Research paper

Prognosis of myocarditis stratified by initial clinical presentation: Does "intermediate" risk still play a role?

Daniela Di Lisi [a,d], Cristina Madaudo [a,d,*], Maria Gabriella Carmina [b], Francesco Clemenza [c], Domenico Scelfo [a,d], Eluisa La Franca [c], Michela Pieri [b], Giuseppe Vitale [b], Alfredo Ruggero Galassi [a,d], Giuseppina Novo [a,d]

[a] *Department of Health Promotion, Mother and Child Care, Internal Medicine and Medical Specialties (ProMISE) University of Palermo, Italy*
[b] *Cardiology Unit Vincenzo Cervello Hospital, Palermo, Italy*
[c] *Department for the Treatment and Study of Cardiothoracic Diseases and Cardiothoracic Transplantation, IRCCS – ISMETT, Palermo, Italy*
[d] *Cardiology Unit, University Hospital Paolo Giaccone, Palermo, Italy*

A B S T R A C T

Background/aims: Myocarditis is an inflammatory disease with diverse clinical presentations. It is known that low-risk patients have a good prognosis compared to high-risk patients. There are few data regarding the prognosis of intermediate-risk patients. This study aimed to analyze the long-term outcomes of patients with acute myocarditis with different risk profiles at presentation, focusing on the intermediate risk one.
Methods: A retrospective multicenter study was conducted, enrolling patients who met the diagnostic criteria for clinically suspected myocarditis with acute presentation. Patients were stratified into high, intermediate and low risk, according to the classification proposed by Sinagra and his team. Cardiovascular adverse events (AEs) were assessed after a median follow-up of 19 months. Echocardiographic and cardiac magnetic resonance (CMR) parameters predictive of adverse events have been reported.
Results: We enrolled 127 patients (mean age 30 ± 13 years; 103 men, 24 women). High-risk patients had a higher frequency of adverse events (80 %) compared to other groups (16 %–16 %, p < 0.0001). An association was observed between the number of segments with late gadolinium enhancement (LGE) at baseline CMR and the occurrence of adverse events (p < 0.0037). The sum of segments with LGE was statistically correlated with lower left ventricular GLS (p < 0.009). The number of segments with LGE that most accurately identified the occurrence of adverse events was 2.5 [AUC 0.5; p = 0.24].
Conclusions: Our study confirms the higher incidence of AE in the high group; the prognosis of patients at intermediate risk is not very different from those at low risk. It can be hypothesized that the extent of LGE at baseline is the main predictor of adverse events in patients at intermediate risk.

1. Introduction

Myocarditis is an inflammatory myocardium disease characterized by significant clinical presentation and evolution heterogeneity [1]. Clinical presentation varies from asymptomatic or paucisymptomatic myocarditis to fulminant forms [2]. Myocarditis can resolve itself spontaneously, or it can recur or progress towards a hypokinetic dilated or non-dilated cardiomyopathy [3]. The diagnosis of myocarditis needs histological, immunological and immunohistochemical criteria [4,5]. Myocarditis predominantly affects young male adults, with a median age of onset between 30 and 40 years [6] and can depend on different

causes and mechanisms [7,8].

Clinical suspicion of acute myocarditis is the presence of a suggestive clinical presentation (acute/new onset chest pain, dyspnea, signs of left and/or right heart failure and/or unexplained arrhythmias or sudden resuscitated death) in association with one or more positive mandatory diagnostic tests (preferably cardiac magnetic resonance - CMR), in the absence of significant coronary artery disease, valve disease, or other causes. Compulsory other diagnostic tests are electrocardiogram, Color-Doppler echocardiogram, and cardiac biomarkers (troponin, C-reactive protein) [9].

In fact, in the diagnosis of myocarditis, Lake Louise Criteria increased

diagnostic accuracy by increasing sensitivity to 87.5 % and specificity to 96.2 % [16,17]. The presence of 2 criteria at CMR (myocardial edema at T2 mapping or dark-blood T2-weighted short tau inversion recovery sequence; non-ischemic myocardial injury: abnormal T1, ECV or non-ischemic pattern of LGE) allowed the diagnosis of myocarditis.

The identification of prognostic elements in myocarditis has always been an important research topic because it allows the identification of patients at higher risk of cardiovascular events who need intense follow-up and adequate therapy.

