SCUOLA DI DOTTORATO
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PROGNOSTIC PERFORMANCE OF CLINICAL PRESENTATION AND CARDIAC MAGNETIC RESONANCE IMAGING PARAMETERS IN PATIENTS WITH ACUTE MYOCARDITIS

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INTRODUCTION

1. Clinical Presentation and Outcome in a Cohort of Patients With Acute Myocarditis. Data From Multicenter Lombardy Registry.

Acute myocarditis (AM) is defined as heart inflammatory disease that may occur as a consequence of infection (predominantly viral), as an exposure to toxic substances, as a result of altered immune reactivity, isolated or as part of a systemic autoimmune disease (1). Clinical presentation of AM is very heterogeneous and varies from completely asymptomatic forms to conditions presenting with ventricular arrhythmias, conduction abnormalities, heart failure and cardiogenic shock. Moreover, autoptic studies showed that AM was associated with sudden cardiac death in young adults: postmortem examinations in young adults have demonstrated that AM was responsible for 3% to 12% of cases of sudden cardiac death.

In-hospital and long-term outcomes of patients admitted with clinically suspected AM remain undetermined. There is evidence that the prognosis of patients with AM can be predicted, at least in part, on the basis of the clinical presentation. Patients presenting with ventricular arrhythmias (VAs) or symptoms of heart failure have worse prognosis compared with those presenting with chest pain.

In a previous work of our Centre we report characteristics, in-hospital management, and long-term outcome of patients with AM based on a retrospective multicenter registry from 19 Italian hospitals (2). In this retrospective multicenter study of 443 patients with AM, we analized the natural history of the condition from the time of its diagnosis up to a median follow-up of 35 months. We studied patients without concurrent cardiac disorder and with symptom onset within 1 month. We enrolled symptomatic patients with a diagnosis of AM based on either histology or increased troponin plus edema and LGE on cardiac magnetic resonance (CMR). Here, we evaluated beyond cardiac mortality and need for heart transplantation (HTx), major events related to AM, and in approximately half of cases the changes in volumes and left ventricular (LV) ejection fraction (EF) on CMR.

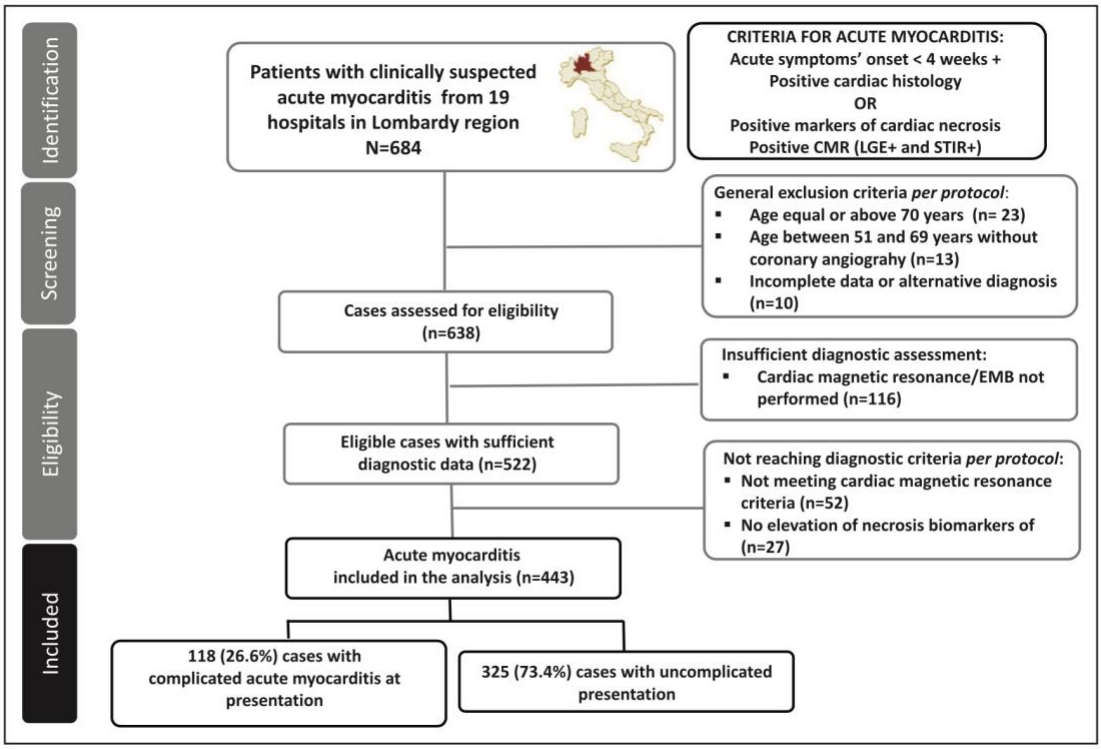


Figure 1. Flow diagram illustrating screening and inclusion criteria.
CMR indicates cardiac magnetic resonance; EMB, endomyocardial biopsy; LGE, late gadolinium enhancement; and STIR, short tau inversion recovery.

The main characteristics of the study population are reported in Table 1(2). Median age at presentation was 34 years, and 19.4% of the patients were female. The most frequent symptom at presentation was chest pain (86.7% of patients), followed by dyspnea (19.2%); 80.5% of patients had prodromal symptoms. An associated autoimmune disorder was observed in up to 7.2% of patients. Eosinophilic granulomatosis with polyangiitis and mixed connective tissue disease were the most frequently observed autoimmune or systemic inflammatory disorders (Table 2)(2).

The 443 patients were subdivided into 2 groups based on the clinical presentation at the time of hospital admission. Group 1 (complicated AM) included 118 patients (26.6%) with AM complicated by LV systolic dysfunction (ie, LVEF <50% on the first in-hospital echocardiogram), with documented sustained VAs, or with a fulminant presentation (ie, low cardiac output syndrome requiring inotropes or mechanical circulatory support). Group 2 (uncomplicated AM) included the remaining 325 patients (73.4%). Follow-up was completed in all but 5 patients (1.1%), who were lost after discharge (2 non-

European citizens and 3 Italian citizens not resident in Lombardy). Median follow-up was 35 months (interquartile range [Q1–Q3], 15–59 months) with a maximum follow-up of 188 months. The median length of follow-up did not differ between the 2 groups (P=0.38).

Women were more prevalent in the group with complicated AM. Symptoms of heart failure were more frequent in patients with complicated AM who had lower LVEF on the first echocardiogram compared with patients with uncomplicated AM. Right ventricular EMB was performed in 56 of 443 patients (12.6%). EMB was performed in 47 of 118 patients (39.8%) with complicated AM compared with 9 of 325 patients (2.8%) with uncomplicated AM. Histological evidence of active myocarditis, based on Dallas criteria, was observed in 50 of the 56 EMBs (89.3%). The most common histological subtype was lymphocytic myocarditis in both complicated and uncomplicated AM (67.3% and 66.7%, respectively).

Baseline CMR was performed in 415 of the 443 patients (93.7%) and was acquired earlier in patients with uncomplicated AM (median delay from hospitalization, 4 days; Q1–Q3, 3–7 days) compared with those with complicated AM (6 days; Q1–Q3, 3–15 days; P=0.006). As per protocol, all 415 patients scanned had evidence of myocardial edema and LGE.

Immunosuppressive agents, in particular intravenous steroids, were used in up to 37.2% of patients presenting with complicated AM compared with 2.8% of those with uncomplicated presentation (P<0.0001). Nonsteroidal anti-inflammatory drugs were used more frequently in patients with uncomplicated presentation than in those with complicated presentation (67.6% versus 44%; P<0.0001). Adrenoceptor blockers were used frequently in both groups (61.9% in complicated versus 53.8% in uncomplicated forms; P=0.18), whereas angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers were used more frequently in patients with complicated AM (72.4% versus 49.1%; P<0.0001).

Table 1. **Clinical Presentation and Initial Diagnostic Findings in 443 Patients Admitted With Clinically Suspected AM**

	Patients With Available Data, n	AM			*P* Value
		All	Complicated Presentation	Uncomplicated Presentation	
n		443	118	325	
Age, median (Q1–Q3), y	443	34 (24–42)	35 (22–45)	33 (24–42)	0.46
Age <15 y, n (%)		14 (3.2)	7 (5.9)	7 (2.2)	0.06
Female, n (%)	443	86 (19.4)	37 (31.4)	49 (15.1)	0.0002
White, n (%)	443	407 (92.1)	104 (88.1)	303 (93.2)	0.11
Clinical presentation, n (%)					
Dyspnea	437	84 (19.2)	64 (55.7)	20 (6.2)	<0.0001
Chest pain	437	379 (86.7)	68 (59.1)	311 (96.6)	<0.0001
Syncope	437	27 (6.2)	19 (16.5)	8 (2.5)	<0.0001
Fulminant presentation*	443	38 (8.6)	38 (32.2)	0 (0)	<0.0001
Fever, n (%)	437	282 (64.5)	73 (63.5)	209 (64.9)	0.82
Prodromal symptoms, n (%)	437	352 (80.5)	94 (81.7)	258 (80.1)	0.78
Sore throat, n (%)	437	161 (36.8)	44 (38.3)	117 (36.3)	0.74
Respiratory tract infection, n (%)	437	10 (2.3)	6 (5.2)	4 (1.2)	0.02
Gastrointestinal disorders, n (%)	437	126 (28.8)	36 (31.3)	90 (28.0)	0.55
Patients with associated autoimmune disorders,† n (%)	430	31 (7.2)	18 (15.4)	13 (4.2)	0.0002
Previous myocarditis, n (%)	443	5 (1.1)	2 (1.7)	3 (0.9)	0.61
ECG at admission, n (%)	426				
Normal		61 (14.3)	8 (7.6)	53 (16.5)	<0.0001
ST-segment elevation		245 (57.5)	45 (42.9)	200 (62.3)	
Other abnormal ST-T segment		100 (23.5)	39 (37.1)	61 (19.0)	
Bundle-branch block		20 (4.7)	13 (12.4)	7 (2.2)	
Any AV block, n (%)	427	13	10 (9.6)	3 (0.9)	<0.0001
Laboratory findings, n (%)					
Increased CRP at admission	414	333 (80.4)	89 (84.0)	244 (79.2)	0.32
Increased troponin T/troponin I/CK-MB at admission	437	434 (99.3)	111 (99.1)	323 (99.4)	1
Echocardiography at admission, n (%)	431	431 (97.3)	112 (94.9)	319 (98.2)	0.09
LVEF (Q1–Q3), %	428	55 (50–60)	35 (20–45)	60 (55–60)	<0.0001
LVEDD, median (Q1–Q3) (only patients ≥15 y old), mm	246	49 (46–52)	50 (46–55)	48 (46–50)	0.050
RV-TAPSE <18 mm or evidence of visual dysfunction, n (%)	259	22 (8.5)	19 (30.6)	3 (1.5)	<0.0001
Presence of pericardial effusion, n (%)	397	102 (25.7)	41 (38.7)	61 (21.0)	0.0007
Coronary angiography or CT angiography performed, n (%)	434	203 (46.8)	57 (50.0)	146 (45.6)	0.45
No evidence of CAD	203	203 (100)	57 (100)	146 (100)	…

AM indicates acute myocarditis; AV, atrioventricular; CAD, coronary artery disease; CK-MB, creatine kinase isoenzyme MB; CRP, C-reactive protein; CT, computed tomography; LVEDD, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; Q1–Q3, first through third quartile; and RV-TAPSE, right ventricular tricuspid annular plate systolic excursion.

