Prognostic Role of Left Ventricular Intramyocardial Fatty Metaplasia in Patients With Previous Myocarditis (MYOFAT Study)

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Left ventricular intramyocardial fat (LV-IMF) is often found in patients with previous irreversible myocardial damage and may be detected by cardiac magnetic resonance (CMR). No data are currently available about the prevalence of LV-IMF in patients with previous myocarditis. Our aim was to assess the prevalence of LV-IMF in patients with previous myocarditis by repeating after >3 years a follow-up CMR examination and to evaluate its clinical and prognostic role. Patients with clinical suspected myocarditis who underwent CMR within the first week from the onset of their symptoms and underwent repeated CMR were enrolled. LV-IMF was detected as areas of left ventricular intramyocardial "India ink" black boundary with or without a hyperintense core. Overall, in 235 patients with a definitive diagnosis of acute myocarditis, CMR was repeated after a median of 4 (3 to 6) years from symptom onset. LV-IMF positive patients (n = 35, 15%) presented greater ventricular volumes and more frequently a mid-wall late gadolinium enhancement than those without LV-IMF (both $p < 0.05$). Patients presenting major cardiac events (sudden cardiac deaths, resuscitated cardiac arrest, and appropriate implantable cardioverter-defibrillator-firing) at follow-up had a greater prevalence of LV-IMF than those without (55% vs 11%, $p < 0.001$). Patients with LV-IMF had a higher incidence myocarditis relapse (27% vs 9%, $p = 0.003$) and a greater risk of major cardiac events ($p < 0.0001$) than those without. At logistic regression analysis, LV-IMF was an independent predictor of major cardiac events. In conclusion, LV-IMF is not an uncommon finding in patients with previous myocarditis and is associated with worse ventricular remodeling and prognosis. **(Am J Cardiol 2021;143:135−144)**

Myocarditis is a complex disease that is typically caused by direct viral damage, viral-induced immune reaction, or both.[1−4] Previous data suggested a strong correlation between myocarditis and other cardiomyopathies.[5,6] Particularly, recent data have shown that subjects with a pathogenic genetic mutation for arrhythmogenic cardiomyopathy are more susceptible to have myocarditis.[7] On the other hand, a pathogenic mutation was found in only half of the cases of arrhythmogenic cardiomyopathy, and previous myocarditis is often considered as a potential cause of this condition when genetic testing is negative.[8,9] In patients with ventricular arrhythmias, the identification of left ventricular (LV) fibrosis with or without associated LV intramyocardial fat (LV-IMF) might suggest the presence of LV dominant arrhythmogenic cardiomyopathy, but in such cases, it is impossible to exclude a previous myocarditis with fibrosis and subsequent LV-IMF in absence of a pathogenic mutation. Cardiac magnetic resonance (CMR) has high accuracy in detecting LV-IMF in the context of chronic ischemic scar or cardiomyopathies.[10,11] LV-IMF was observed in 11% of patients with long-standing myocardial infarction by CMR studies. In cardiomyopathies the LV-IMF is associated with malignant arrhythmic events and worse prognosis.[11,12] The principal aims of our study are: (1) to detect the presence and prevalence of LV-IMF in patients with a previous diagnosis of myocarditis by repeating CMR after >3 years from symptoms onset; and (2) to evaluate the clinical and prognostic impact of LV-IMF in these patients.

Methods

In consecutive patients with suspected acute myocarditis and different clinical presentations (new onset of chest pain, dyspnea, or arrhythmic events), a CMR (CMR-I) was performed within the first week from symptom onset. Patients in whom the diagnosis of acute myocarditis was confirmed were enrolled. As previously described, to confirm the diagnosis of myocarditis, we applied a modified European Society of Cardiology guidelines diagnostic algorithm.[3,13] Briefly, acute myocarditis was clinically

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See page 143 for disclosure information.

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suspected when symptomatic patients (chest pain, dyspnea, palpitation, fatigue, and/or fewer) fulfilled 1 or more diagnostic criteria (new electrocardiographic modification, elevated troponin, wall motion abnormalities with preserved LV ejection fraction at echocardiography), in case of asymptomatic presentation 2 or more diagnostic criteria were necessary. A definite diagnosis of myocarditis was then made with CMR when 2 or more CMR Lake Louise criteria (myocardial edema, hyperemia, and late gadolinium enhancement [LGE]) were identified.[13−15]

Endomyocardial biopsy was performed when CMR results were inconclusive (≤1 CMR criterion). To exclude obstructive coronary artery disease, coronary artery angiography was performed in all patients, with the exception of those <30 years old with a low risk of coronary artery disease. At hospital admission, all patients underwent clinical evaluation and laboratory testing. Informed consent was obtained from all patients at the time of CMR examination.

A follow-up CMR examination (CMR-II) was performed at least >3 years after the first CMR. The same protocol was repeated at CMR-II. A clinical follow-up was performed in all patients.

CMR examinations were performed with 1.5-T systems (CVi, HD release, GE Healthcare, Milwaukee; Magnetom Avanto, Siemens Medical Systems, Erlangen, Germany; Gyroscan NT and Achieva 1.5, Philips Healthcare, Best, The Netherlands) using dedicated cardiac software, phased-array surface receiver coil, and vectocardiogram triggering. According to the standardized Society for Cardiovascular Magnetic Resonance recommended protocols, cine steady-state free precession (cine-SSFP) images, T2-weighted imaging, and LGE 10 minutes after gadolinium injection were acquired in the short-axis (9 to 13 images covering the entire LV), 2-chamber, and 4-chamber planes. If T2-weighted imaging and LGE images were negative or unclear, cine-SSFP images after gadolinium injection for hyperemia assessment were constantly acquired.[13] Proton density (PD)-weighted FSEs (with and without fat saturation pulse) were acquired.