Recently, Ammirati et al. showed that patients with acute myocarditis and pathogenetic desmosomal gene variants had a higher incidence of adverse cardiovascular events (recurrence of myocarditis and ventricular tachycardias) as well as a higher presence of late gadolinium enhancement (LGE) at follow-up, compared to patients without desmosomal gene mutation [10].

Other adverse prognostic parameters have been investigated in patients with acute myocarditis, such as the presence of LGE in the mid-wall layer of the atrial septum, [11] the extension of LGE at follow-up, [12] the clinical presentation at onset. Patients with complicated clinical presentation at onset had a worse prognosis in the Lombardy registry than patients without complicated myocarditis [13].

In the past, Sinagra and his team proposed a risk stratification model for patients with clinically suspected myocarditis based on the different patterns of presentation: low-risk, intermediate-risk and high-risk myocarditis [14]. Each risk category has a different prognosis and requires different follow-ups.

Notably, patients presenting with chest pain and/or supraventricular arrhythmias with preserved left ventricular ejection fraction (LVEF) typically have an excellent prognosis (low-risk syndromes). Conversely, patients presenting with new-onset heart failure with severe left ventricular dysfunction, life-threatening arrhythmias, and advanced AV blocks in the presence of left ventricular dysfunction (high-risk syndromes) have a consistent probability of major clinical events in long-term follow-up [14]. Myocarditis associated with refractory heart failure is characterized by a poor prognosis, with a 10-year transplant-free survival of 60 % [2,15]. The prognosis depends on the response to medical therapy and the evolution of the clinical and functional parameters. Therefore, it is necessary to start these patients on a close follow-up [14]. Intermediate-risk myocarditis includes patients with intermediate characteristics between low-and high-risk syndromes (patients with mild to moderate ventricular dysfunction, frequent non-sustained ventricular arrhythmias, persistent regional wall motion and/or electrocardiographic anomalies, presence of LGE). These patients represent a "gray zone" because their prognosis is mainly unknown [14].

Thus, considering the previous classification proposed by Sinagra and the uncertain prognostic significance of the "intermediate risk", our study aimed to analyze the long-term outcomes of patients with clinically suspected myocarditis with acute presentation with different risk profiles at the time of presentation, focusing on "intermediate risk".

2. Materials and methods

A retrospective multicenter study enrolled patients with clinically suspected myocarditis with an acute presentation from July 2011 to May 2021 in three different Italian hospital centres. The appropriate ethics committee approved the study. Data were retrospectively screened, centrally revised, and included in the final data set based on precise inclusion and exclusion criteria.

The inclusion criteria were:

- patients with confirmed acute myocarditis after endomyocardial biopsy (EMB)

or

- patients with clinically suspected myocarditis with acute presentation (onset of cardiovascular symptoms within 30 days before admission)

The exclusion criteria were:

- age < 15 years old
- previous or current diagnosis of ischemic heart diseases
- previous or current diagnosis of severe valve diseases or other clinical conditions associated with cardiac biomarkers increases (congenital heart diseases, hyperthyroidism)

During hospitalization, all patients underwent a complete cardiological examination with evaluation of laboratory tests, including complete blood count, markers of myocardial necrosis and inflammation. All patients had an electrocardiogram at admission, and the presence of ST-segment elevation or depression, or T-wave inversion was assessed.

A baseline echocardiogram was performed in all patients using a GE Vivid E95 ultrasound system prime echocardiography machine and a 4Vc-D (1.4–5.2 MHz) linear transducer. An assessment of the cardiac chamber dimensions and an evaluation of the systolic and diastolic ventricular function were performed following current guidelines [18,19]. LVEF was calculated using Simpson's biplane method. The presence of pericardial effusion was assessed. Wall motion abnormalities with non-coronary territorial distribution have been evaluated. Speckle Tracking Echocardiography (STE) was used to measure left ventricular global longitudinal strain (LV GLS) using GE software (Echopac V.202, GE). LV GLS was obtained using automated function imaging in standard 2D cine loops with a frame rate > 50 frames/s (2-, 4-chamber and long-axis apical views).

In agreement with ESC Guidelines and expert recommendations, [5,8,9] the diagnosis of clinically suspected myocarditis was performed in patients with a suggestive clinical presentation (acute/new onset chest pain, dyspnea, palpitations/unexplained arrhythmia symptoms or unexplained cardiogenic shock) in association with one or more diagnostic criteria from different categories (preferably the presence of myocardial changes at CMR: modified Lake-Louise criteria; electrocardiographic features of cardiac injury, elevated markers of myocardial necrosis, functional/structural abnormalities on echocardiogram or CMR) in the absence of significant coronary artery disease or valve diseases. Especially the absence of coronary artery stenosis ≥50 % and the presence of Lake Louise Criteria at CMR were critical for making the diagnosis of clinically suspected myocarditis.