*Fulminant presentation indicates patients with low cardiac output syndrome requiring inotropes or mechanical circulatory support.

†See Table 2 for details on associated autoimmune disorders.

Table 2. Associated Autoimmune or Systemic Inflammatory Disorders in Patients With Clinically Suspected AM (Available Data for 430 of 443, 97.1%)

	All AM, n (%)	AM With Other Autoimmune/ Inflammatory Disorders, n (%)	Complicated AM With Other Autoimmune/ Inflammatory Disorders, n (%)	Uncomplicated AM With Other Autoimmune/ Inflammatory Disorders, n (%)
Patients with associated autoimmune/ inflammatory disorders, n/N		31/430	18/117	13/313
Patients with multiple autoimmune/ inflammatory disorders	2/430 (0.5)	2/31 (6.5)	1 (5.5)	1 (7.7)
EGPA	6/430 (1.4)	6/31 (19.4)	6 (33.0)	0 (0)
Mixed connective tissue disease	5/430 (1.2)	5/31 (16.1)	3 (16.7)	2 (15.4)
Autoimmune hypothyroidism	4/430 (0.9)	4/31 (12.9)	2 (11.1)	2 (15.4)
Inflammatory bowel disease	4/430 (0.9)	4/31 (12.9)	1 (5.5)	3 (23.1)
Sarcoidosis	3/430 (0.7)	3/31 (9.7)	2 (11.1)	1 (7.7)
Isolated asthma	3/430 (0.7)	3/31 (9.7)	1 (5.5)	2 (15.4)
Autoimmune hyperthyroidism	2/430 (0.5)	2/31 (6.5)	1 (5.5)	1 (7.7)
SLE	1/430 (0.2)	1/31 (3.2)	1 (5.5)	0 (0)
Antiphospholipid syndrome	1/430 (0.2)	1/31 (3.2)	1 (5.5)	0 (0)
Psoriasis	1/430 (0.2)	1/31 (3.2)	0 (0)	1 (7.7)
Celiac disease	1/430 (0.2)	1/31 (3.2)	0 (0)	1 (7.7)
Autoimmune hepatitis	1/430 (0.2)	1/31 (3.2)	1 (5.5)	0 (0)
Multiple sclerosis	1/430 (0.2)	1/31 (3.2)	1 (5.5)	0 (0)
GVHD	1/430 (0.2)	1/31 (3.2)	0 (0)	1 (7.7)
Unknown	1/430 (0.2)	1/31 (3.2)	1 (5.5)	0 (0)

AM indicates acute myocarditis; EGPA, eosinophilic granulomatosis with polyangiitis; GVHD, graft-versus-host disease; and SLE, systemic lupus erythematosus.

In-hospital mortality and HTx in the whole study population (n=443) was 3.2% (10 cardiac deaths and 4 HTx), and these events occurred exclusively in patients with complicated AM. Furthermore, a venous-arterial extra- corporeal membrane oxygenation or a ventricular assist device was used in 23 of 443 patients (5.2%), all with complicated AM. Estimated cardiac mortality and HTx at 1, 3, and 5 years of follow-up were 3.0%, 3.3%, and 4.1%, respectively (Figure 2A). As shown in Figure 2B, cardiac mortality and HTx rates at 1, 3, and 5 years of follow-up were 11.3%, 12.5%, and 14.7%, respectively, in the group with complicated AM compared with 0% in those with uncomplicated AM (log- rank P<0.0001). Death resulting from all causes and HTx rate in the whole population at 5 years was 5.2%, with a higher incidence in complicated versus uncomplicated cases (18.0% versus 0.3%, respectively; log- rank P<0.0001). Major AM-related cardiac events after the acute phase occurred in

2.8% at the 5-year follow-up, with a significantly higher incidence in patients with complicated AM (10.8% versus 0% in uncomplicated AM; log-rank P<0.0001; Figure 3 and Table 3).

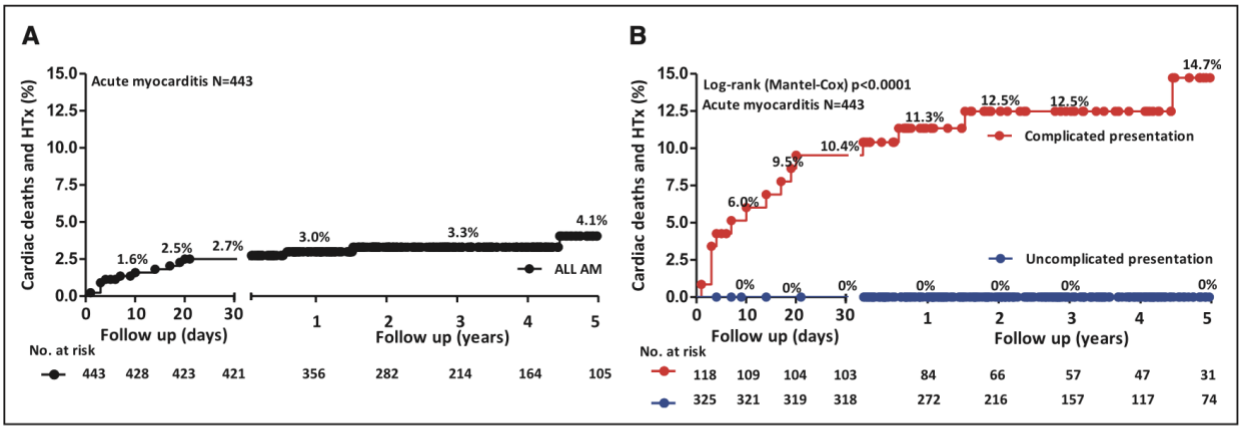


Figure 2. Kaplan-Meier estimates of 5-year cardiac mortality and heart transplantation (HTx).
A, Events in the whole study population with acute myocarditis (AM) and (**B**) events in patients with AM complicated at presentation by left ventricular ejection fraction <50%, sustained ventricular arrhythmias (VAs), or a low cardiac output syndrome compared with patients without such complications at presentation. Of total cardiac deaths and HTx, 16 patients initially presented with fulminant presentation and 1 with VAs. One cardiac death occurred after HTx and was omitted.

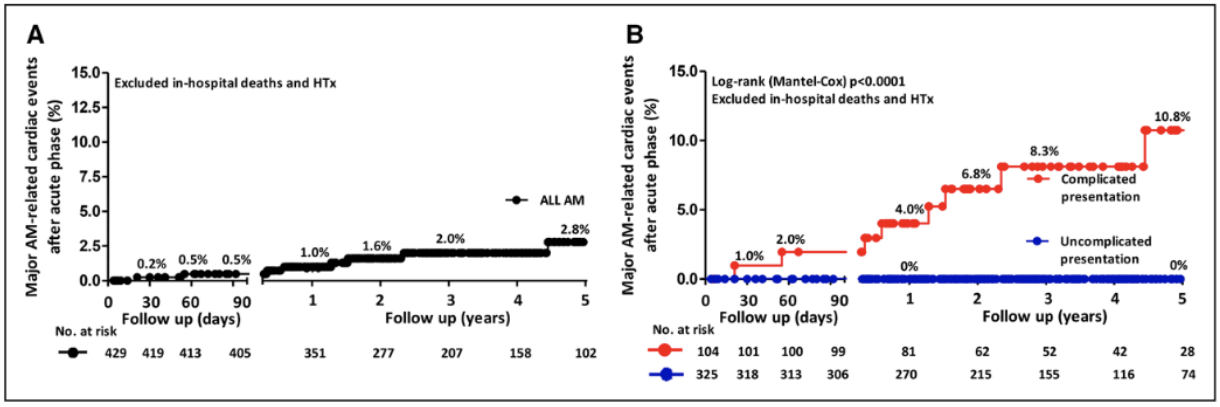


Figure 3. Kaplan-Meier estimates of 5-year composite of major acute myocarditis (AM)–related cardiac events after the acute episode.
A, Events in the overall population of patients with AM and (**B**) events in patients with AM complicated at presentation by left ventricular ejection fraction (LVEF) <50%, sustained ventricular arrhythmias (VAs), or a low cardiac output syndrome compared with patients with uncomplicated AM at presentation. The composite of major AM-related cardiac events that occurred after the acute phase included cardiac death and heart transplantation (excluding in-hospital events), sustained VAs treated with electric shock or ablation, and symptomatic heart failure needing device implantation. Three patients who died during follow-up initially had a fulminant presentation; 2 patients who were transplanted during follow-up initially had a fulminant presentation; 2 patients who had a sustained ventricular arrhythmias treated with shock or ablation in the follow-up initially had a sustained ventricular arrhythmias and 2 patients had a fulminant presentation; and 1 patient who was implanted with a cardiac resynchronization therapy device because of symptomatic heart failure during follow-up initially had an LVEF <50%. HTx indicates heart transplantation.