All CMR studies were analyzed off-line in consensus by 3 experienced observers blinded to clinical presentation results, using a workstation with dedicated cardiac software. For the evaluation of LV and RV global function and calculation of LV mass, the endocardial and epicardial borders were manually drawn in the end-diastolic and end-systolic short-axis cine-SSFP images. LV and RV end-diastolic volume (EDV), end-systolic volume, EF, and LV mass were normalized for age, gender, and body surface area. LV and RV dilatation were evaluated using previously published reference values of normality.[16]

LGE was qualitatively evaluated and presented as a non-ischemic pattern of distribution (i.e., subepicardial or mid-ventricular enhancement), and the number of myocardial segments with LGE was counted.[13−15] The increase and decrease of extent in the LGE ≥ 1 LV segment between CMR-I and CMR-II were defined as increased LGE and decreased LGE, respectively.[17]

LV-IMF was detected using cine-SSFP and confirmed by PD-weighted FSE with and without fat saturation pulse. In SSFP, LV-IMF was identified as a hyperintense region bordered by a thin hypointense boundary (''India Ink'') and surrounded by normal myocardium using cine-SSFP.[11,12] When regions of LV-IMF were small, only the dark boundaries of India ink are detected. PD-weighted FSEs (with and without fat) were used to confirm the presence of the LV-IMF in doubtful cases.

To acquire clinical data, a clinical physician compiled a clinical questionnaire during periodic ambulatory visitations in each hospital and/or telephonically contacted the relatives, the general practitioner, or consulted the office of vital statistics at the municipality of residence of the patient. The following major cardiac events were collected: cardiac death, resuscitated cardiac arrest, ventricular assist device implantation, cardiac transplantation, and appropriate implantable cardioverter-defibrillator (ICD) shock; relapse of acute myocarditis and hospitalization for worsening heart failure were collected as minor cardiac events. A complete analysis of the ICD was performed by the referring physician to confirm the appropriateness of the shock. CMR during follow up was acquired and analyzed similarly to the first examination.

Values are presented as the mean ± SD or the median (Quartile 1, Quartile 3) for variables with normal and non-normal distributions, respectively. Values with non-normal distribution, according to the Kolmogorov-Smirnov test, were logarithmically transformed for parametric analysis. Qualitative data are expressed as percentages.

Categorical variables were compared using the chi-square test or Fisher's exact test when appropriate. Continuous variables were compared by the Student's independent *t* test and ANOVA or by the Wilcoxon nonparametric test when appropriate.

The Kaplan-Meier time-to-event method was used to calculate and compare the probability of major or minor cardiac events over time between groups. The time-dependent area under the curve (AUC) for predicting major cardiac events was calculated for the LV-IMF.

Logistic regression analysis was used to explore the impact of each significant variable in univariate analysis to predict the LV-IMF. Logistic regression analysis was also used to explore the impact of each significant variable in univariate analysis to predict major cardiac events. A p value lower than 0.05 was considered statistically significant. Multiple models of Bivariate analysis were tested for the prediction of major cardiac events. The risk of multicollinearity among the covariates was evaluated by the variance inflation factor. For all the covariates analyzed, variance inflation factor values were <10, indicating a low risk of multicollinearity.

Results

The final population included 235 patients (185 males, mean age 36 ± 15 years) with a definitive diagnosis of acute myocarditis who completed CMR-I and CMR-II (Figure 1). The baseline characteristics of the entire population at admission are shown in Table 1. At admission, the main clinical presentation was chest pain in 181 (77%), heart failure presentation in 23 (10%), and arrhythmic presentation in 31 (13%). Endomyocardial biopsy was performed in 18 patients (8%). Coronary angiography was negative for obstructive coronary artery

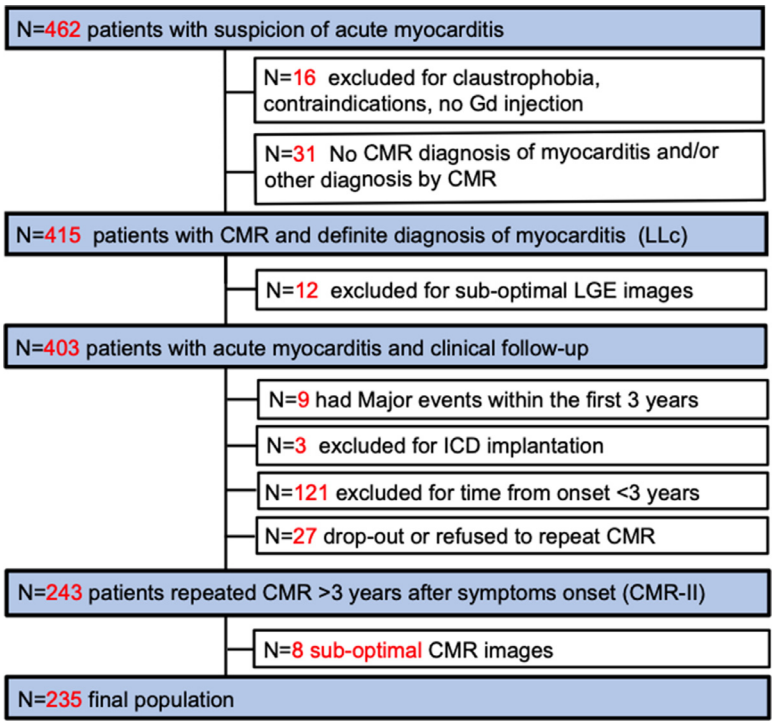

Figure 1. Flow chart visualizing the derivation of the study population. CMR = cardiac magnetic resonance; Gd = gadolinium; LGE = late gadolinium enhancement; LLc = Lake Louise criteria