CMR was performed in all patients with clinically suspected myocarditis during hospitalization and after six months. For almost all patients, mapping was not performed so the original Lake Louise criteria were used. In addition, we assessed the following CMR parameters left ventricular (LV) end-diastolic and end-systolic volume, LVEF, cardiac mass and stroke volume. As regards the tissue characterization analysis, the presence of edema and LGE was evaluated, describing its wall distribution (subepicardial or intramyocardial) and assessing its extension in terms of the number of myocardial segments involved. Coronary angiography or coronary tomography was performed in patients aged >20 years to rule out coronary artery disease.

In agreement with current recommendations and guidelines, endomyocardial biopsy was performed only in patients with clinically suspected myocarditis with progressive or persistent severe cardiac dysfunction and/or life-threatening ventricular arrhythmias and/or Mobitz type 2 s-degree or higher AV block with lack of short-term (<1–2 weeks) expected response to usual medical treatment [8,9]. The histological report of the sample analyzed was reported. Research for parvovirus, cytomegalovirus, adenovirus, enterovirus, and herpes virus genomes was performed.

The eventual use of inotropic or mechanical support for circulation during hospitalization and the therapy prescribed upon discharge was

reported in all patients.

Patients were stratified according to the risk stratification proposed by Sinagra et al. (Fig. 1) [14].

- low-risk forms characterized by presentation with chest pain, supraventricular arrhythmias (SVA) or advanced AV blocks but with preserved left ventricular function and the presence of LGE on CMR.

- intermediate risk forms represented by a gray area of unclear prognostic significance, characterized by the persistence of mild-moderate left ventricular dysfunction, ECGgraphic changes or segmental motion changes, presence of extended DE on cardiac MRI (at least 2 segments affected by LGE) in the absence of severe left ventricular dysfunction and ventricular remodeling, or the finding of frequent non-sustained ventricular tachycardias (NSVA).

- high-risk forms, which include new-onset heart failure with severe left ventricular dysfunction, life-threatening arrhythmias, advanced AV blocks in the presence of left ventricular dysfunction.

This study aimed to analyze the long-term outcomes of patients with acute myocarditis with different risk profiles at presentation, focusing on the intermediate risk one. The recorded events were divided into relapses of myocarditis and major adverse cardiovascular events (MACE). MACE included death, heart transplant, hospitalization for acute heart failure and life-threatening arrhythmias. Relapses were defined as recurrent myocarditis after >one month from the acute event. Furthermore, the same patient may have had both a relapse and a MACE, so the global events are expressed as total events.

Follow-up was performed after a median time of 19 months (interquartile range 9–38.5 months) in only 96 (76 % of total patients) among 127 enrolled patients.

2.1. Statistical analysis

Continuous variables were expressed as means and standard deviations or medians with interquartile range when appropriate. Categorical variables were expressed as percentages of the total population and compared using the χ^2 test and Fisher's exact test. The Student's t-test or, when necessary, the Mann-Whitney test was used to compare the two groups. Pearson's correlation helped evaluate the correlations of echocardiographic and CMR parameters with events. ROC analysis was performed to assess the predictive ability of edema and LGE against events and discriminative cut-off values. A Kaplan-Meier survival analysis measured the number of subjects free from events or survived. A two-tailed p-value <0.05 was considered statistically significant. Bonferroni's correction was used to correct the significance of multiple tests. All statistical analyses were performed using R studio software (version 1.4.1103 2009–2021 RStudio).

3. Results

3.1. Baseline characteristics of study patients and groups

Our study enrolled 127 patients (103 men, 24 women; mean age 30 ± 13 years) with clinically suspected myocarditis or confirmed myocarditis. The characteristics of the population are summarized in Table 1. Chest pain was the most frequent symptom reported by patients (87 %) at admission, followed by dyspnea, palpitations, and syncope. Fulminant presentation, i.e. with severe hemodynamic compromise and need for pharmacological or mechanical support, was observed in 6 patients (5 % of our population). Among the most interesting anamnestic features, we found comorbidity for autoimmune pathogenic diseases in 9 % of the population. By the classification proposed by Sinagra

Table 1
Baseline characteristics of study patients.

