LBBB = left bundle branch block; LGE = late gadolinium enhancement; LLC = Lake Louise criteria; LVEDVi = left ventricular end-diastolic volume (indexed); LVEF = left ventricular ejection fraction; NSVT = nonsustained ventricular tachycardia; PCR = polymerase chain reaction; RVEDD = right ventricular end-diastolic diameter (RV2); SCD = sudden cardiac death; SD = standard deviation; SIDs = systemic immune diseases; STIR = short-tau inversion recovery; TAPSE = tricuspid annulus plane systolic excursion; TCL = T-cell lymphocytes; VA = ventricular arrhythmia; VE = ventricular ectopies; VF = ventricular fibrillation; VT = ventricular tachycardia.

3.2. EST Results

Complete data about EST are summarized in Table 2. EST was performed on average after 15 ± 4 months from the diagnosis of myocarditis, with a later timing for the arrhythmic group. In addition, patients presenting with VA more commonly were tested on beta-blockers and/or antiarrhythmics (59 vs. 20, respectively, $p < 0.001$), accounting for lower average exercise performance. Overall, five patients (4%) experienced malignant VA, all of them belonging to the arrhythmic group. The same group showed a significantly higher occurrence of any kind of VA (43 vs. 4 cases, respectively, $p < 0.001$). Conversely, signs and/or symptoms of myocardial ischemia were more commonly documented in the nonarrhythmic group (6 vs. 1 cases, respectively, $p = 0.115$). Representative examples of EST findings are shown in Figure 2. Case-by-case management based on EST results is shown in Table 3.
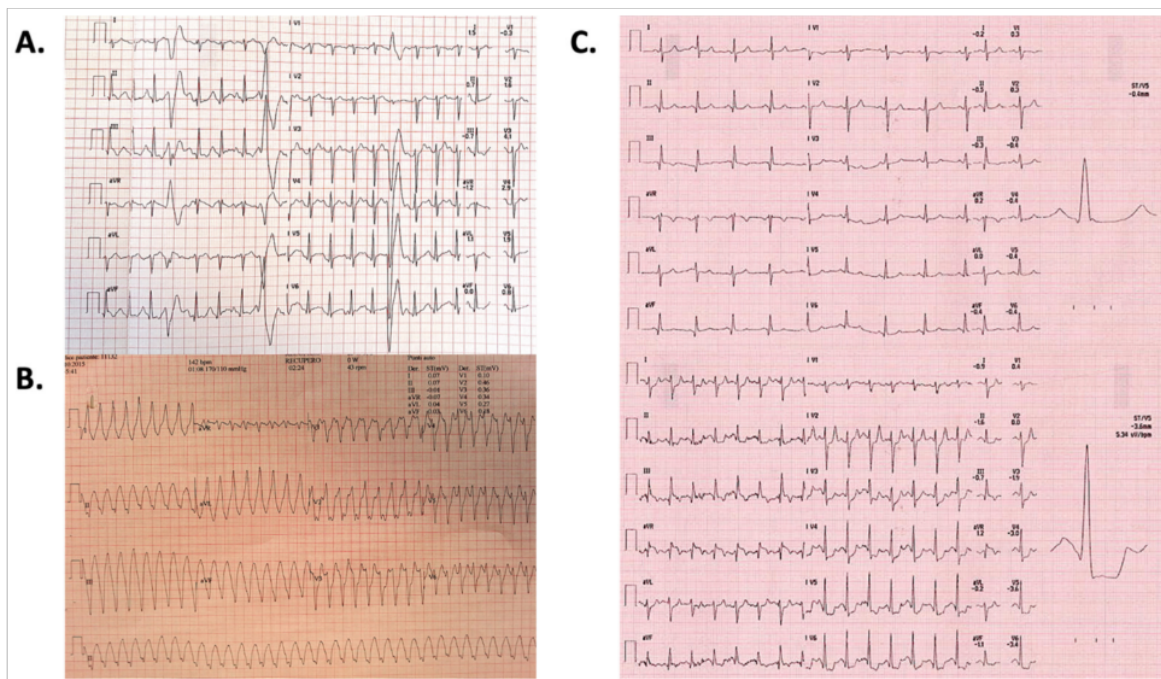
Table 2. Exercise stress test.