Table 3. Events That Occurred in 443 Patients Admitted With Clinically Suspected AM

	AM			
	All	Complicated at Presentation	Uncomplicated at Presentation	*P* Value
n	443	118	325	
In-hospital events, n (%)				
Overall deaths	10 (2.3)	10 (8.5)	0 (0)	<0.0001
Cardiac deaths	10 (2.3)	10 (8.5)	0 (0)	<0.0001
Noncardiac deaths	0 (0)	0 (0)	0 (0)	…
HTx	4 (0.9)	4 (3.4)	0 (0)	0.005
VAD	5 (1.1)	5 (4.2)	0 (0)	0.001
Va-ECMO	18 (4.1)	18 (15.3)	0 (0)	<0.0001
Lost after discharge, n (%)	5 (1.1)	2 (0.8)	3 (0.9)	
Postdischarge events, n (%)				
n	428	106	322	
Overall deaths	7 (1.6)	6 (5.7)	1 (0.3)	0.001
Cardiac deaths	2* (0.5)	2* (1.9)	0 (0)	…
Noncardiac deaths	5 (1.2)	4 (3.8)†	1 (0.3)†	0.014
HTx	2 (0.5)	2 (1.9)	0 (0)	…
SVT treated with shock/ ablation	4 (0.9)	4 (3.8)	0 (0)	0.004
CRT implantation	1 (0.2)	1 (0.8)	0 (0)	…
Other events, n (%)				
ICD implantation	9 (2.0)	8 (6.8)	1 (0.3)‡	<0.0001
Recurrence of AM	11 (2.6)	1 (0.9)	10 (3.1)	0.31
STEMI	2 (0.5)	0 (0)	2 (0.6)	…

AM indicates acute myocarditis; CRT, cardiac resynchronization therapy; HTx, heart transplantation; ICD, implantable cardiac defibrillator; STEMI, ST-segment–elevation myocardial infarction; SVT, sustained ventricular tachycardia; VAD, ventricular assist device; and Va-ECMO, venoarterial extracorporeal membrane oxygenation.

*One patient died after HTx as a result of severe graft rejections and graft dysfunction (initial diagnosis, giant cell myocarditis).

†Noncardiac deaths were caused by suicide in 2 patients, cancer in 1 patient, and infection in another patient in the complicated AM group and by cancer in 1 patient in the uncomplicated AM group.

‡The patient was initially admitted for a syncope and diagnosed with a suspected AM. During follow-up, an ambulatory electrocardiographic monitoring demonstrated a nonsustained asymptomatic ventricular arrhythmia; thus, he was implanted. No ventricular arrhythmias were further recorded after ICD implantation.

Of the 415 patients with a baseline CMR scan, 200 (48.2%) also had a follow-up CMR scan after a median time of 196 days (Q1–Q3, 126–349 days). The time interval between the 2 CMR scans did not differ between complicated (n=55) and uncomplicated (n=145) AM (228 days [Q1–Q3, 115–464 days] versus 192 days [Q1– Q3, 132–306 days], respectively; P=0.68). In the group with complicated AM, there was a slight improvement in LVEF at follow-up, whereas the LVEF at follow-up was unchanged in uncomplicated AM (Figure 4A and 4B). The proportion of patients with reduced LVEF on follow-up CMR was larger among patients with complicated AM compared with those with uncomplicated AM (Figure 4C). At follow-up, only 1 of 145 patients (0.7%) with uncomplicated AM had an LVEF <50% compared with 8 of 55 (14.5%) of those with complicated AM. Similar results were obtained when indexed LVEDV was considered (n=190). A larger proportion of patients with complicated AM had LV enlargement at follow-up compared with those with uncomplicated AM (17.3% versus 2.9%; relative risk, 1.17; 95% con- fidence interval, 1.03–1.33; P=0.003).

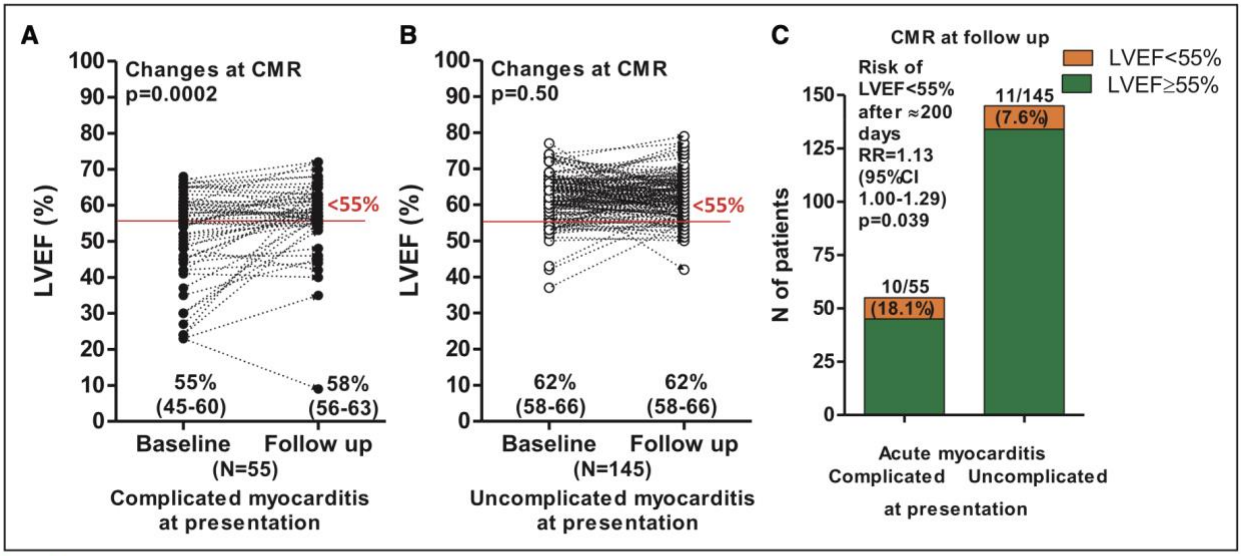


Figure 4. Changes in left ventricular (LV) ejection fraction (EF) between baseline and follow-up (median time, 196 days) cardiac magnetic resonance (CMR).
A, Patients with complicated acute myocarditis (AM) at presentation had a significant improvement in LV systolic function. **B**, Patients with uncomplicated AM had a similar LVEF at follow-up (Wilcoxon matched-pair signed-rank test was used for comparisons). **C**, Proportion of patients with an LVEF <55%, considering that a threshold for impaired LV systolic function on CMR was higher among patients with complicated AM. Categorical variables were compared with the Fisher exact test, and relative risk (RR) was calculated. CI indicates confidence interval.

The main finding of this multicenter study in patients with AM is that cardiac death and HTx occurred in 3.2% of patients during hospitalization and in 4.1% of patients at the 5-year follow-up. The second relevant result is that cardiac mortality and HTx in both the short (in-hospital, 11.9%) and long (18.0% at the 5-year follow-up) term occurred *exclusively in patients with complicated AM, presenting at admission with LVEF <50% on the first echocardiogram, sustained VAs, or hemodynamic instability*. Patients with uncomplicated AM had more benign short- and long-term outcomes, although all patients had evidence of increased necrosis biomarkers and LGE on CMR. One important message that can be derived from this study is that patients can be effectively stratified on the basis of their initial clinical presentation, main vital signs, and instrumental findings (ECG and echocardiography; Figure 5).

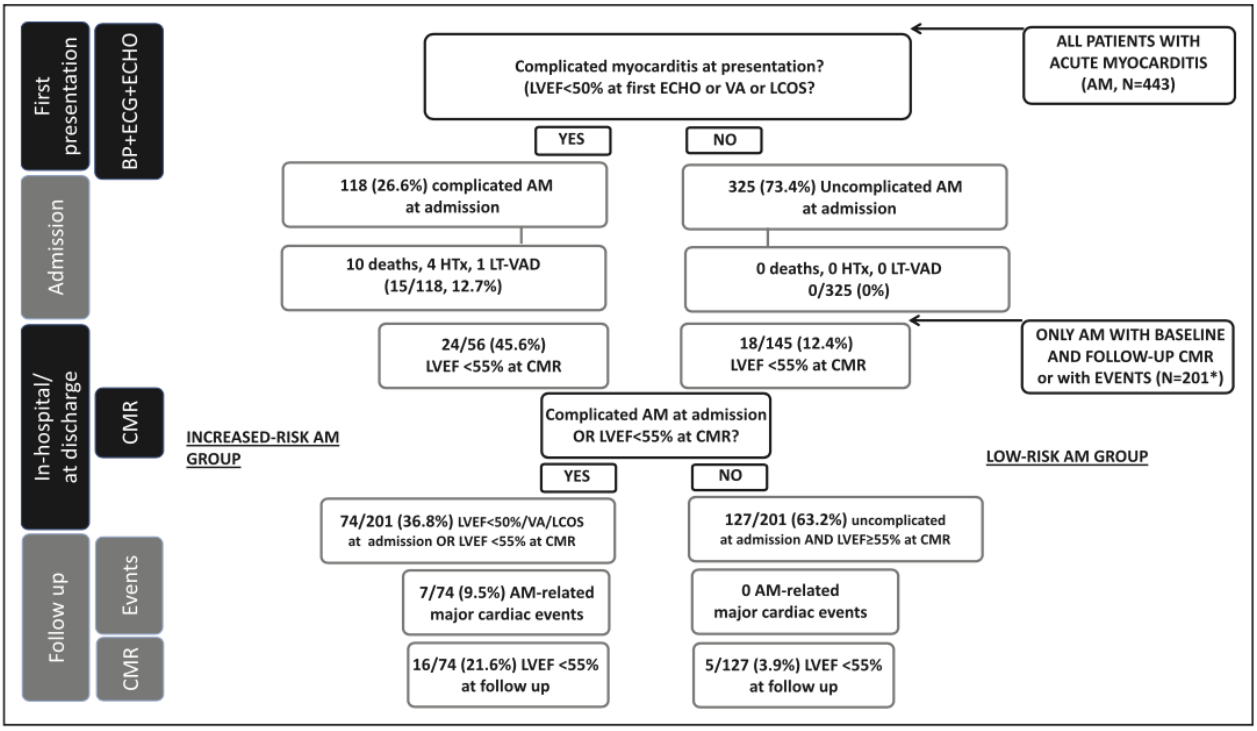


Figure 5. Risk stratification of patients with acute myocarditis (AM) based on initial clinical presentation, main vital signs, and instrumental findings.

According to the results of the registry, complicated AM based on left ventricular (LV) ejection fraction (EF) <50% at first echocardiogram (ECHO), presence of ventricular arrhythmias (VAs) on ECG, or evidence of hemodynamic instability (low cardiac output syndrome [LCOS]) at hospital admission can effectively identify patients at risk of death, heart transplantation (HTx), and long-term ventricular assist device (LT-VAD) during hospitalization (increased-risk AM group). Further information on reduced LVEF (<55%) on the baseline cardiac magnetic resonance (CMR) associated with the initial clinical presentation can effectively identify those patients at risk of further major AM-related cardiac events (composite of cardiac death, HTx, sustained VAs treated with electric shock or ablation, and symptomatic heart failure needing device implantation) during follow-up or those at risk of having a reduced LVEF on a follow-up CMR. In particular, the prognosis in term of events and risk of LVEF impairment is minimal in patients with uncomplicated AM at presentation and LVEF ≥55% on the baseline CMR (low-risk AM group). The proportion of AM-related events was significantly higher in the high-risk group compared with the low-risk group (9.5% vs 0%; *P*=0.0008, Fisher exact test). Similarly, the proportion of patients with LVEF <55% at follow-up was significantly higher in the high-risk group compared with the low-risk group: 21.6% vs 3.9% (relative risk for LVEF <55% at follow-up, 5.49; 95% confidence interval, 2.10–14.4; *P*=0.0002). BP indicates blood pressure. *The number of patients included in the follow-up after discharge was the sum of those with a baseline and a follow-up CMR (n=200) plus 1 patient (with complicated presentation) who had a baseline CMR and had an event in the follow-up that prevented the patient from undergoing the follow-up CMR.