Variables[a]	Baseline
Age (years)	30 ± 13
Men % (n)	81 % (103)
Women % (n)	19 % (24)
Hypertension % (n)	10 % (13)
Diabetes % (n)	7 % (9)
Smoking % (n)	30 % (38)
Dyslipidemia % (n)	8 % (10)
Fever on admission % (n)	37.3 % (47)
Fever in the previous 30 days % (n)	69 % (87)
Chest pain % (n)	87 % (110)
Syncope % (n)	4 % (5)
Palpitations % (n)	6 % (8)
Fatigue % (n)	19 % (24)
Dyspnea % (n)	11 % (14)
Shock and fulminant presentation	5 %
WBC/mm3	$9.84 \pm 5.14 \times 10^3$
Neutrophils %	62.42 ± 13.90
Troponin I ng/L median (CI)	5880 (1112–12,800)
Troponin Hs ng/L median (CI)	784 (339–1796)
ECG ST-segment elevation % (n)	50 % (63)
Negative T waves % (n)	22 % (27)
ST-segment depression % (n)	7 % (9)
S-V arrhythmias % (n)	3 % (3)
NSVT % (n)	10 % (13)
SVT and VF % (n)	4 % (5)
Advanced AVB% (n)	2 % (2)
LVEF (%) Mean ± SD	55.38 ± 10.62 %
GLS (%) Mean ± SD	−18.41 ± 2.54 %
Edema % (n)	76 % (96)
Subepicardial distribution % (n)	63 % (80)
Intramyocardial distribution % (n)	20 % (25)
LGE % (n)	94 % (119)
Subepicardial distribution % (n)	83 % (105)
Intramyocardial distribution % (n)	25 % (31)

[a] AVB: atrioventricular blocks; GLS: global longitudinal strain; LGE: late gadolinium enhancement; LVEF: Left ventricle ejection fraction; NSVT: Non-sustained ventricular tachycardias; S-V: Supraventricular; SVT: Sustained ventricular tachycardia; VF: Ventricular fibrillation; WBC: White blood cells.
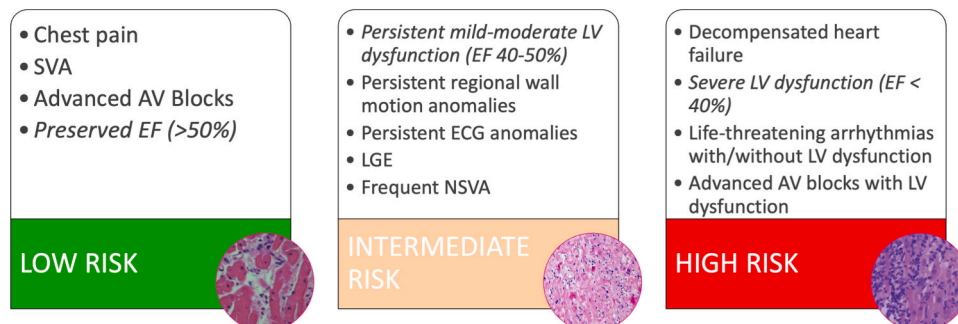

- Chest pain
- SVA
- Advanced AV Blocks
- *Preserved EF (>50%)*

LOW RISK

- *Persistent mild-moderate LV dysfunction (EF 40-50%)*
- Persistent regional wall motion anomalies
- Persistent ECG anomalies
- LGE
- Frequent NSVA

INTERMEDIATE RISK

- Decompensated heart failure
- *Severe LV dysfunction (EF < 40%)*
- Life-threatening arrhythmias with/without LV dysfunction
- Advanced AV blocks with LV dysfunction

HIGH RISK

Fig. 1. Risk stratification proposed by Sinagra et al.

et al., we found 17 high-risk patients (13 %), 71 intermediate-risk patients (56 %), and 39 low-risk patients (31 %).

Main echocardiographic parameters and CMR data are reported in Table 2 in each group. High-risk patients had a baseline LVEF of 34.02 ± 12.9 % and a mean GLS of −16 ± 4.43 %; regarding CMR parameters, 78 % had edema at baseline, and 90 % had LGE at baseline. The sum of baseline edema segments was 5.9 ± 5.2, and that of baseline LGE segments was 6 ± 4.32. At follow-up, it was possible to highlight a statistically significant improvement in the LVEF (p = 0.01), GLS (p = 0.001) and the percentage and in the number of edema segments involved (p = 0.0004 and p = 0.01).