Table 1
Patients' characteristics and CMR data at baseline in entire myocarditis population and in myocarditis with and without intra myocardial fat

Variable	Myocarditis Entire population	LV-IMF		p value
		YES	NO	
	(n = 235)	(n=35)	(n=200)	
Age (years)	36 ± 15	35 ± 16	36± 15	0.69
men	185 (79%)	29 (83%)	156 (78%)	0.52
Diabetes mellitus	1 (0.5%)	0	1 (0.5%)	0.64
Hypertension	6 (2.5%)	0	6 (3%)	0.23
Smokes	9 (4%)	0	9 (4.5%)	0.14
Dyslipidemia	4 (2%)	1 (3%)	3 (1.5%)	0.72
Obesity	3 (1)	0	3 (1.5%)	0.40
Fever	136 (58)	21 (60)	111 (55)	0.62
ESR (mm/h)	29 ± 18	29 ± 17	28 ± 19	0.77
Leukocytes (100 cells/ml)	10.355 ± 3.75	10.089± 3.565	10.876± 4.015	0.27
Troponin (> 0.05 μg/L)	235 (100)	35 (100)	200 (100)	0.99
Pericardial effusion	17 (7%)	2 (6%)	15 (7.5%)	0.69
CMR-I data:				
LV-EDVi (ml/m2)	83 ± 18	91 ± 19	82 ± 17	0.008
LV-ESVi (ml/m2)	34 ± 15	40 ± 16	33 ± 16	0.03
LV-EF (%)	59 ± 10	57 ± 10	60 ± 10	0.14
LV dysfunction (EF<50%), n (%)	26 (11)	4 (11)	22 (11)	0.99
LV Mass (gr/m2)	68 ± 16	72 ± 16	67 ± 16	0.08
RV-EDVi (ml/m2)	81 ± 23	92 ± 25	80 ± 22	0.015
RV-EF (%)	60 ± 8	58 ± 5	60 ± 9	0.4
Edema	235 (100%)	35 (100%)	200 (100%)	0.99
Hypermia	60 (25%)	12 (34%)	48 (24%)	0.21
LGE	199 (85%)	26 (74%)	173 (87%)	0.30
Number of edema segments, n	3(2-6)	4(2-8)	3(2-5)	0.63
Number of LGE segments, n	3 (2−5)	4 (3−7)	3 (2−5)	0.09
Mid-wall septal LGE	60 (26%)	14 (40%)	48 (24%)	0.048

LV = left ventricular; IMT= intramyocardial fat; ESR = erythrocyte sedimentation rate; EDV = end-diastolic volume EF = ejection fraction; ESV = end-systolic volume; LGE = late gadolinium enhancement; RV = right ventricular,

Dyslipidemia (LDL cholesterol >130 mg/dl); obesity (BMI>30).

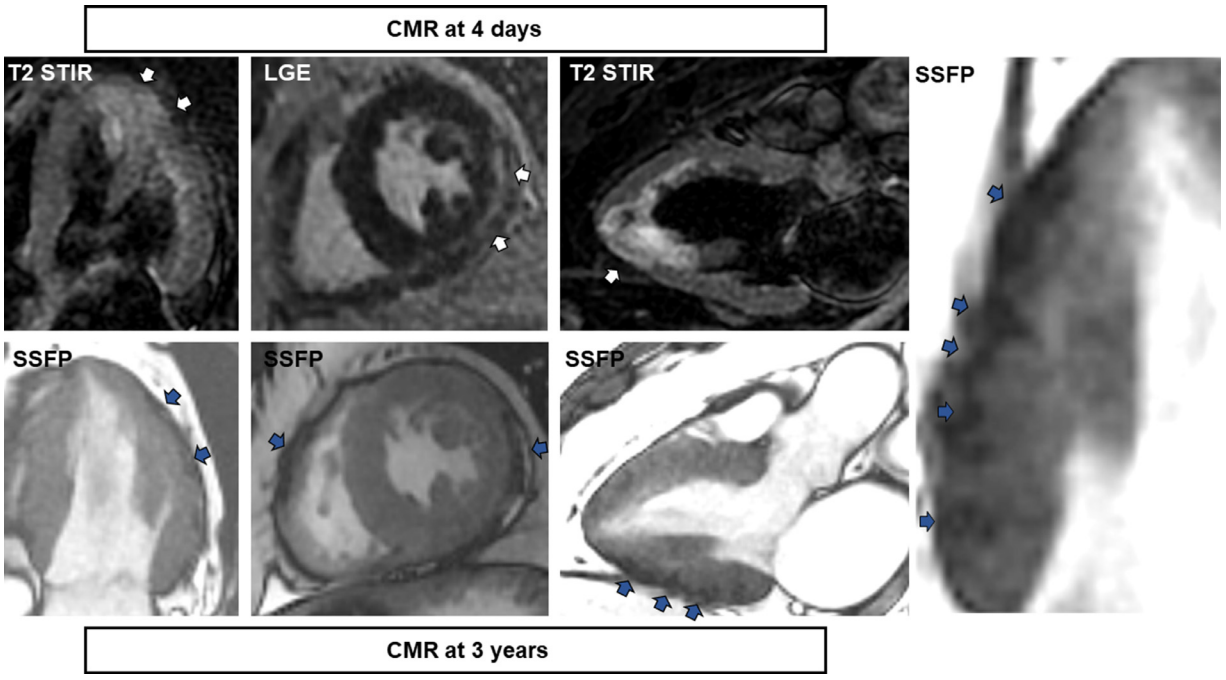

Figure 2. Example of cardiac magnetic resonance performed within the first week and after 3 years from onset of myocarditis. In the upper panels, T2-STIR images and a short axis LGE image, acquired during the first week, show myocardial edema and LGE in the lateral wall (white arrows). In the lower panels, cine-SSFP images acquired after 3 years demonstrate the presence of intramyocardial fat (blue arrows) as area of intramyocardial "india ink" which is more evident in the magnification (rightmost panel).

disease in all the 211 (89%) of patients whom it was performed.