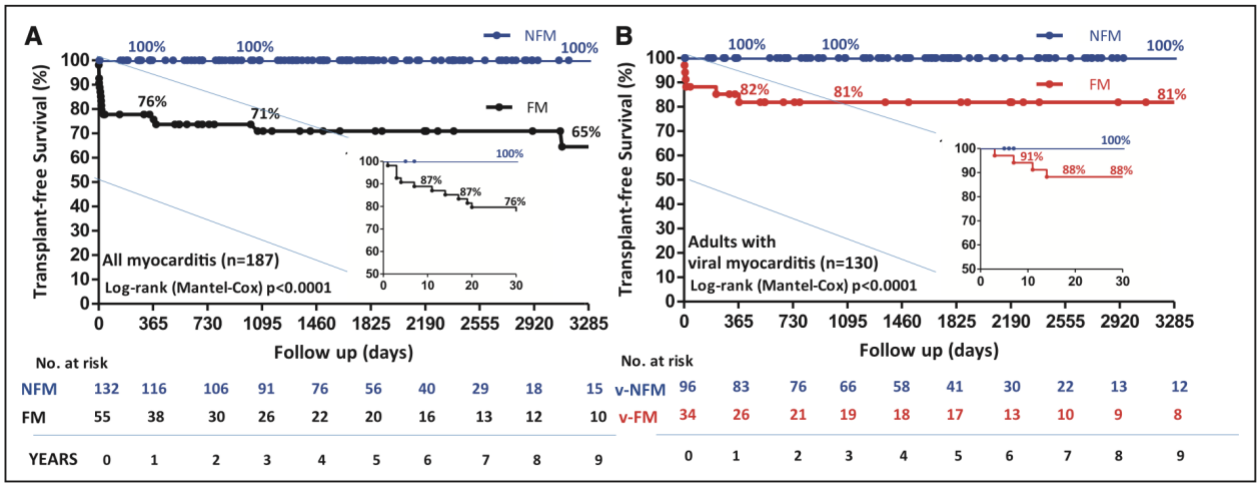
2. Survival and Left Ventricular Function Changes in Fulminant Versus Nonfulminant Acute Myocarditis.

In our retrospective study (3), we analysed outcome and changes in left ventricular ejection fraction (LVEF) in a cohort of patients with Fulminant Myocarditis (FM) compared with patients with Non Fulminant Myocarditis (NFM). We enrolled 187 consecutive patients admitted in Niguarda Hospital, Milan, and San Matteo Hospital, Pavia, with a diagnosis of acute myocarditis between May 2001 and November 2016. Of those, 55 required inotropes and/or mechanical circulatory support (FM) and the remaining 132 were hemodynamically stable (NFM). We also performed a subanalysis in 130 adult patients with acute viral myocarditis and viral prodrome within 2 weeks from the onset, which includes 34 with FM and 96 with NFM. Similar differences between FM and NFM were observed both in the whole population and in the subgroup of adults with viral forms. The proportion of female patients was larger, and dyspnea, prodromal gastrointestinal manifestations, left bundle- branch block, and arrhythmias at presentation were more frequent in FM than in NFM in both the whole patient population and the subgroup of adults with the viral form. Women were significantly older than men (median age, 38 versus 31 years; P=0.01). As expected, because of the significantly larger prevalence of women with the fulminant form (P<0.0001), they more frequently had dyspnea (P<0.0001), prodromal gastrointestinal disorders (P=0.0007), associated autoimmune disorders (P=0.01), reduced LVEF (median, 35% versus 55%; P=0.0002), and need for MCS (P<0.0001).

Regarding clinical outcome, in-hospital mortality was 18.2% (10 deaths) in the FM group compared to 0% (P<0.0001) in the NFM group. The composite of mortality and HTx was 25.5% (10 deaths and 4 HTx) and 0% (P<0.0001), respectively. *KM curves of HTx-free survival were significantly reduced in FM compared with NFM at 9 years of follow-up* (64.5% versus 100% respectively; log-rank P<0.0001; Figure 1). In the FM group, the majority of adverse events occurred during hospitalization: 10 deaths (all from cardiac causes), 4 HTxs, and 1 LVAD implantation in a patient

who was transplanted within 1 year. Among the 10 in-hospital deaths, 1 patient had GCM, 2 patients had eosinophilic myocarditis, and 7 patients had lymphocytic myocarditis. Four transplanted patients had GCM, and 1 patient discharged on LVAD had lymphocytic myocarditis. We did not observe major events in the NFM group. After discharge, 3 noncardiac deaths occurred in the FM group (1 due to lung cancer, 1 due to brain cancer, and 1 due to suicide). When only verifiable cardiac deaths are considered, KM curves showed worse survival for FM compared with NFM at 9 years of follow-up (74.9% versus 100%; log-rank P<0.000). Likewise, when children were excluded; HTx-free survival was significantly reduced in the FM compared with the NFM group (63.8% versus 100%; log-rank P<0.0001). In the 14 children (age <15 years), we had 3 in-hospital deaths among the 8 children with FM (all lymphocytic myocarditis) and no events among the 6 with NFM. In a comparison of the FM group with 48 NFM patients with hemodynamically stable presentation but with LV systolic dysfunction (ie, LVEF <55%, median LVEF, 45%; Q1–Q3, 40%–50%), FM was more frequently associated with death or HTx during hospitalization (P<0.0001).

Figure 1.



A, Kaplan-Meier curves of transplantation-free survival in FM vs NFM in the entire population (n=187) and **(B)** in the adult patients with viral myocarditis (n=130). Events that occurred in the first 30 days after hospitalization are shown in the **inset**. It is clearly shown that most adverse events in patients with FM occurred during this initial period, whereas no adverse events occurred in patients with NFM.

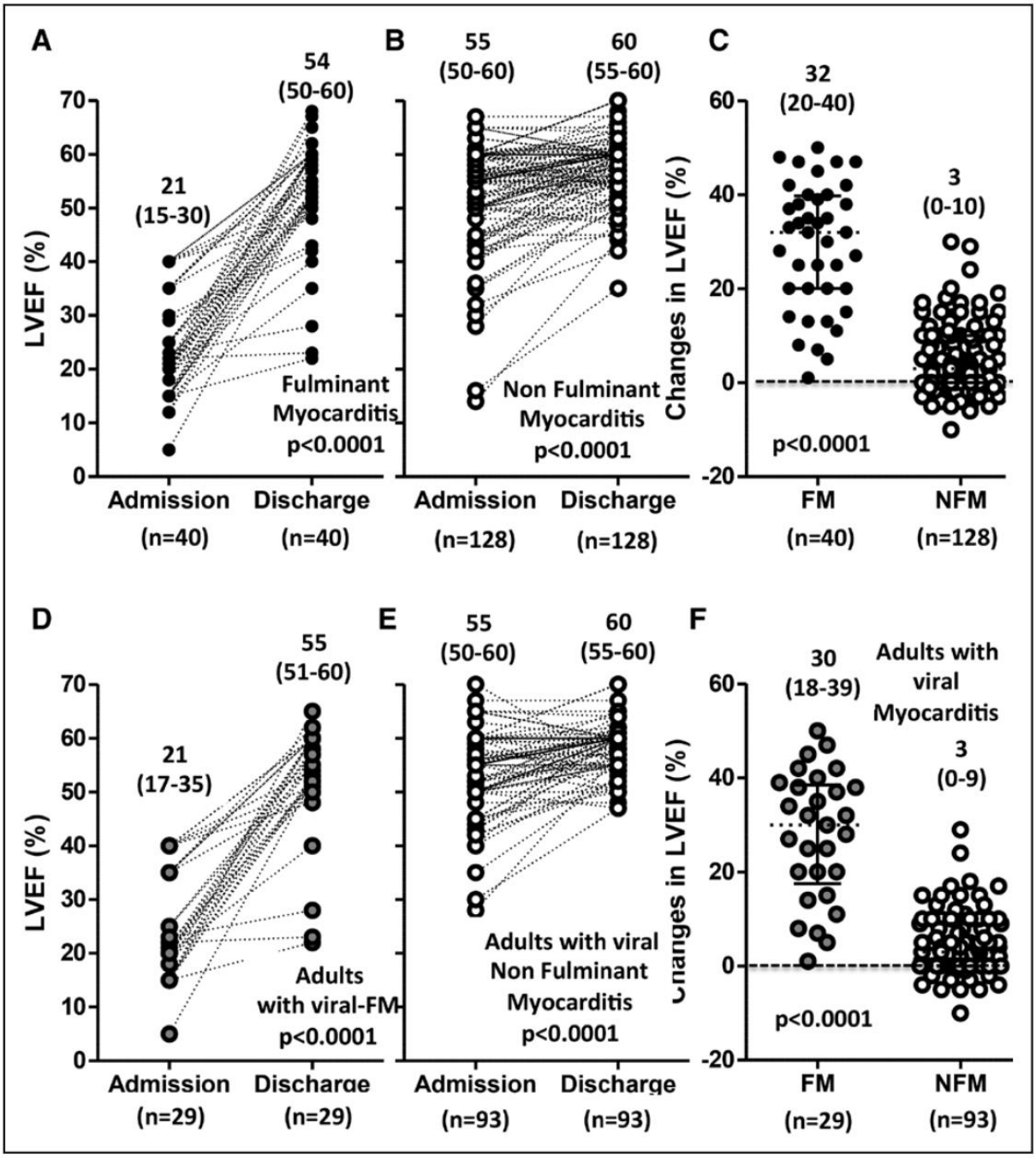
LVEF improved significantly (P<0.0001) in both groups during hospitalization, although LVEF at discharge was significantly lower in the FM group (P=0.0006). LVEF improvement was larger in FM compared with NFM (P<0.0001; Figure 5C). This also holds true in the comparison of the improvement in LVEF in patients with FM and the 47 patients with NFM with LV systolic dysfunction (P<0.0001). Similar results were obtained in the subanalysis including only adults with viral myocarditis.