Low-risk patients had a baseline LVEF of 59.24 ± 3.8 % and a mean GLS of −19 ± 2.37 %; at baseline, 10 % of patients had segmental motion changes, totally regressed at follow-up; regarding CMR parameters, 72 % of patients had baseline edema, and 85 % had LGE at baseline. The sum of baseline edema segments was 1.36 ± 1.46, and the sum of segments of LGE at baseline was 2,26 ± 1,63. At follow-up, we found a statistically significant improvement in edema (p < 0.0001) in the number of segments with edema (p = 0.0045) and the number of segments with LGE (p = 0.022).

Intermediate-risk patients had a baseline LVEF of 58.41 ± 5.2 % and a mean GLS of −18 ± 2.06 %; at baseline, 34 % of patients had segmental motion changes at the follow-up, and in 6 % of patients, there was the persistence of segmental motion changes; regarding CMR parameters, 75 % of patients had baseline edema, and 97 % had LGE at baseline. The sum of baseline edema segments was 3.73 ± 2.57, and the sum of baseline LGE segments was 4.82 ± 2.75. At the follow-up, we found a statistically significant improvement in edema (p < 0.0001), in the sum of the segments with edema (p = 0.01), in the LGE (p = 0.0004), and, at the limits of significance, in the sum of the LGE segments involved (p = 0.05).

3.2. Cardiovascular events during follow-up

Follow-up was completed in 96 patients. Analysing cardiovascular events at follow-up, we recorded events in 22 patients (23 %) with 25 total events. Furthermore, 3 patients had both a MACE and a recurrence. The recorded total events were divided into recurrences of myocarditis observed in 16 (17 %) patients and MACE followed in 9 (9 %) patients. MACE included death (2 patients), cardiac transplantation (5 patients, of which four subsequently died), and severe arrhythmias (2 patients).

Notably, we found that cardiovascular events occurred in 80 % of high-risk patients, 16 % of intermediate-risk patients, and 16 % of low-risk patients. Events were significantly more frequent in the high-risk group, considered globally (percentual of total events) or individually as only MACE. In contrast, the incidence of total events was not significantly different between the low and intermediate-risk groups

Table 3
The incidence of total events, MACE and relapses in the three groups at follow-up.

Variables	Low risk group	Intermediate risk group	High risk group	p value
	Follow-up (n = 31)	Follow-up (n = 50)	Follow-up (n = 15)	
Total events % (n)	16 % (5)	16 % (8)	80 % (12)	<0,0001
Relapses % (n)	16 % (5)	14 % (7)	27 % (4)	0,5
MACE[a] % (n)	0 % (0)	2 % (1)	53 % (8)	<0,0001

[a] MACE: major adverse cardiovascular events.

(Table 3). Relapses did not differ significantly between all groups.

Kaplan – Meier curves for MACE, relapses and transplants showed good prognoses in low and intermediate-risk patients and worse prognoses in high-risk patients (Fig. 2) during follow-up. At ROC curves analysis, the extent of edema (AUC 0.97, CI 0.9170–0.9967, p = 0.0027) and LGE (AUC 0.90, IC: 0.8287–0.9933 and a p = 0.0017) was associated with a higher risk of events.

Thus, intermediate-risk patients have a good prognosis and are not dissimilar from low-risk patients. Analysing events in intermediate-risk patients, we observed a correlation between the number of segments affected by LGE at baseline CMR and events (Fig. 3). Patients with no events at follow-up had fewer segments with LGE at baseline CMR than those with follow-up (4,5 ± 2,3 vs 7,5 ± 4,8; p < 0.0037). The number of segments involved by LGE that, with the best sensitivity and specificity, identifies the intermediate-risk patients most likely to develop events was 2.5 [AUC 0.5; IC (0,4167–0,7536) p = 0.24, sensitivity 60.78 %, specificity 52.63 %]. In intermediate-risk patients, we also observed a statistically significant correlation between the presence of edema at baseline CMR and the number of events (p < 0.003); the sum of the segments involved by LGE was statistically correlated to a lower mean GLS (p < 0.009). Moreover, we found a correlation between NT-proBNP levels and follow-up events (p < 0.006).

3.3. Endomyocardial biopsy and therapy: results

The endomyocardial biopsy was performed in 10 patients (8 %): in one case, we found giant cell myocarditis; in another case, eosinophilic myocarditis; and in the rest of the cases, lymphocytic and macrophagic interstitial inflammatory infiltrate was reported.