CMR-I was performed for a median of 4 days (range, 2 to 7 days) after the onset of symptoms of MY and repeated (CMR-II) after a median of 4 years (range, 3 to 6 years).

No patients showed LV-IMF at first examination, while LV-IMF was found in 35 (15%) patients at CMR-II (examples of LV-IMF images from these groups are shown in Figures 2 and 3). Right ventricular IMF was also found in 2 patients with LV-IMF (Figure 2). The time between CMR-I and CMR-II was not different between patients with and without LV-IMF.

The data of patients with and without LV-IMF are reported in Table 1. The entire population was composed of young adults (36 ± 15 years old) with a low prevalence of risk factors for coronary heart disease. We detected no significant differences between patients with and without LV-IMF for the initial clinical presentation.

Patients with LV-IMF had significantly higher LV, RV EDV, and LV mass index than those without (Tables 2).

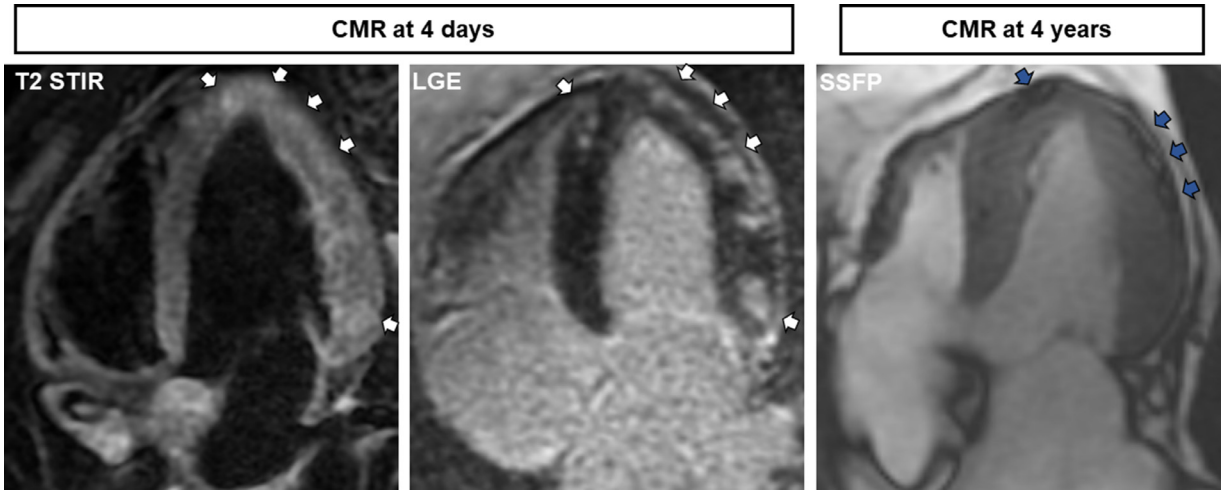

Figure 3. cardiac magnetic resonance performed within the first week and 4 years from onset of myocarditis. T2-STIR and LGE images show edema and enhancement in the lateral wall, apex and distal septum (white arrows). After 4 years, SSFP images show intramyocardial fat (blue arrows). (Color version of figure is available online.)

Table 2
Data of CMR-II in entire myocarditis population and in myocarditis with and without Intra Myocardial Fat

Variable	Myocarditis entire population (n = 235)	LV-IMF		p value
		YES	NO	
		(n=35)	(n=200)	
CMR-II data				
Time from CMR-I (days)		1693 (1110-1880)	1430 (1003-1880)	0.38
LV-EDVi (ml/m^2)	83 ± 16	90 ± 22	82 ± 15	0.02
LV-EF (%)	59 ± 8	59 ± 10	59 ± 8	0.95
Decrease EF <5% from CMR I	22 (9)	1 (3)	21 (10)	0.21
LV dysfunction (EF<50 (%)	18 (7)	4 (11)	14 (7)	0.32
LV Mass index (gr/m^2)	61 ± 13	71 ± 14	59 ± 11	<0.001
RV-EDVi (ml/m^2)	85 ± 21	99 ± 39	83 ± 16	0.001
RV-EF (%)	58 ± 8	58 ± 8	58 ± 7	0.88
RV dysfunction (EF<40 (%)	2 (1%)	0	2 (1%)	0.58
LGE, n (% of pts)	128 (54)	22 (63)	106 (53)	0.88
Number LGE segments	3 (1-5)	3 (2-9)	3 (1-5)	0.11
Increasead LGE	38 (16%)	13 (37%)	25 (12.5%)	<0.001
Decreasead LGE	104 (44%)	12 (34%)	92 (46%)	0.41
Deseappered LGE	22 (9%)	2 (5%)	20 (10%)	0.74
Un-changed LGE	71 (30%)	8 (23%)	63 (32%)	0.4

IMF = intra myocardial fat; CMR = cardiac magnetic resonance; EDV = end-diastolic volume; EF = ejection fraction; LGE = late gadolinium enhancement; LV = left ventricular; RV = right ventricular.

The involved LGE segments were similar between the myocarditis group with and without LV-IMF at CMR-I. Patients with LV-IMF were more likely to have a mid-wall septal pattern of LGE at CMR-I (p = 0.048).

At CMR-I, LGE was sub-epicardial in 171 patients (73%) and septal mid-wall in 64 (27%). The segmental distribution of LGE did not change from CMR-I and CMR-II in the whole population. CMR-II patients with LV-IMF showed a more frequent increase of LGE extent than others (p < 0.001). However, the extent of LGE was not significantly different between groups both at CMR-I and -II (Table 2).