		Total *n* = 128	Arrhythmic *n* = 64	Nonarrhythmic *n* = 64	*p*
Time from clinical presentation	Mean $\pm$ SD	15 ± 4	19 ± 4	12 ± 3	<0.001
Treadmill	*n* (%)	117 (91)	59 (92)	58 (91)	1.000
Bicycle	*n* (%)	11 (9)	5 (8)	6 (9)	1.000
On treatment	*n* (%)	79 (62)	59 (92)	20 (31)	<0.001
on betablockers	*n* (%)	75 (59)	55 (86)	20 (31)	<0.001
on antiarrhythmics	*n* (%)	14 (11)	14 (22)	0 (0)	<0.001
Off treatment	*n* (%)	49 (38)	5 (8)	44 (69)	<0.001
Maximal power (W)	Mean $\pm$ SD	142 ± 9	133 ± 8	151 ± 11	<0.001
Maximal METs	Mean $\pm$ SD	10 ± 3	9 ± 2	11 ± 4	0.001
Peak SBP (mmHg)	Mean $\pm$ SD	157 ± 14	153 ± 16	159 ± 15	0.031
Peak HR (bpm)	Mean $\pm$ SD	150 ± 12	146 ± 13	154 ± 14	0.001
Peak RPP ($*10^2$)	Mean $\pm$ SD	24 ± 5	23 ± 5	25 ± 6	0.043
% MTHR (%)	Mean $\pm$ SD	85 ± 6	84 ± 6	86 ± 6	0.062
Maximal negative test	*n* (%)	64 (50)	14 (22)	50 (78)	<0.001
on betablockers	*n* (%)	24 (19)	8 (13)	16 (25)	0.112
off betablockers	*n* (%)	40 (31)	6 (9)	34 (53)	<0.001
Submaximal negative test	*n* (%)	10 (8)	6 (9)	4 (6)	0.744
on betablockers	*n* (%)	9 (7)	6 (9)	3 (5)	0.492
off betablockers	*n* (%)	1 (1)	0 (0)	1 (2)	1.000
Positive test	*n* (%)	54 (42)	44 (69)	10 (16)	<0.001
on betablockers	*n* (%)	42 (33)	41 (64)	1 (2)	<0.001
off betablockers	*n* (%)	12 (9)	3 (5)	9 (14)	0.127
VA	*n* (%)	47 (37)	43 (67)	4 (6)	<0.001
Sustained VT/VF *	*n* (%)	5 (4)	5 (8)	0 (0)	0.058
NSVT	*n* (%)	24 (19)	24 (38)	0 (0)	<0.001
VE	*n* (%)	40 (31)	36 (56)	4 (6)	<0.001

Table 2. *Cont.*

		Total $n = 128$	Arrhythmic $n = 64$	Nonarrhythmic $n = 64$	p
Ischemia *	n (%)	7 (5)	1 (2)	6 (9)	0.115
ST-T changes	n (%)	4 (3)	0 (0)	4 (6)	0.119
Angina-like chest pain	n (%)	3 (2)	1 (2)	2 (3)	1.000
Uninterpretable for LBBB	n (%)	8 (6)	3 (5)	5 (8)	0.718

Results of the exercise stress test are shown for the whole cohort and study groups. * Detail about baseline features and subsequent management of patients with sustained VT/VF or evidence of ischemia during exercise stress tests are shown in Table 3. HR = heart rate; METs = metabolic equivalents; MPHR = maximal predicted heart rate; NSVT = nonsustained ventricular tachycardia; RPP = rate pressure product; SBP = systolic blood pressure; VA = ventricular arrhythmia; VE = ventricular ectopies; VF = ventricular fibrillation; VT = ventricular tachycardia.

Figure 2. Exercise stress test findings. Representative examples of remarkable findings on exercise stress tests are shown. (Panel (**A**)). Female patient, 32-year-old, with evidence of frequent polymorphic ventricular ectopies on the effort at exercise stress test performed 12 months after cardiac magnetic resonance-proven acute myocarditis presenting with nonsustained ventricular tachycardia and syncope. After the exercise stress test, he underwent an endomyocardial biopsy and subsequent immunosuppressive treatment for virus-negative lymphocytic myocarditis. (Panel (**B**)). Male patient, 44-year-old (P123, Table 3) with evidence of sustained monomorphic ventricular tachycardia causing syncope during an exercise stress test performed late after presentation with arrhythmic myocarditis. The subsequent workup is shown in Table 3. (Panel (**C**)). Male patient, 68-year-old (P37, Table 3) with exercise stress test showing dynamic ST segment depression in inferolateral leads with ST elevation in lead aVR (exercise peak, bottom; compared to baseline, top). He was asymptomatic for angina or dyspnea. After normal coronary angiography, he had both cardiac magnetic resonance and endomyocardial biopsy with a final diagnosis of chronically active myocarditis from parvovirus B19. Further details are reported in Table 3.