In all 10 patients with high-risk myocarditis, inotropic support was used. In addition, immunosuppressive and corticosteroid therapies were
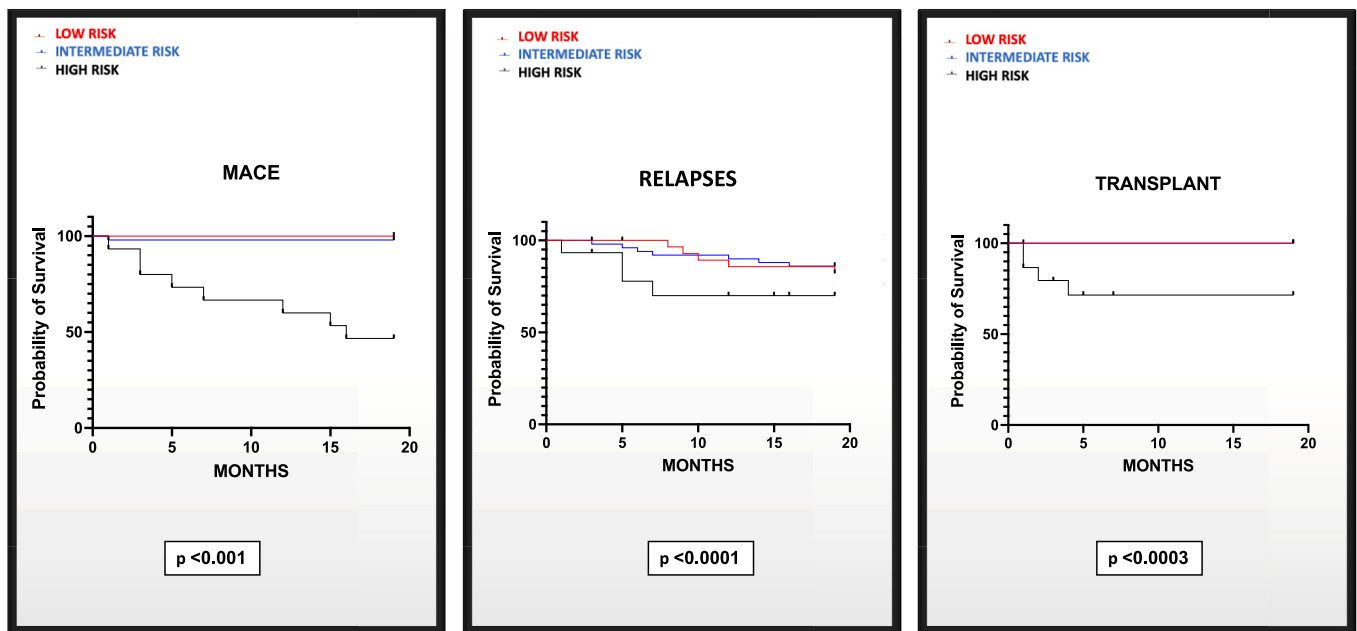
Table 2
The echocardiographic and magnetic resonance variables for the three subgroups.

Variables[a]	Low risk group			Intermediate risk group			High risk group		
	Baseline	Follow-up	p-value	Baseline	Follow-up	p-value	Baseline	Follow-up	p-value
	n = 39	n = 31		n = 71	n = 50		n = 17	n = 15	
LVEF (%) Mean ± SD	59.24 ± 3,8	58.71 ± 12.3	0.7	58.41 ± 5.2	60,7 ± 4,18	0.1	34.02 ± 12.9	50.98 ± 9.5	0.01
GLS (%) Mean ± SD	−19 ± 2.37	−20.44 ± 2.4	0.27	−18 ± 2.06	−18,97 ± 2,1	0.47	−16 ± 4,43	−19.2 ± 2.26	0.001
Edema % (n)	72 % (28)	5 % (1)	<0.0001	75 % (53)	3 % (1)	<0.0001	78 % (7)	0 % (0)	0.0004
Edema n. of segments involved	1.36 ± 1,46	0.21 ± 0.92	0.0045	3.73 ± 2.57	0.03 ± 0.16	0.01	5.9 ± 5.2	0	0.01
LGE % (n)	85 % (33)	74 % (14)	0.42	97 % (63)	75 % (27)	0.0004	90 % (9)	70 % (7)	0.4
LGE n. of segments involved	2.26 ± 1.63	1.3 ± 0.7	0.022	4.82 ± 2.75	3.3 ± 3.4	0.05	6 ± 4.32	4.4 ± 4.6	0.18

[a] GLS: global longitudinal strain; LGE: late gadolinium enhancement; LVEF: left ventricle ejection fraction.