Among the clinical and CMR parameters evaluated at the time of CMR-I, only LV EDVi (OR 1.04, 95% CI 1.01 to 1.06, p = 0.003), LV mass index (OR 1.03, 95% CI 1.01 to 1.06, p = 0.004), and RV EDVi (OR 1.04, 95% CI 1.01 to 1.06, p = 0.001) were predictors of LV-IMF at univariate analysis. LV EDVi was the only independent predictor of LV-IMF at multivariate logistic regression analysis (OR 1.04, 95% CI 1.02 to 1.07, p = 0.001). At ROC curve analysis, LV EDVi had a 0.665 (95% CI 0.59 to 0.72) AUC to predict LV-IMF with a best threshold of >94 ml/m^2 (sensitivity 58%, specificity 81%).

During the median follow up of 7 years (25th to 75th percentile: 6 to 8) after CMR-II, major cardiac events were detected in 20 patients (7 sudden cardiac deaths; 4 resuscitated cardiac arrest, 9 appropriate ICD firing). Characteristics of patients with and without major events are shown in Table 3. The prevalence of LV-IMF was higher in patients with major events than in those without (55% vs. 11%, p < 0.001). As evidenced by the Kaplan-Meier curves of Figure 4, patients with LV-IMF had a greater risk of major events than those without LV-IMF (p < 0.0001). During the follow-up, 26 patients (11%) had a relapse of acute myocarditis, which was observed in 9 (27%) patients with LV-IMF and in 17 (9%) without (p = 0.003). Twenty-two patients had hospitalizations for heart failure without a significant difference between LV-IMF and no LV-IMF (6 vs. 16, p = 0.13). However, aThe risk of minor events wasn't

Table 3
characteristics of patients with or without major cardiac events

Variable	Major cardiac events		p value
	Yes (n=20)	No (N=215)	
Men	12 (60%)	173 (80%)	0.15
Age (years)	35 ±18	36 ±16	0.80
Hypertension	0	6 (3%)	0.47
Hypercholesterolemia	0	4 (2%)	0.38
Diabetes Mellitus	0	1 (0.5%)	0.77
Smokes	0	9 (4%)	0.37
Pericardial effusion	2 (10%)	15 (7%)	0.48
Baseline CMR (CMR-I):			
LV-EDVi (ml/m^2)	93 ±20	82 ±16	0.005
LV-EF (%)	51 ±11	60 ±11	<0.001
LVMi (g/m^2)	73 ±15	67 ±17	0.12
RV-EDVi, (ml/m^2)	94 ±32	81 ±23	0.02
RV-EF (%)	55 ±10	60 ±8	0.02
Segments with edema	4 (2 − 10)	3 (2 − 5)	0.07
Segments with LGE	3 (2 − 6)	3 (1 − 5)	0.37
Mid-wall septal LGE (% of pts)	12 (60)	51 (24)	<0.001
Follow up CMR (CMR-II):			
LV-IMF	11(55%)	24 (11%)	<0.0001
LV-EDVi (ml/m^2)	98 ±25	81 ±14	<0.001
LV-EF (%)	53 ±12	60 ±8	0.001
LVMi (g/m^2)	71 ±14	60 ±12	0.003
RVEDVi (ml/m^2)	102 ±21	82 ±10	0.001
RV-EF (%)	56 ±10	58 ±7	0.43
Segments with LGE	5 (2-9)	3 (1-5)	0.03
Increased LGE (% of pts)	11 (31)	27 (13)	<0.009

LV: left nentricular; IMF = intramyocardial fat; EDV = end diastolic volume; EF = ejection fraction; LVM = left ventricular max; RV = right ventricular: LGE : late gadolinium enhancement.