Table 3. Management of patients with ischemia and malignant VA during exercise stress test.

PID	Age (y)	Gender	Presentation	Baseline LVEF (%)	Baseline Myocarditis	Baseline Treatment	Malignant VA during EST	Management
P45	54	Male	NSVT	55	EMB-proven, virus-negative	sotalol, ramipril	Presyncopal sustained VT	ICD implant. EMB: chronically active virus-negative lymphocytic myocarditis. IST for 12 months until FDG-PET normalization
P64	32	Male	Sustained VT	60	CMR-proven	metoprolol	Tolerated sustained VT	EMB: chronically active virus-negative lymphocytic myocarditis. IST for 12 months until CMR normalization. Flecainide
P67	34	Male	VF	51	EMB-proven, viral	metoprolol, amiodarone, ICD	Presyncopal sustained VT	VT ablation. Subsequent uneventful follow-up
P78	34	Male	Sustained VT	66	EMB-proven, virus-negative	flecainide, metoprolol, prior IST (prednisone, azathioprine), ICD	Tolerated sustained VT	FDG-PET: normal. EMB: replacement fibrosis, no myocarditis. VT ablation. Subsequent uneventful follow-up
P124	44	Male	Sustained VT	60	EMB-proven, virus-negative	flecainide, metoprolol, prior IST (prednisone, azathioprine), ICD	Syncopal sustained VT	EMB: replacement fibrosis, no myocarditis. VT ablation. Subsequent uneventful follow-up

PID	Age (y)	Gender	Presentation	Baseline LVEF (%)	Baseline Myocarditis	Baseline Treatment	Ischemia during EST	Management
P37	68	Male	ACS-like	58	CMR-proven	ramipril, ivabradine	ST-T changes, asymptomatic	Coronary angiography: normal. CMR: persistently active myocarditis. EMB: chronically active viral lymphocytic myocarditis (parvovirus B19). No etiology-specific treatment
P41	59	Male	ACS-like	60	CMR-proven and EMB-proven, virus-negative	ramipril, prior IST (prednisone, azathioprine)	Angina-like chest pain, no ST-T changes	Coronary CT scan: normal. CMR: persistently active myocarditis. EMB: chronically active virus-negative lymphocytic myocarditis. IST for additional 6 months until CMR normalization
P63	41	Male	HF	25	CMR-proven after LVEF recovery up to 50%	enalapril, furosemide	ST-T changes, asymptomatic	Coronary CT scan: normal. CMR: normal. Bisoprolol. No additional diagnostic workup
P98	40	Male	HF	38	CMR-proven	sacubitril/valsartan	ST-T changes, asymptomatic	Coronary CT scan: normal. CMR: persistently active myocarditis. EMB: chronically active virus-negative lymphocytic myocarditis. Bisoprolol and IST for 12 months until CMR normalization
P99	52	Male	ACS-like	55	EMB-proven, virus-negative	ramipril, prior IST (prednisone, azathioprine)	Angina-like chest pain, no ST-T changes, abnormal T-troponin	Coronary CT scan: normal. CMR: persistently active myocarditis. EMB: chronically active virus-negative lymphocytic myocarditis. Bisoprolol and IST for additional 6 months until CMR normalization
P103	64	Male	ACS-like	62	CMR-proven	none	Angina-like chest pain, no ST-T changes	CMR: normal. Coronary CT scan: normal. No additional diagnostic workup
P119	23	Female	Sustained VT	44	CMR-proven and EMB-proven, virus-negative	metoprolol, ramipril, prior IST (prednisone, azathioprine), ICD	Angina-like chest pain, no ST-T changes, abnormal T-troponin	FDG-PET scan: persistently active myocarditis. EMB: chronically active virus-negative lymphocytic myocarditis. IST for additional 12 months until FDG-PET normalization