Fig. 2. Kaplan–Meier curves for MACE, relapses, and transplants in the three risk classes.

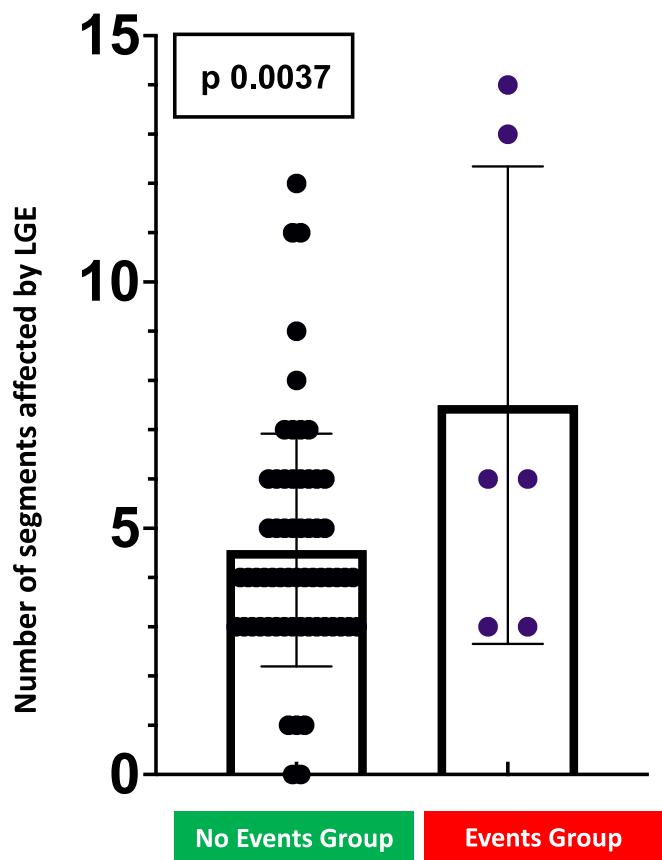**Fig. 3.** Correlation between the number of segments affected by LGE at baseline MRI and the occurrence of events.

% of patients (also in patients with low and intermediate risk).

ESC guidelines recommend heart failure therapy in patients with suspected myocarditis if left ventricular systolic dysfunction is present at presentation. Immunosuppression for at least 6–12 months is required in acute myocarditis with clinical or EMB evidence of auto-immune disease, including giant cell myocarditis, vasculitis or sarcoidosis. EMB is essential in guiding therapy for specific types of myocarditis [8,9,20].

4. Discussion

Our study confirms the presence of a higher incidence of cardiovascular events in patients with high-risk myocarditis, according to the risk stratification proposed by Sinagra et al. A lower rate of total events was found in the intermediate and low-risk groups, with no significant difference between the two groups. No low-risk patients had MACE but recurrent myocarditis.

Thus, low-risk patients have an excellent prognosis compared to high-risk patients. The prognosis of the intermediate-risk group is more uncertain. This group's cardiovascular events were associated with extended LGE at baseline (>2.5 segments involved).

In addition, we found a regression of edema during follow-up in all groups. Regarding LGE, we found a significant reduction in LGE segments involved in low-risk patients but not in high-risk patients. This reduction resulted in borderline significance in intermediate-risk patients. Our data agree with the literature data. Still, probably given the absence of significant differences between low-risk and intermediate-risk and the absence of MACE in low-risk myocarditis patients, it would be more appropriate not to consider intermediate-risk but to divide the patients into complicated myocarditis (intermediate and high-risk) and uncomplicated myocarditis.

In our study, events appear to correlate with the extent of LGE at baseline and the persistence of LGE at follow-up. The role of LGE in myocarditis has been investigated by other clinical studies and meta-analyses [21,22]. The presence of LGE without oedema at 6-month CMR is known to be associated with a worse prognosis, mainly when distributed with a mid-wall septal pattern than another. During follow-up in patients with myocarditis, LGE could increase or decrease. Patients with an increased extent of LGE have a worse prognosis than those with decreased/unchanged LGE [11,12].

used in patients with high-risk non-viral myocarditis.