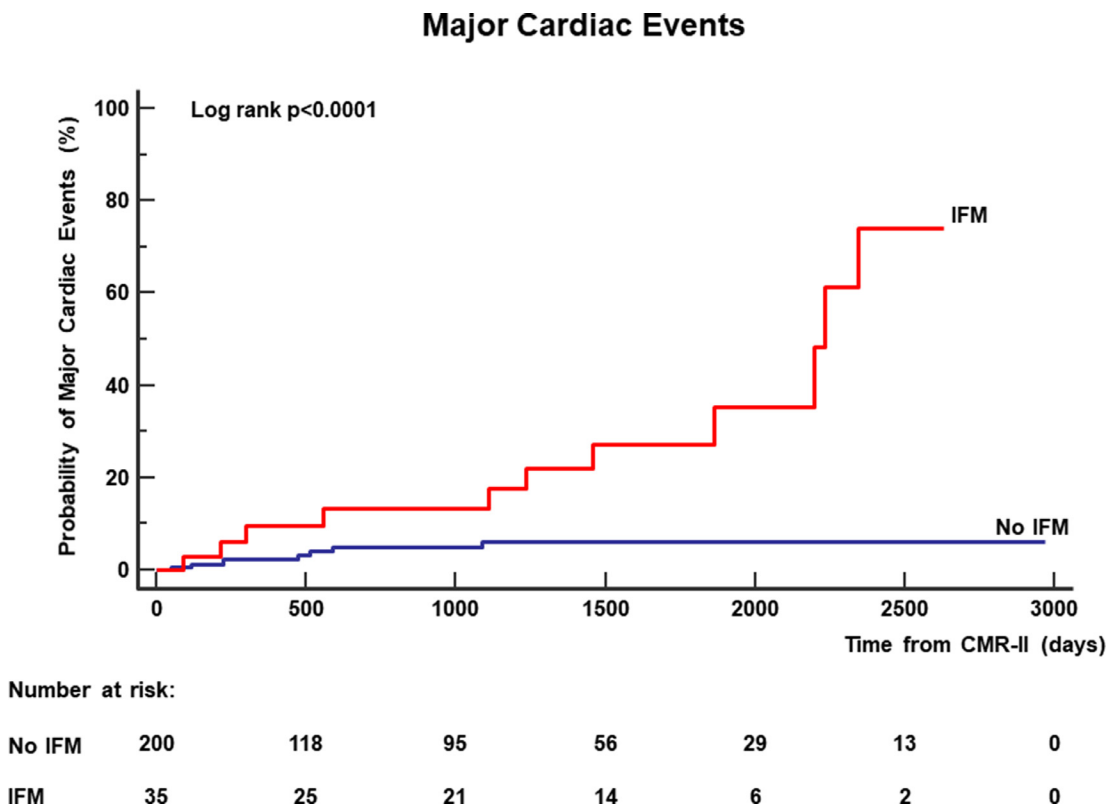

Figure 4. The Kaplan-Meier curves. Patients with intramyocardial fat (IMF) had greater risk of major cardiac events than those without.

higher in patients with LV-IMF than in others p = 0.13, Figure 5).

Figure 6 shows the time-dependent AUC curves of LV-IMF and mid-wall septal LGE for predicting major cardiac events. The median time-dependent AUC was 0.66 for LV-IMF and 0.68 for mid-wall septal LGE.

The time-dependent AUC of LV-IMF increased after 4 to 5 years of follow-up, whereas that of mid-wall septal LGE decreased after 5 years of follow-up.

At univariate analysis, several variables of CMR-II were associated with major cardiac events (Table 4). Considering the low number of major cardiac events (n = 20), the LV-IMF was tested in various bivariate models with all of the parameters with significant p-values at univariate analysis. The LV-IMF remains a significant independent predictor of major events in all models (Table 4).

Discussion

In this cohort of patients with a previous myocarditis, we observed that: (1) LV-IMF is detected in approximately 15% of patients; (2) LV-IMF is an independent predictor of major cardiac events (sudden cardiac deaths, resuscitated cardiac arrest, appropriate ICD intervention); and (3) relapse of myocarditis is more observed in patients with LV-IMF (27%) than in patients without (9%).

LV-IMF, for metaplasia or infiltration, represents an adverse healing mechanism that can be detected in various cardiac conditions, such as healed myocardial infarction, arrhythmogenic cardiomyopathies, and myotonic dystrophy,[12,18–21] with different prognostic meanings. IMF of RV myocardial wall is a common finding in elderly subjects, and it is not associated with a worse prognosis.[22]

LV-IMF in myocarditis might represent an unspecific reparative process starting from cellular deaths with architectural disarrangement, reparative myocardial fibrosis, and subsequent fatty metaplasia, similar to that observed in ischemic cardiomyopathy (adipose metaplasia).[18] Recently, a relationship between genetic mutation and myocardial inflammation was found in both experimental and clinical studies.[14,15] Histological signs of myocarditis were demonstrated in mice with pathogenic mutation for arrhythmogenic cardiomyopathy or dilated cardiomyopathy.[23,24] Furthermore, experimental studies in mice have observed a genetic susceptibility of major histocompatibility complex to coxsackie virus-induced myocarditis.[25] Lopez-Ayala observed a high incidence (about 3.5%) of clinically suspected myocarditis during a median follow-up of 34 months in patients and relatives with a definite genetic diagnosis of arrhythmogenic cardiomyopathy.[26] In that study, the authors suggest that myocarditis presenting with chest pain and troponin level increases is an alternative clinical presentation of arrhythmogenic cardiomyopathy. Recently, in patients with myocarditis, Belkaya et al observed a higher incidence of homozygous or compound heterozygous mutations in genes that have been implicated in synthesis of desmosomes.[7] If the results of such studies were confirmed, a genetic disease, such as arrhythmogenic or dilated cardiomyopathy, could predispose to myocardial inflammation. In this setting, LV-IMF could be a normal evolution of a