Details about patients with sustained VT/VF (*n* = 5) or evidence of ischemia during EST (*n* = 7) are shown, together with the subsequent case by case management. ACS = acute coronary syndrome; CT = computed tomography; EMB = endomyocardial biopsy; EST = exercise stress test; FDG-PET = ^{18}F-Fluorodeoxyglucose positron emission tomography; HF = heart failure; ICD = implantable cardioverter defibrillator; IST = immunosuppressive therapy; LVEF = left ventricular ejection fraction; NSVT = nonsustained ventricular tachycardia; VA = ventricular arrhythmia; VF = ventricular fibrillation; VT = ventricular tachycardia.
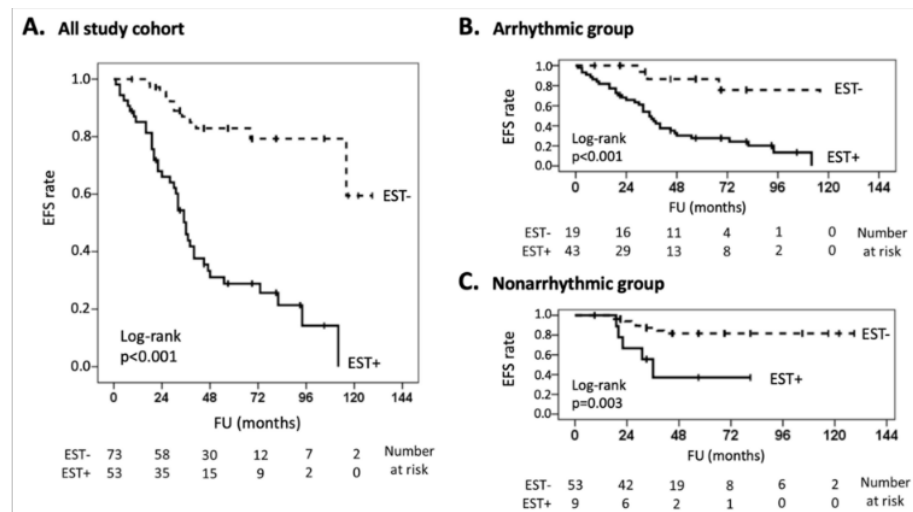
3.3. Outcomes

After average follow-up of 58 months, 52 patients (41%) experienced adverse events, including cardiac death (*n* = 3), rehospitalization (*n* = 37), malignant VA (*n* = 23) and proven myocarditis (*n* = 10). The global occurrence of adverse events was 39 (61%) in the arrhythmic vs. 13 (20%) in the nonarrhythmic group (*p* < 0.001). Event details are shown in Table 4. Remarkably, adverse events occurred more frequently among patients with abnormal EST findings (40/54 vs. 12/74, *p* < 0.001). As shown by the Kaplan-Meier curves in Figure 3, this difference was observed in both the arrhythmic and nonarrhythmic groups.

Table 4. Outcomes after exercise stress test.

|		Total *n* = 128	Arrhythmic *n* = 64	Nonarrhythmic *n* = 64	*p*	EST+ *n* = 54	EST- *n* = 74	*p*
Adverse events	*n* (%)	52 (41)	39 (61)	13 (20)	<0.001	40 (74)	12 (16)	<0.001
Cardiac death	*n* (%)	3 (2)	3 (5)	0 (0)	0.244	3 (6)	0 (0)	0.073
Disease-related hospitalizations	*n* (%)	37 (29)	24 (38)	13 (20)	0.050	27 (50)	10 (14)	<0.001
Malignant VA *	*n* (%)	23 (18)	21 (33)	2 (3)	<0.001	19 (35)	4 (5)	<0.001
Proven active myocarditis	*n* (%)	10 (8)	7 (11)	3 (5)	0.324	8 (15)	2 (3)	0.017

Outcomes of the whole cohort and study groups are shown. * Malignant VA include sustained ventricular tachycardia, ventricular fibrillation, and appropriate implantable cardioverter defibrillator therapy. EST = exercise stress test; VA = ventricular arrhythmia.

Figure 3. Outcomes after exercise stress test. Kaplan-Meier curves are shown for the occurrence of adverse events after EST. Adverse events included cardiac death, disease-related hospital readmissions, malignant ventricular arrhythmia (sustained ventricular tachycardia, ventricular fibrillation, appropriate implantable cardioverter defibrillator treatment), and active myocarditis, proven by endomyocardial biopsy or myocardial imaging. For each graph, *x*-axis indicates follow-up months after EST, and *y*-axis indicates event-free survival. The continuous line refers to patients with EST positive for ventricular arrhythmia or ischemia (EST+), whereas the dashed line refers to patients with uneventful EST (EST-). Numbers at risk are reported below each chart. Curves are shown for the whole patient cohort (panel (**A**)) and arrhythmic and nonarrhythmic subgroups (panels (**B,C**), respectively). EFS = event-free survival; EST = exercise stress test; FU = follow-up.