Anti-inflammatory therapy was used in 59 % of total cases at admission to control pain and in patients with pericardial effusion; beta-blockers were used in 37 % of patients, and ACE inhibitors or ARBs in 46

Other studies showed a correlation between cardiovascular events in myocarditis patients and echocardiographic or CMR parameters. For example, Anzini et al. showed that the improvement of LVEF in the short term (defined as an absolute increase in LVEF of 20 % or LVEF >50 % six months after the first evaluation) is a predictor of favorable long-term prognosis, independent from baseline left ventricular function [2]. Also, the prognostic role of GLS was analyzed in myocarditis patients. In our study, the sum of the segments involved by LGE was statistically correlated to a lower GLS value; high-risk patients with worse prognoses had significantly lower GLS values.

Porcari et al. demonstrated that impaired GLS assessed by CMR (>−20 %), unlocalized LGE, and mid-wall were associated with cardiovascular events (cardiac death, life-threatening arrhythmias, development of heart failure, or LVEF <50 %) in myocarditis patients [23]. In myocarditis induced by immune checkpoint inhibitors, low GLS values were associated with more major adverse cardiovascular events [24]. In another study, LGE mass and GLS were shown to be predictors of supraventricular arrhythmias in patients with myocarditis and preserved LVEF [25]. Thus, carefully stratifying patients with myocarditis at the time of diagnosis and during the follow-up is essential to evaluate the prognosis and devise the most appropriate follow-up.

CMR and echocardiographic parameters add important information; especially, the reduction of LGE segments during follow-up seems to be associated with a better prognosis. In addition, CMR is more important during follow-up to detect the progression to dilated cardiomyopathy; in acute myocarditis, CMR has a different sensitivity that correlates with the extent of cell necrosis-promoting expansion of interstitial space [26]. Based on our findings, intermediate risk should not be considered a risk category. Still, the in-intermediate risk should be included in high-risk patients (complicated myocarditis) if extended LGE exists, considering the correlation between cardiovascular events and the extended LGE at baseline.

5. Study limitations

Our study has several limitations. First, it is a retrospective observational study, which inherently limits the ability to establish causality. Additionally, the COVID-19 pandemic significantly impacted our follow-up process, resulting in incomplete follow-up for some patients. This loss to follow-up was particularly notable in the intermediate risk group, where 19 out of 71 individuals were not adequately monitored. The pandemic's disruption also constrained our ability to perform a comprehensive quantitative evaluation of the number of segments with LGE. Moreover, we lacked sufficient data on resonance mapping and CMR-GLS. Finally, the low number of events and the relatively short follow-up period further limit the generalizability and robustness of our findings.

6. Conclusions

Based on our study, it appears that there is a higher incidence of cardiovascular events in patients with high-risk myocarditis compared to those categorized as low-risk, suggesting that low-risk patients might have a relatively better prognosis. Although no significant differences in the total number of events were observed between the low- and intermediate-risk groups, it is conceivable that the intermediate-risk category cannot be clearly separated and could potentially be integrated into the high-risk group, particularly in cases where extensive LGE at CMR occurs. This hypothesis, if further substantiated by additional research, could lead to a reevaluation of current risk stratification practices in myocarditis, ultimately refining patient management and therapeutic approaches.

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Institutional review board statement

The study was conducted in accordance with the Declaration of Helsinki, and approved by the Palermo Ethics Committee 1 A.O.U.P. "P. Giaccone" of University of Palermo (Report no. 5; Approval Date: 17 May 2023).

Informed consent statement

Informed consent was obtained from all subjects involved in the study.

CRediT authorship contribution statement

Daniela Di Lisi: Formal analysis, Investigation, Writing – original draft, Writing – review & editing. **Cristina Madaudo:** Investigation, Validation, Writing – original draft, Writing – review & editing. **Maria Gabriella Carmina:** Data curation, Formal analysis, Methodology. **Francesco Clemenza:** Data curation, Methodology, Supervision, Validation. **Domenico Scelfo:** Data curation, Software. **Eluisa La Franca:** Conceptualization, Data curation, Formal analysis, Validation. **Michela Pieri:** Data curation, Investigation, Visualization. **Giuseppe Vitale:** Data curation, Resources, Supervision. **Alfredo Ruggero Galassi:** Project administration, Supervision. **Giuseppina Novo:** Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability statement

The data presented in this study are available on request from the corresponding author due to (specify the reason for the restriction).

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