Last, the proportion of patients with LVEF <55% at discharge was larger in the FM (21 of 40, 53%) than in the NFM (24 of 128, 19%; P<0.0001) group, with an RR of being discharged with reduced LVEF of 2.80 (95% CI, 1.76–4.46). Likewise, considering adults with viral myocarditis, the proportion of patients with LVEF <55% at discharge was larger in the v-FM (14 of 29, 48%) than in the v-NFM (14 of 93, 15%; P=0.0006) group, with an RR of being discharged with LVEF <55% of 3.21 (95% CI, 1.74–5.92).

Regarding Long-Term Changes in LVEF, considering the last available LVEF after discharge with a median follow-up of 22 months (Q1–Q3, 11–52 months), the proportion of patients with LVEF <55% was still higher in patients with FM (9 of 31, 29%) than in patients with NFM (9 of 103, 9%; P=0.007). The RR of a reduced LVEF at follow-up was 3.32 in the FM group (95% CI, 1.45–7.64). Likewise, considering adults with viral myocarditis, the proportion of patients with LVEF <55% at the last echocardiographic assessment was higher in the v-FM (5 of 22, 23%) than in the v-NFM (2 of 71, 3%; P=0.008) group, with an RR of being discharged with LVEF <55% of 8.01 (95% CI, 1.68– 38.7). In patients with available echocardiographic data, a further modest improvement in LVEF was observed in the whole population of FM and NFM after discharge, as well as in the subgroup with viral FM and NFM. None of the patients with NFM and LVEF 55% at discharge had a significant decrease in LVEF (a decrease >10% or to <50%) during follow-up, whereas in the FM group, only a 3-year-old child had a decrease of LVEF from 68% to 43%, although he remained asymptomatic.

One patient with lymphocytic FM was on the waiting list for HTx at the end of follow-up (LVEF at discharge, 23%; last LVEF, 23% after 6 months).

Figure 2. Changes in left ventricular ejection fraction (LVEF) during hospitalization in patients with acute myocarditis.



A, Echocardiographic data of LVEF at admission and discharge in the entire population of fulminant myocarditis (FM; available data, n=40 of 55) **(B)** and nonfulminant myocarditis (NFM; available data, n=128 of 132). Wilcoxon matched-pair signed-rank test was used for comparisons. **C**, Delta of LVEF improvement in FM vs NFM (Mann-Whitney *U* test was used for comparison). **D** through **F,** Similar analyses in the subgroup of adults with viral FM (available data, n=29 of 34) vs NFM (available data, n=93 of 96) after exclusion of pediatric age and those with giant-cell and eosinophilic forms.

The findings from this study showed that overall patients with FM have an increased mortality and need for HTx compared with those with NFM. Moreover patients with FM have more severely impaired LVEF at admission that, despite steep improvements during hospitalization, remains lower than in patients with NFM at long-term follow-up. All these findings also hold true if one confines the analysis to adults with viral myocarditis.

3. Persistent left ventricular dysfunction after acute lymphocytic myocarditis: Frequency and predictors.

Acute lymphocytic myocarditis (LM) presenting with left ventricular (LV) systolic dysfunction represents a challenge in terms of diagnosis, management and prognostication. Patients with acute LM with fulminant presentation, characterized by hemodynamic instability, have a worse in hospital prognosis and are more prone to exhibit LV systolic dysfunction during follow-up with respect to those with non-fulminant presentation. However, the natural history of the specific subgroup of patients presenting with acute LM and LV systolic dysfunction is widely unknown, particularly regarding the frequency and the early predictors of persistent LV dysfunction in the long term.

In our previous work in collaboration with the Trieste and Pavia Hospitals we analyzed all the patients with histologically proven acute myocarditis consecutively admitted at Hospital from 2000 to 2016.

This study evaluates a cohort of patients with acute LM, presenting with HF symptoms of recent onset (< 30 days) and LV dysfunction (mean LVEF at admission 26%). To the best of our knowledge, this study is the first report on persistent LV systolic dysfunction in histologically proven lymphocytic myocarditis, and provides some important insights: 1) more than half of the patients surviving the index hospitalization exhibited persistent LV systolic dysfunction, at discharge and during follow-up; 2) fulminant forms were characterized by a poor outcome during hospitalization 3) increased LV size, poor lymphocytic infiltrate at EMB, non-fulminant presentation at admission, and lack of improvement of LVEF at pre-discharge echocardiography predicted persistent LV systolic dysfunction at follow-up in survivors.

Furthermore our study shows that at 1-year follow-up, LVEF is <50% in more than half of patients with LM presenting with LV systolic dysfunction at admission. Intriguingly, features of a sub-acute inflammatory disease already present at the clinical onset, suggesting an evolving progressive cardiomyopathy process (i.e. poor lymphocytic infiltrate at EMB, dilated LV and non-fulminant

presentation), appear to be related to persistent LV dysfunction at follow- up. Despite a maximum of 30 days of symptoms as inclusion criterion of this study, it is possible that patients with persistent LV dysfunction had been evaluated and treated later along the course of the inflammatory process in comparison with patients who fully recovered. In fact, a younger age as well as an increased C-reactive protein and pericardial effusion at admission were more frequent in patients who recovered compared with those who did not. While inflammation tend to spontaneous resolution over time, patients that did not recover showed only a poor inflammatory infiltrate as probably a relevant quota of damage already occurred with lower probability of LVEF recovery despite the implementation of optimal therapeutic strategies (including early supportive therapy, standard HF therapy, immunosuppression). Finally, patients with persistent LV systolic dysfunction showed a trend of worse long-term prognosis compared to patients that normalized LVEF.

Fulminant forms comprised almost half of our cohort. It must be noted that more than 80% of fulminant cases who survived presented at least moderate inflammatory infiltration and most of them were treated with steroids. More than 75% of patients with fulminant myocarditis who survived after the acute phase showed a normal LV systolic function already at the discharge. This could explain the apparently paradoxical low percentage of beta-blockers in the group of patients with LVEF recovery at follow-up evaluation. However, 26% of survived fulminant myocarditis were characterized by persistent LV systolic dysfunction at 1 year. Notably, they were characterized by a poor inflammation at EMB performed at index hospitalization. These finding underscores the need of individualized long-term follow-up and therapy.

This study considers one of the largest cohorts of biopsy-proven acute LM patients with LV systolic dysfunction at presentation, and some clinical implications for patient management and further studies may be derived: 1) *early endomyocardial biopsy is highly recommended in patients with clinically suspected myocarditis and newly diagnosed significant LV dysfunction: these patients*

should be promptly referred to experienced centers for both diagnosis and treatment, that may include advanced circulatory support and transplantation; 2) *time course of LV dysfunction must be followed and characterized during index hospitalization, since significant improvement of LVEF may occur, and pre-discharge LVEF predicts long-term LV function*; 3) *fulminant myocarditis portends a high risk for early death or need for HTX, but full recovery is possible, often persistent over time.*

Table 1. Baseline characteristics of study population divided on the basis of persistent left ventricular (LV) systolic dysfunction.

	Study population (N = 48)	Persistent LV dysfunction at follow-up (N = 27, 56%)	Normal LV function at follow-up (N = 21, 44%)	p
Age (years)	38±16	43±14	32±15	0.03
Age <15 (%)	2 (4)	1 (4)	1 (5)	0.856
Male gender, n (%)	25 (52)	14 (52)	11 (52)	0.601
Duration of symptoms (days)	11 (5–26)	20 (14–28)	5 (3–6)	<0.001
Admission Heart Rate (bpm)	95±34	81±25	114±36	0.001
Admission SBP (mmHg)	103±21	110±16	87±23	0.002
NYHA Class				
II	17 (35)	11 (41)	7 (33)	0.880
III	14 (29)	12 (44)	2 (10)	0.008
IV	16 (33)	4 (15)	12 (60)	0.001
Fulminant forms, n (%)	23 (48)	6 (22)	17 (81)	<0.001
Flu-like symptoms, n (%)	40 (83)	20 (74)	20 (95)	0.087
Increased CRP, n (%)	24 (50)	8 (30)	16 (76)	<0.001
Atrial Fibrillation, n (%)	5 (10)	1 (4)	4 (19)	0.09
LBBB, n (%)	3 (6)	1 (4)	2 (10)	0.693
1st, 2nd, 3rd AV Blocks, n (%)	7 (15)	4 (15)	3 (14)	0.623
LVEDD (mm)	57±9	60±6	51±10	<0.001
Baseline LVEF (%)	26±9	28±7	24±11	0.211
LVEF at discharge (%)	42±13	32±8	53±8	<0.001
Pericardial effusion, n (%)	13 (27)	4 (15)	9 (43)	0.039
Poor lymphocytic Infiltrate*, n (%)	15 (31)	13 (48)	2 (10)	0.008
Moderate-to severe fibrosis at EMB	16 (33)	10 (37)	6 (29)	0.550
Beta-blockers at discharge, n (%)	38 (79)	25 (93)	13 (62)	0.012
ACE-inhibitors-ARBs at discharge, n (%)	43 (90)	24 (89)	19 (90)	0.621
Aldosterone receptors antagonist at discharge, n (%)	18 (38)	12 (44)	6 (29)	0.205
Immunosuppressive therapy (%)	35 (73)	20 (74)	15 (71)	0.838

Values are expressed as mean±SD or median with interquartile range as appropriate, and as percentage.
ACE, angiotensin converting enzyme; ARBs, angiotensin receptor blockers; AV, atrioventricular; CRP, C-reactive protein; EMB: endomiocardial biopsy; LBBB, left bundle branch block; LM: lymphocytic myocarditis; LVEDD, left ventricular end-diastolic diameter; LVEDV, left ventricular end-diastolic volume; LVEF, ejection fraction; MR, mitral regurgitation; RFP, restrictive filling pattern; SBP, systolic blood pressure;
*vs. moderate to plentiful