Of 47 patients with VA documented during EST, 35 (74%) underwent myocarditis restaging either by CMR (*n* = 19), FDG-PET (*n* = 15), or EMB (*n* = 8): prevalence of polymorphic and/or irregular VA during EST were observed in patients with subsequent

documentation of active myocarditis (6 of 7), whereas regular and monomorphic VA were more common among patients with no signs of active myocarditis (26 of 28, *p* < 0.001). Examples are shown in Figure 4.
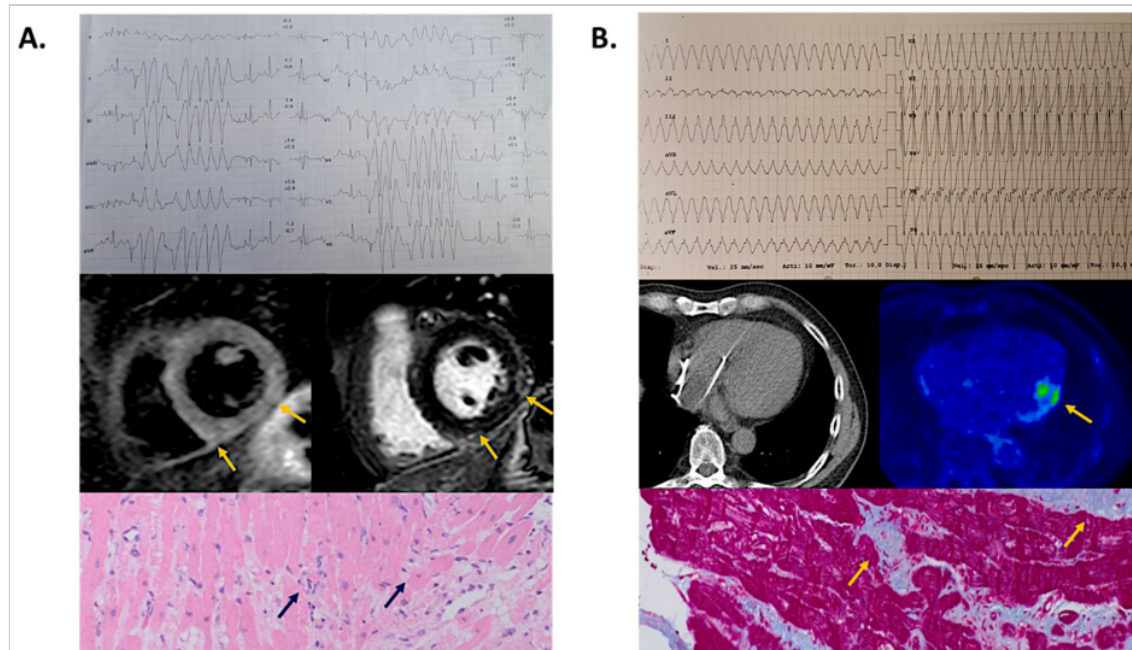
Figure 4. Relationship between exercise stress test-induced ventricular arrhythmia and myocarditis staging. Representative examples of ventricular arrhythmia features on exercise stress test and subsequent myocarditis restaging are shown. (Panel (**A**)). Female patient, 40-year-old, with evidence of irregular nonsustained ventricular tachycardia immediately after exercise peak on stress test. She underwent cardiac magnetic resonance showing both T2 short-tau inversion recovery (mid panel, left) and late gadolinium enhancement sequences (mid panel, right) involving the subepicardial layer of the inferolateral left ventricular wall (arrows), fulfilling the Lake Louise criteria for active myocarditis. She underwent an endomyocardial biopsy showing multifocal lymphocytic inflammatory infiltrates (lower panel, arrows) confirming the diagnosis of chronically active virus-negative myocarditis, subsequently treated by immunosuppressants. (Panel (**B**)). Male patient, 66-year-old (P78, Table 3) with evidence of regular and monomorphic sustained ventricular tachycardia causing syncope during an exercise stress test performed late after presentation with arrhythmic myocarditis. Being an implantable cardioverter defibrillator carrier (mid panel, left), he underwent ^{18}F-Fluorodeoxyglucose positron emission tomography (mid panel, right) with physiological glucose uptake in the mid-lateral left ventricular wall (arrow) and no signs of active myocarditis. Consistently, endomyocardial biopsy (lower panel) showed only replacement fibrosis (arrows) and no signs of persistent myocardial inflammation. He successfully underwent catheter ablation of monomorphic ventricular tachycardia (Table 3).

Among the 33 patients with uneventful EST on treatment, 16 (48%) had beta-blocker withdrawn (2/14 arrhythmic vs. 14/19 nonarrhythmic, *p* = 0.001) and subsequently underwent EST under off-treatment conditions: there were no cases of inducible ischemia and no major VA. Only two patients, those belonging to the arrhythmic group, required beta-blocker resumption, respectively, because of NSVT and frequent VE. Of the 27 athletes of the cohort, 12 cases (44%), all belonging to the nonarrhythmic group, were readmitted to competitive sports participation.