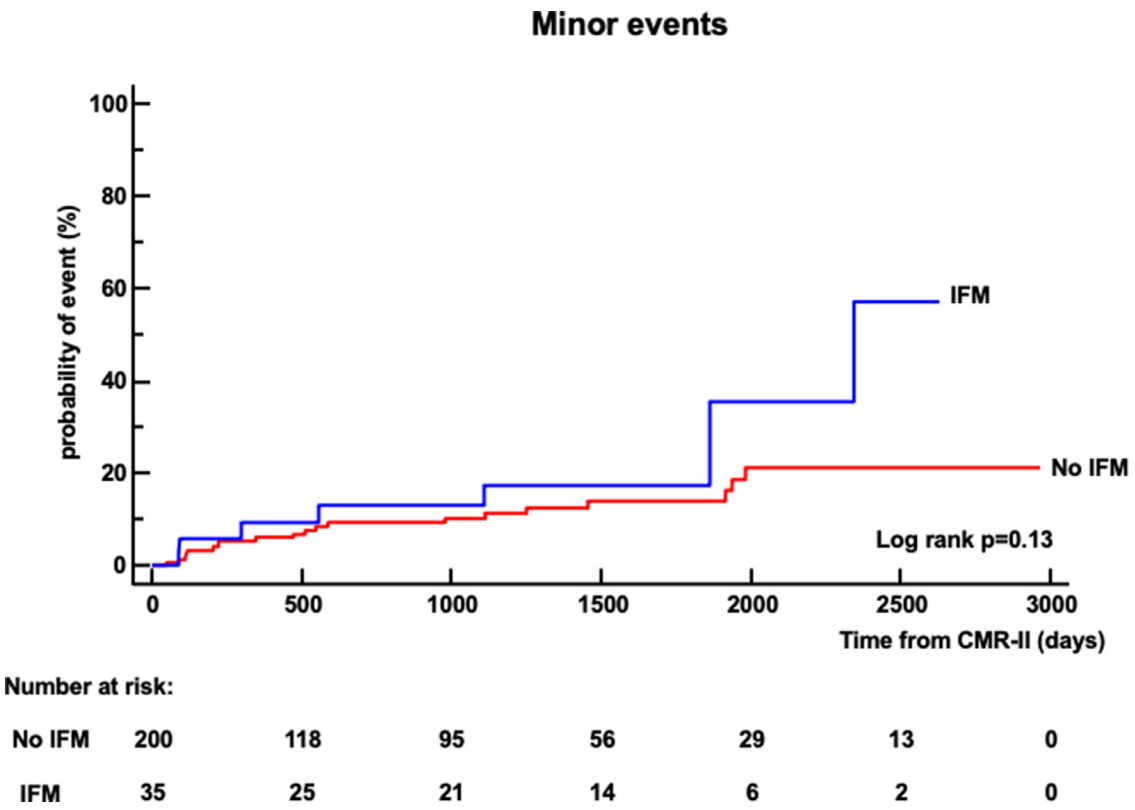

Figure 5. The Kaplan-Meier curves. Left ventricular intramyocardial fat (IMF) was not associated with a greater risk of minor cardiac events (hospitalization for heart failure and relapse of myocarditis).

chronic scar but potentially also a sign of a covert genetic disease. In our study design, genetic testing was not included, and further studies are necessary to investigate the relationship between myocarditis and pathogenic genetic mutation for arrhythmogenic or dilated cardiomyopathy and to assess whether the presence of LV-IMF was associated with such mutations.

It is noteworthy that we found that the relapse of acute myocarditis was more frequent in patients with LV-IMF than those without. It is possible that relapse of inflammatory events could be a mechanism of progression of myocardial damage in arrhythmogenic cardiomyopathies, and LV-IMF is a sign of the evolution of this damage. Indeed, the CMR phenotype observed in our study, with LV-IMF infiltration and sub-epicardial/mid-wall LGE, is similar to the phenotype of

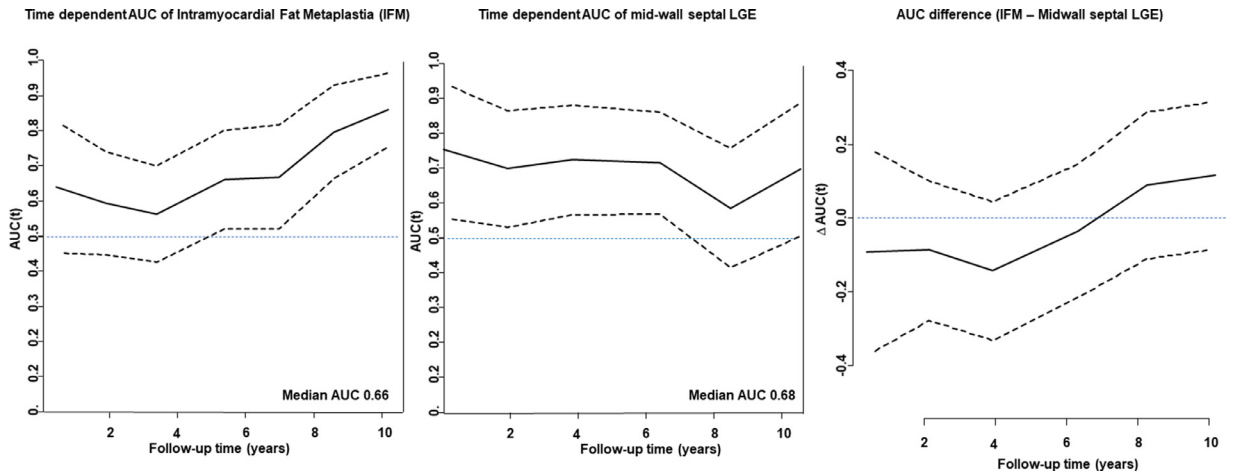

Figure 6. Time dependent area under the curve (AUC) and major cardiac events for left ventricular intramyocardial fat (IMF) and mid-wall septal pattern of LGE. Time dependent AUC curve is higher than the AUC = 0.5 for both parameters in all the time points. However, the time dependent AUC of mid-wall septal LGE tends to decrease after 4 year of follow-up, whereas IMF shows a progressively increase of AUC after 4 years. In the rightmost panel, the difference of AUC (IMF − mid-wall septal LGE) is plotted for every time-points.

Table 4
Univariate analysis and multivariable models at follow-up CMR examination for predicting major cardiac events

