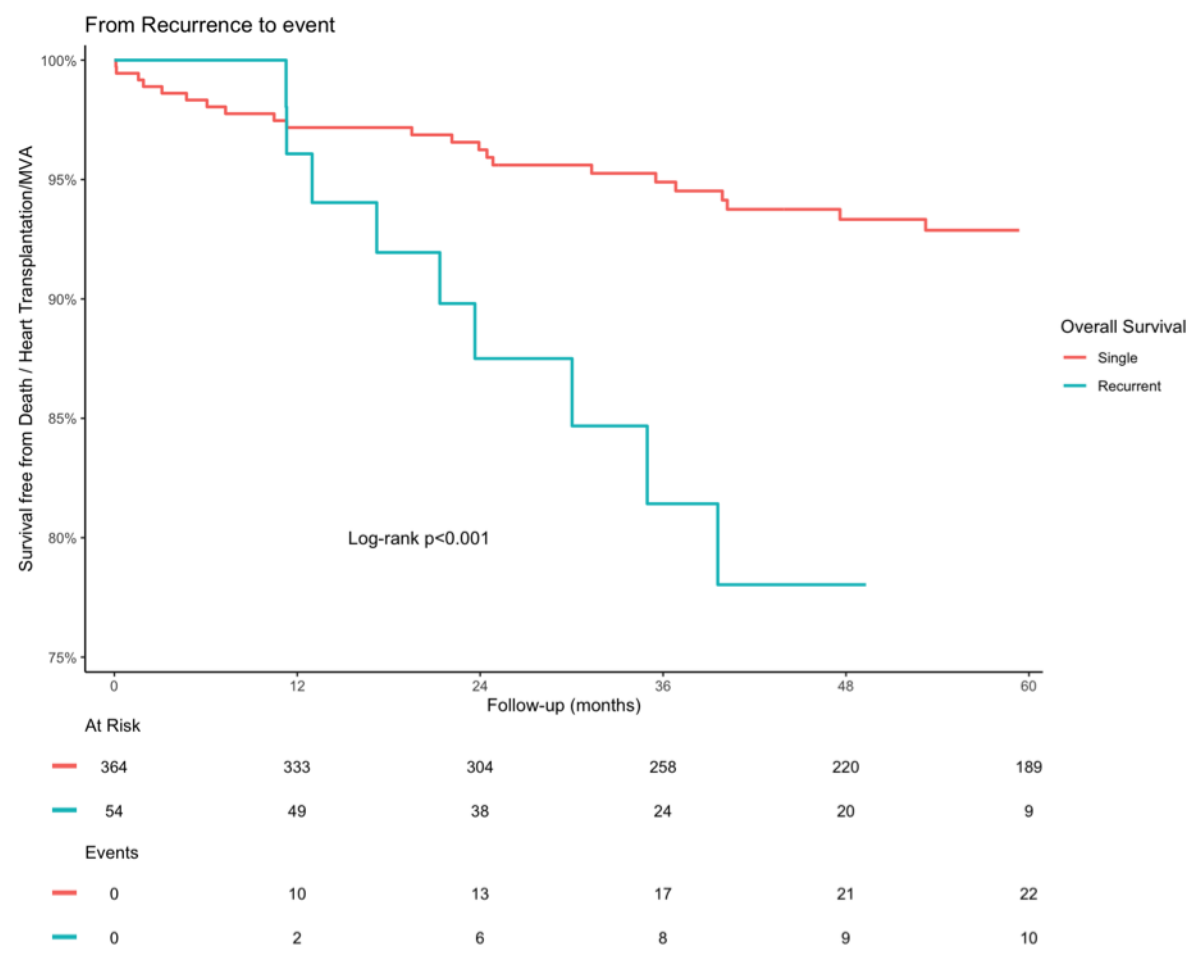
HR = Hazard Ratio, CI = Confidence Interval. Abbreviations as in **Table 1** and **Supplementary Table 1**.

Figure S1. Comparison of secondary outcome (all-cause death and heart transplantation) between the recurrent acute myocarditis and single acute myocarditis populations.



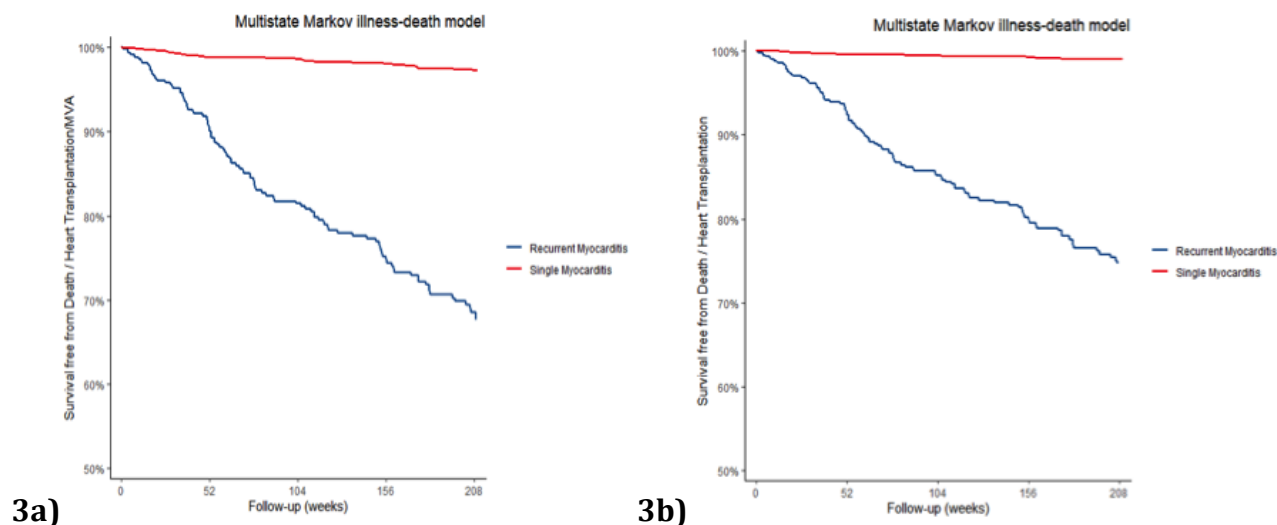
Kaplan-Meier estimated cumulative incidence of secondary endpoint (all-cause mortality and heart transplantation) in the two populations. The log-rank test P value of the comparison between the 2 groups is reported ($p=0.036$).

Figure S2. Sensitivity analysis of survival free from death, heart trasplantation, or major ventricular arrhythmias (primary endpoint) in centres contributing to both cohorts.



Kaplan–Meier curves comparing event-free survival between patients with recurrent acute myocarditis (Re-AM, blue line) and single-episode acute myocarditis (S-AM, red line), restricted to the subset of centres contributing patients to both groups. Results were consistent with the main analysis, with Re-AM patients exhibiting a higher incidence of the primary endpoint during follow-up (log-rank $p<0.001$), although statistical power was limited due to reduced sample size.

Figure S3a-S3b. Multistate Markov illness-death model for the primary endpoint (3a) and the secondary endpoint (3b) between the recurrent acute myocarditis and single acute myocarditis populations.



Multistate Markov illness-death models comparing survival free from death, heart transplantation, or major ventricular arrhythmias (3a: primary endpoint) and survival free from death or heart transplantation (3b: secondary endpoint) between patients with recurrent acute myocarditis and those with a single episode. The plots illustrate reduced event-free survival in the recurrent myocarditis group over the follow-up period.

Figure S4. Complete time scale model from first observation.