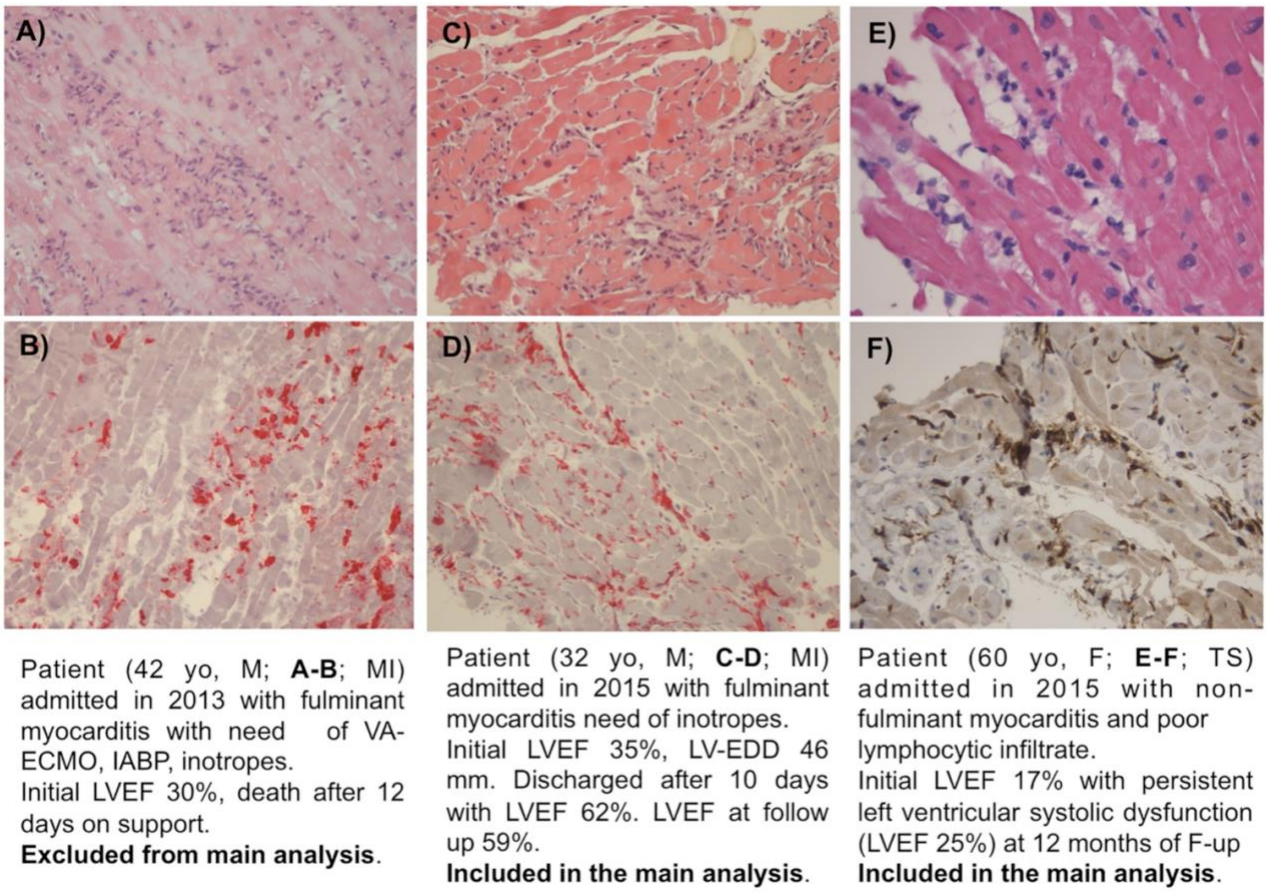


Fig 2. Histological images of three patients with acute LM presenting left ventricular dysfunction at admission. A-B) Fulminant form with plentiful lymphocytic infiltrate and necrosis, he died during the acute phase (excluded from main analysis); C-D) Fulminant form with plentiful lymphocytic infiltrate, he normalized systolic function during follow-up (included in the main analysis); E-F) non-fulminant form with poor lymphocytic infiltrate, he will maintain LV dysfunction during follow-up (included in the main analysis). LM: Lymphocytic Myocarditis; LV: Left Ventricular. A) HE showing diffuse inflammatory infiltrates and myocardial necrosis. B)Immunohistochemistry showing diffuse CD8+ T cells infiltrates (in red). C) HE showing moderate inflammatory infiltrates and mild myocardial necrosis. D) Immunohistochemistry showing diffuse HLA-DR+ cells (in red). E) HE showing poor inflammatory infiltrates and myocardial necrosis. F) Immunohistochemistry showing mild HLA-DR+ cells (in brown).

Table 2. Univariable and multivariable analyses for persistent LV systolic dysfunction.

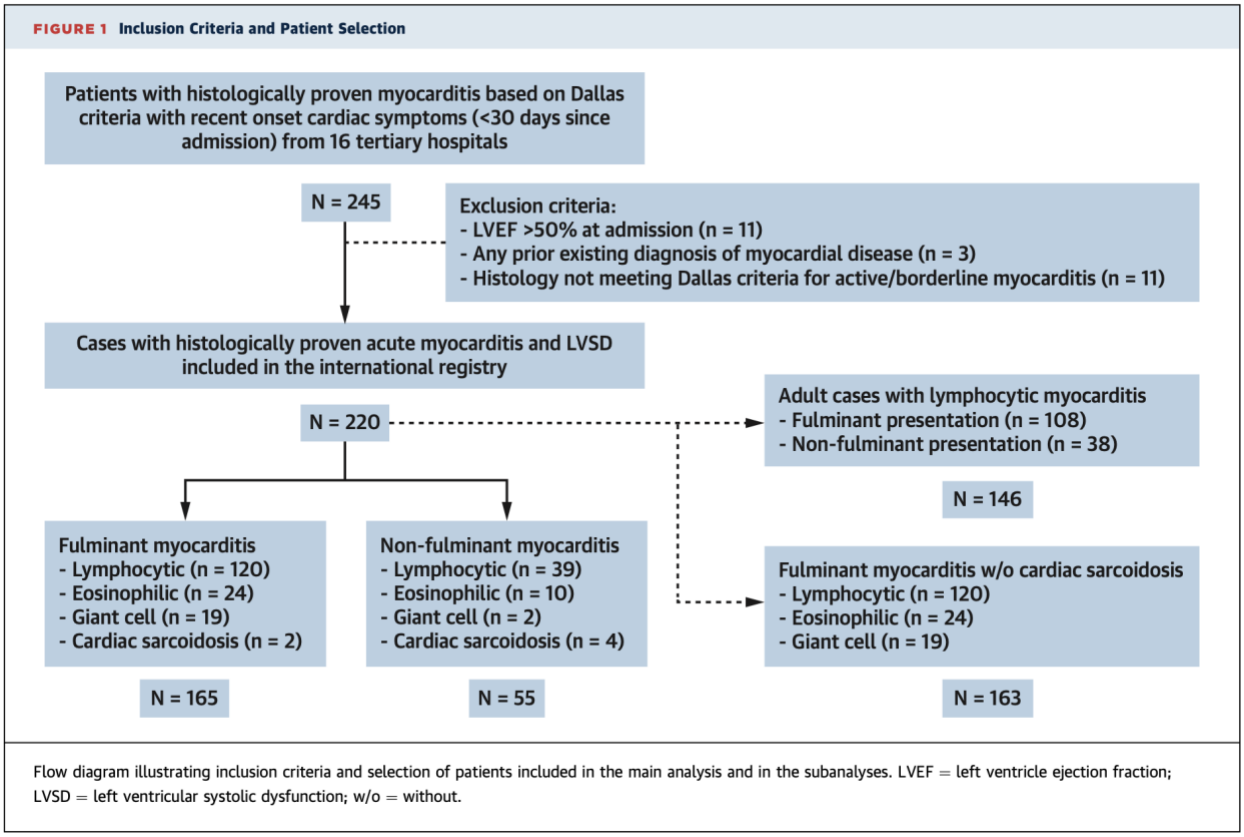
	Univariable			Multivariable		
	OR	**95% C.I.**	**p**	**OR**	**95% C.I.**	**p**
Age[a]	1.06	1.01–1.11	0.015			
Heart Rate[a]	0.96	0.93–0.98	0.001			
SBP[a]	1.10	1.020–1.192	0.014			
Non-fulminant forms (if surviving to the acute phase)	**14.87**	**3.60–61.39**	**<0.001**	**8.46**	**1.28–55.75**	**0.013**
Poor Lymphocytic Infiltrate	**9.45**	**1.77–50.47**	**0.009**	**12.4**	**1.23–124.97**	**0.010**
Baseline LVEDD[a]	**1.19**	**1.06–1.34**	**0.003**	**1.22**	**1.04–1.43**	**0.002**
Baseline LVEDV[a]	1.02	1.00–1.04	0.018			
Pericardial Effusion	0.18	0.04–0.80	0.024			
Baseline increased CRP	0.089	0.02–0.39	0.001			

SBP, systolic blood pressure; EF, ejection fraction; LVEDD, left ventricular end-diastolic diameter; LVEDV, left ventricular end-diastolic volume; MR, mitral regurgitation; RFP, restrictive filling pattern; TAPSE, tricuspid annular plane systolic excursion; IABP, intra-aortic balloon pump; ECMO, extracorporeal membrane oxygenation; CRP, C-reactive protein; EMB, endomyocardial biopsy;

[a]. Odds ratio estimation is referred to every unit increase for continuous variables.

4. Fulminant Versus Acute Nonfulminant Myocarditis in Patients With Left Ventricular Systolic Dysfunction.

Regarding patients with fulminant myocarditis, i report the data of a previous retrospective, international, multicenter cohort study coordinated by Niguarda Hospital in Milan, to which they contributed sixteen tertiary hospitals (13 [81.3%] with an HTx program) across the United States (n 3), Europe (n 9), and Japan (n 4). In this study all consecutive patients with a diagnosis of histologically proven myocarditis were searched from the local pathology database from January 1, 2001 to March 31, 2018 (4).



Flow diagram illustrating inclusion criteria and selection of patients included in the main analysis and in the subanalyses. LVEF = left ventricle ejection fraction; LVSD = left ventricular systolic dysfunction; w/o = without.

The overall population included 220 patients (FM 165, NFM 55). Among patients with FM, LM was diagnosed in 120, GCM in 24, and EM in 19, and cardiac sarcoidosis in 2. The median follow-up for those surviving the index hospitalization did not signicantly differ (1,082 days [IQR: 258 to 2,558

days] vs. 1,002 days [IQR: 244 to 2,425 days] in FM and NFM, respectively). Four cases (1.8%) were lost after discharge and were censored as alive at the time of discharge. Of these, 2 patients belonged to the NFM group (last LVEF at discharge 58% and 50%) and 2 patients belonged to the FM group (last LVEF 30% and 70%). Main characteristics of the study population and a comparison between patients with FM (n 165) and NFM (n 55) are presented in Table 1. Median age was 42 years (IQR: 27 to 57 years) with a female prevalence of 46.3%. Prodromal symptoms were more commonly observed in FM patients. At baseline, patients with FM, compared with those with NFM, had lower LVEF, and higher levels of C-reactive protein, biomarkers of myocardial necrosis, creatinine, and transaminases. Cardiac arrest requiring resuscitation maneuvers, ventricular defibrillation, and sustained ventricular tachycardia occurred more frequently in FM patients. With regard to the histologic subtypes, *GCM was more common in FM* patients and *cardiac sarcoidosis in NFM patients*.