	Univariate analysis				
	OR	(95% CI)	p value		
Age	3.11	(0.98 − 9.8)	0.07		
LV EDVi	1.06	(1.02-1.09)	0.002		
LV EF < 50%	5.4	(1.6 − 18)	0.007		
RV EDVi	1.04	(1.01 − 1.06)	0.005		
RV EF	2.7	(0.9 − 6.2)	0.08		
LGE segments	1.2	(1.05 - 1.4)	0.01		
Mid-wall septal LGE	5.6	(2.1 - 15)	0.0006		
Increased LGE	5.9	(2 - 17.8)	0.002		
LV-IMF	10.9	(4.0 - 29.7)	<0.0001		
	Bivariate model I: IMF and Midwall septal LGE				
	OR	(95% CI)	p value	AUC (95% CI)	AIC
LV-IMF	9.8	(3.4-28)	<0.0001		
Midwall septal LGE	5	(1.7-14)	0.003		
Model				0.82(0.76-0.87)	115
	Bivariate model II: IMF and LV EDVi				
	OR	(95% CI)	p value	AUC(95% CI)	AIC
LV-IMF	6.1	(1.8-21)	0.004		
LVEDVi	1.04	(1.01-1.08)	0.003		
Model				0.76 (0.68 -0.82)	87
	Bivariate model III: IMF and LV EF				
	OR	(95% CI)	p value	AUC(95% CI)	AIC
LV-IMF	7.9	(2.5-25)	0.0004		
LV EF	5.2	(1.4-20)	0.0015		
Model				0.79(0.72-0.85)	40
	Bivariate model IV: IMF and RV EDVi				
	OR	(95% CI)	p value	AUC(95% CI)	AIC
LV-IMF	7.9	(2.5-25)	0.0004		
RV EDVi	0.98	(0.85-1.10)	0.14		
Model				0.74(0.66-0.81)	83
	Bivariate model V: IMF and LGE segments				
	OR	(95% CI)	p value	AUC(95% CI)	AIC
LV-IMF	5.5	(1.7-17.2)	0.004		
LGE segments	1.2	(1.01-1.37)	0.04		
Model				0.74(0.66-0.81)	99
	Bivariate model VI: IMF and increased LGE				
	OR	(95% CI)	p value	AUC(95% CI)	AIC
LV-IMF	4.3	(1.33-14)	0.013		
Increased LGE	4.1	(1.2-12)	0.016		
Model				0.74(0.66-0.81)	93

left dominant arrhythmogenic cardiomyopathy. Interestingly, patients with LV-IMF had significantly higher LV EDVi and LV mass than those without, and LV EDVi was the only independent predictor of LV-IMF. Taken together, these results suggest that LV-IMF could be a marker of tissue damage progression in patients with previous myocarditis.

Another important result of our study is that the development of LV-IMF in patients with previous clinical suspected myocarditis is an independent predictor of adverse outcomes together with the mid-wall septal pattern of LGE. The time-dependent AUC of LV-IMF was not significantly different from that of the mid-wall septal LGE. However, its time-course was different because the AUC of LV-IMF increased after 4 to 5 years of follow-up, whereas the AUC of mid-wall septal LGE decreased progressively along with during follow-up. This means that the prognostic effect of LV-IMF is mostly seen a longer time after the onset of myocarditis, because this time is probably necessary to have a greater amount of damaged myocardium also caused by multiple relapses of myocarditis. Therefore, LV-IMF, being a late manifestation, is associated with long-time prognostic risk. On contrast, the pattern of LGE could play a prognostic role since the first years from the onset of myocarditis. Further studies are needed to confirm this hypothesis in a larger population of patients with myocarditis.

Particularly, the coexistence of the surviving myocytes, reparative fibrous, and adipose tissues alter electrical properties and provide the substrate for slow conduction and reentrant ventricular arrhythmias. Many studies have analyzed the electrogenic basis of arrhythmias, suggesting that

the surviving myocytes embedded within fibrous and adipose tissues alter electrical properties and provide the substrate for slow conduction and re-entrant.[27,28] In line with these observations, Cheniti et al recently reported a strong relationship between the recurrence of tachycardia and all-cause mortality in ischemic cardiomyopathy associated with the LV-IMF.[29]

Many hypotheses have been made to explain the worse prognosis associated with the mid-wall septal pattern of LGE in myocarditis, such as different tropism of different viruses with different aggressivity, and a potential higher risk of re-entrant arrhythmias of this presentation than the sub-epicardial LGE.

Whatever the explanation, the finding of a prognostic role of mid-wall septal LGE confirmed previous observation of a prognostic role of this pattern of LGE detected in the acute setting of myocarditis[13] and also at 6-month follow-up CMR.[17]

Some study limitations should be mentioned. First, as mentioned, we did not perform endomyocardial biopsy in all the patients, and the diagnosis was made by the summation of clinical and CMR findings. Previous evidence demonstrated that CMR criteria are highly specific to the diagnosis of myocarditis but with less sensitivity.[5] However, our population is almost completely composed of infarct-like myocarditis patients with chest pain, new electrocardiographic abnormalities, and troponine increase. Yet CMR is very sensitive for diagnosing myocarditis with infarct-like presentation, whereas its sensitivity is low in heart-failure presentation and very low in arrhythmic presentation.[14,30] Second, the study protocol did not include a "core lab" evaluation of all the CMR images. Finally, some important parameters were not included in the univariate analysis: troponin and NT-pro-BNP were not evaluated during follow-up as study protocol; sex was not included in the analysis because of the great disproportion between males and females in our population.

In conclusion, in this multicenter study, about 15% of patients with a previous clinical suspicion of myocarditis detected by CMR had developed LV-IMF. The presence of LV-IMF is associated with worse prognosis. Other studies, including a comprehensive evaluation of imaging data and genetic tests, are now needed to establish the pathological basis of the development of LV-IMF in patients with previous myocarditis.

Authors' Contributions

Gianluca Di Bella: conceptualization, data curation, formal analysis, supervision, validation; visualization, roles/writing writing - review & editing; Giovanni Gentile: investigation, methodology, data curation; Flaviano Irsuti: investigation, methodology, data curation; Romano Giuseppe: investigation, methodology, data curation; Francesco Clemenza: investigation, methodology, data curation; Giuseppe Mamone: investigation, methodology, data curation; Rocco Donato: investigation, methodology, data curation; Antonio De Luca: investigation, methodology, data curation; Jan Bogaert: conceptualization, data curation, formal analysis, supervision, validation, visualization, roles/writing writing - review & editing; Giovanni Donato Aquaro: conceptualization, data curation, formal analysis, supervision, validation, visualization, roles/writing writing - review & editing.

Disclosures

The authors have no conflicts of interest to disclose.

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