Viral genome analysis on myocardial biopsies was performed in 63 patients (28.6% of total; 54.5% of NFM and 20.0% of FM) yielding positive results in only 19.0% of the cases, with parvovirus B19 being the most frequently identified virus. Inotropes were used in all patients with FM for a median time of 10 days (IQR: 6 to 17 days). Intra-aortic balloon pump was the most frequently used temporary MCS (median time of use: 6 days; IQR: 3 to 11 days), alone (18.1%) or in combination with other devices (36.9%). MCS other than intra-aortic balloon pump were used in 50.9% of FM cases (median time on support: 8.5 days; IQR: 5 to 15 days), most frequently a peripheral veno-arterial extra corporeal membrane oxygenation (44.2%). Immunosuppressive therapy was administered to 58.5% of NFM patients and in 66.8% of FM patients (p 0.32), with steroids (alone or in combination) being the most frequently used drug in both groups.

TABLE 1 Clinical Presentation and Initial Diagnostic Findings in Patients Admitted With Histologically Proven FM and Acute NFM

	Patients With Available Data	Acute Myocarditis		
		FM	NFM	p Value
Overall		165	55	
Demographics				
Age, yrs	220	42 (26-57)	40 (28-55)	0.988
Age <15 yrs	220	12 (7.2)	1 (1.7)	0.193
Female	220	81 (49.0)	21 (38.1)	0.211
Presenting symptoms				
Dyspnea	217	120 (73.6)	36 (66.6)	0.472
Chest pain	215	51 (31.6)	20 (37.0)	0.505
Syncope	214	28 (17.5)	9 (16.6)	1.000
Prodromal symptoms	219	120 (72.7)	31 (57.4)	0.042
Fever	216	97 (59.8)	26 (48.1)	0.154
GI symptoms	215	61 (37.8)	9 (16.6)	0.004
Respiratory symptoms	213	49 (30.8)	7 (12.9)	0.012
Autoimmune disorders*	211	28 (17.7)	13 (24.5)	0.317
Active cancer	216	4 (2.5)	0 (0.0)	0.574
Use of ICI	216	2 (1.2)	0 (0.0)	1.000
ECG at admission				
Normal	208	9 (5.8)	5 (9.4)	0.354
ST-segment elevation	208	54 (34.8)	13 (24.5)	0.178
Other ST-T segment abnormalities	208	54 (34.8)	23 (43.4)	0.323
QRS interval >120 ms	198	55 (37.9)	12 (22.6)	0.061
Life-threatening arrhythmias†				
Cardiac arrest	213	41 (25.8)	5 (9.2)	0.012
VT/VF	134	46 (46.9)	6 (16.7)	0.002
Advanced AV block	220	13 (7.9)	2 (3.6)	0.367
Admission laboratory tests				
Increased CRP	195	123 (86.0)	28 (53.8)	<0.0001
Increased troponin T/I or CK-MB	204	133 (86.3)	32 (64.0)	0.001
Increased creatinine	201	75 (48.7)	8 (17.0)	<0.0001
Increased transaminases	200	125 (81.1)	25 (54.3)	<0.0001
Echocardiography at admission				
LVEF, %	220	22 (15-30)	33 (25-42)	<0.0001
LVEDD in patients ≥15 yrs, mm	172	49 (45-56)	56 (51-60)	0.0003
RV-TAPSE <18 mm or evidence of visual dysfunction	114	67 (84.8)	22 (62.8)	0.014
Pericardial effusion	205	75 (48.3)	15 (30.0)	0.033
Coronary angiogram	209	95 (60.5)	30 (57.6)	0.746
Histological diagnosis	220			0.010
Lymphocytic		120 (72.7)	39 (70.9)	0.862
Giant cell		24 (14.5)	2 (3.6)	0.030
Eosinophilic		19 (11.5)	10 (18.1)	0.249
Cardiac sarcoidosis		2 (1.2)	4 (7.2)	0.035

Values are n, median (interquartile range), or n (%). *In the FM group: systemic lupus erythematosus, n = 2; Crohn disease, n = 2; pernicious anemia and autoimmune thyroiditis, n = 1; eosinophilic granulomatosis with polyangiitis, n = 8; sarcoidosis, n = 2; ulcerative colitis and autoimmune thyroiditis, n = 1; mixed connective tissue disease, n = 1, Miller-Fisher disease, n = 1; eosinophilic granuloma (histiocytosis X), n = 1; IgA deficiency, n = 1; myasthenia gravis, n = 1; Kawasaki disease, n = 1; rheumatoid arthritis, n = 1; thrombotic thrombocytopenic purpura, n = 1; scleroderma, n = 1; systemic lupus erythematosus and autoimmune hepatitis and ulcerative recto colitis, n = 1; vitiligo, n = 1; autoimmune thyroiditis, n = 1. In the NFM group: alopecia areata, n = 1; sarcoidosis, n = 2; eosinophilic granulomatosis with polyangiitis, n = 3; autoimmune thyroiditis, n = 2; Still disease, n = 1; acute febrile neutrophilic dermatosis, n = 1; primary biliary cholangitis and polymyositis, n = 1; ulcerative recto colitis, n = 1, rheumatoid arthritis, n = 1. †Defined as ventricular arrhythmias or cardiac arrest requiring resuscitation maneuvers that took place during the acute phase of the disease.

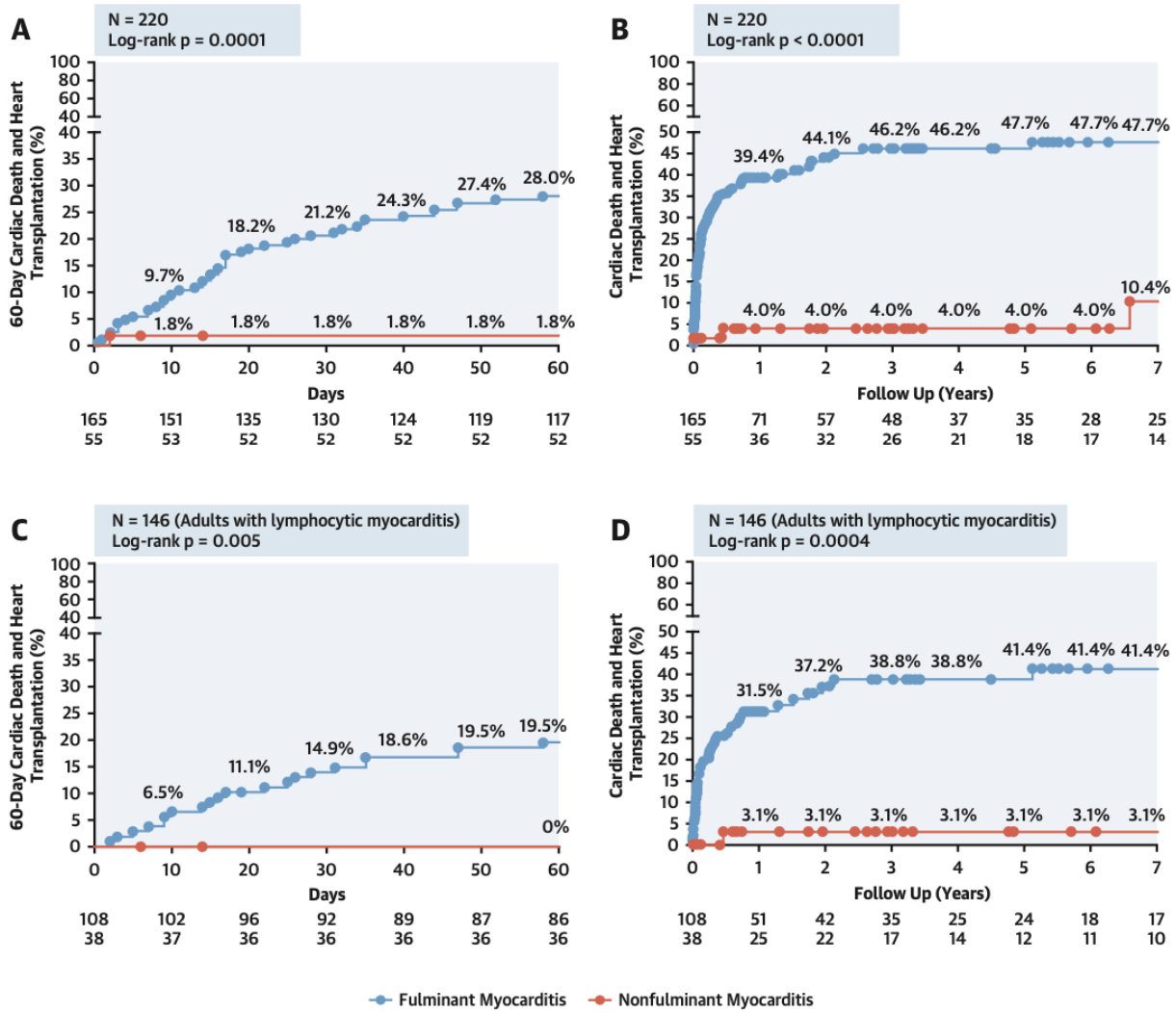
AV = atrioventricular; CK-MB = creatine kinase-MB; CRP = C-reactive protein; ECG = electrocardiogram; FM = fulminant myocarditis; GI = gastrointestinal; ICI = immune checkpoint inhibitors; IgA = immunoglobulin A; IQR = interquartile range; LVEDD = left ventricular end-diastolic diameter; LVEF = left ventricular ejection fraction; NFM = nonfulminant myocarditis; RV-TAPSE = right ventricle tricuspid annular plane systolic excursion; VF = ventricular fibrillation; VT = ventricular tachycardia.

Regarding outcome: cardiac death or HTx within 60 days occurred in 46 FM cases (27.8%) and in 1 patient (1.8%) with NFM. Occurrence of cardiac death or HTx was 43.0% in FM patients (47 cardiac deaths and 24 HTx) and 9.0% in NFM cases (4 cardiac deaths and 1 HTx). There were 3 noncardiac deaths (2 [1.2%] in FM and 1 [1.8%] in NFM), all occurring after discharge from index hospitalization. Kaplan-Meier curves comparing cardiac death or HTx in FM versus NFM patients are reported in the Central Illustration A and B. *The incidence of cardiac death or HTx was higher in FM, compared with NFM, both at 60 days and in the long term (both $p < 0.001$)*. Similarly, in the subanalysis including only adult patients with LM, FM, compared with NFM, patients had a significantly worse prognosis both at 60 days and during follow-up (Central Illustration C and D). Fulminant presentation, giant-cell histology, QRS interval >120 ms on electrocardiography, cardiac arrest and advanced atrioventricular block were significantly associated with the outcome at 60 days using univariate analysis, with FM, GCM, and QRS interval >120 ms remaining significant at multivariate analysis. Fulminant presentation, giant-cell histology, and QRS interval >120 ms were associated with cardiac death or HTx in the long term using multivariate analysis. *Considering the 146 adult patients with LM, the only variable that was associated with cardiac death or HTx in the long term at multivariate analysis was fulminant presentation.*

Regarding characteristics and outcome of FM patients according to main histological subtypes, we observed that patients with LM were signficantly younger than those with GCM or EM. A concomitant autoimmune disorder was diagnosed more frequently in EM. Compared with the other histological subtypes, GCM had a significantly higher rate of occurrence of cardiac arrest, sustained ventricular tachycardia and fibrillation, and increased creatinine. Figures 2A to 2C show Kaplan-Meier curves comparing the composite incidence of cardiac death or HTx in FM patients stratfied according to the 3 main histological subtypes. *A significantly higher incidence of cardiac death or HTx was observed in patients with GCM compared with in those with EM and LM, both at 60 days*

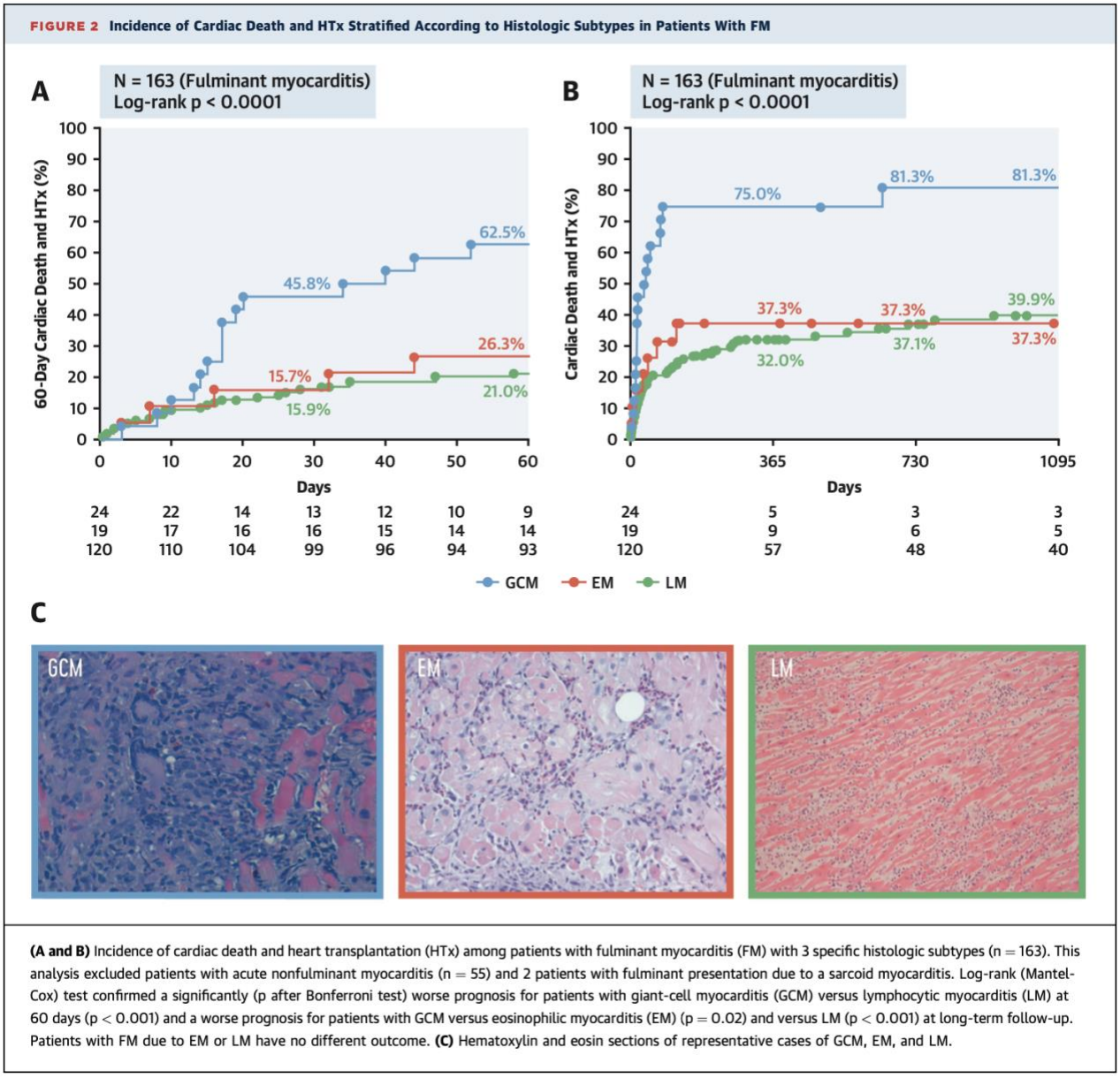
and at 3 years (overall log- rank $p < 0.0001$). At multivariate analysis, giant-cell histology and the use of temporary MCS other than intra-aortic balloon pump were the factors significantly associated with 60-day cardiac death or HTx, whereas giant-cell histology, QRS interval >120 ms, and the use of temporary MCS other than intra-aortic balloon pump emerged as determinants of outcome in the long term.

CENTRAL ILLUSTRATION **Outcome in Histologically Proven Fulminant Myocarditis Versus Acute Nonfulminant Myocarditis With Left Ventricular Systolic Dysfunction**



Ammirati, E. et al. J Am Coll Cardiol. 2019;74(3):299-311.

(A and B) Kaplan-Meier curves comparing the composite incidence of cardiac death and heart transplantation (HTx) in fulminant myocarditis (FM) versus nonfulminant myocarditis (NFM) in the entire population (n = 220) at 60 days and after 7 years of follow-up. **(C and D)** Kaplan-Meier curves in a subset including only adult patients with lymphocytic myocarditis (n = 146) at 60 days and after 7 years of follow-up.



(A and B) Incidence of cardiac death and heart transplantation (HTx) among patients with fulminant myocarditis (FM) with 3 specific histologic subtypes (n = 163). This analysis excluded patients with acute nonfulminant myocarditis (n = 55) and 2 patients with fulminant presentation due to a sarcoid myocarditis. Log-rank (Mantel-Cox) test confirmed a significantly (p after Bonferroni test) worse prognosis for patients with giant-cell myocarditis (GCM) versus lymphocytic myocarditis (LM) at 60 days ($p < 0.001$) and a worse prognosis for patients with GCM versus eosinophilic myocarditis (EM) ($p = 0.02$) and versus LM ($p < 0.001$) at long-term follow-up. Patients with FM due to EM or LM have no different outcome. **(C)** Hematoxylin and eosin sections of representative cases of GCM, EM, and LM.

The main finding derived from this international registry, which is the largest series of histologically proven FM reported to date, is that in patients with acute myocarditis and LVSD, the clinical presentation characterized by severe hemodynamic compromise is the major determinant of both short- and long-term prognoses. Our findings also support the possibility that the histologic subtype is an important determinant of outcomes, with GCM portending the worst prognosis. Within the FM group, patients with GCM had a strikingly higher rate of early death or HTx (up to 62.5% at 60 days)

compared with EM and LM; however, EM and LM still exhibited a poor prognosis (cardiac death and HTx of 26.3% and 21.0% at 60 days, respectively). These data confirm the need for early EMB in patients with clinically suspected myocarditis with fulminant presentation for further risk stratification and guiding treatment when GCM is confirmed at histology, proper immunosuppressive treatment, including anti-thymocyte globulins, should be initiated together with aggressive use of MCS support and rapid screening for HTx.

5. Viral genome search in myocardium of patients with fulminant myocarditis.

The role of viruses in myocarditis aetiology has been historically recognized, with parvovirus (PV) B19, adenoviruses, human herpes virus type 6 (HHV6) and enteroviruses being the most common agents identified in myocardium. It has been stated that the presence of specific viruses in the heart may contraindicate the use of immunosuppression, particularly in lymphocytic forms, where its role is mostly controversial. On the other hand, immunosuppressive therapy, even though not standardized, is the cornerstone of treatment for eosinophilic and giant-cell myocarditis, cardiac sarcoidosis, and, regardless of the underlying histology, for myocarditis related to systemic autoimmune diseases and immune check-point inhibitor therapy. Although the latest scientific statement of the European Society of Cardiology recommends that immunosuppression should be started only after ruling out active infection on EMB by polymerase chain reaction (PCR), the need to search for viral genome by PCR in the setting of FM patients is debatable and its real clinical value remains unclear. In addition, the relative frequency with which viral genome PCR on EMB is being performed in FM has not been reported previously. We thus aimed to characterize the extent of use of PCR-based viral genome search in a large cohort of histologically proven FM patients, mostly focusing on lymphocytic FM.

Data were derived from a retrospective, international, multicentre cohort study (5). In brief, data were collected from patients seen at 16 tertiary hospitals [13 (81.3%) with heart transplant programmes] across the United States (n = 3), Europe (n = 9), and Japan (n = 4) with histologically proven acute myocarditis (onset of symptoms <30 days), all presenting with left ventricular systolic dysfunction (data collection period from January 2001 to March 2018). Data on nested PCR performed in myocardial tissue for the detection of cardiotropic viruses, including enteroviruses, PVB19, adenoviruses, cytomegalovirus, Epstein – Barr virus, and HHV6, were collected.

The study population included 220 patients (FM 165, non-FM 55), of whom 141 were from Europe (64%), 35 from the United States (16%), and 44 from Japan (20%). Among patients with FM, lymphocytic myocarditis was diagnosed in 120, giant-cell myocarditis in 24, eosinophilic myocarditis in 19, and cardiac sarcoidosis in 2. Myocardium PCR-based viral search was performed in 33 FM patients (20%). The use of PCR- based viral genome detection was higher in Europe (34%), compared to United States (17%) and Japan (3%). Viral search was performed in 6/45 non-lymphocytic FM patients (13%), yielding positive results in one patient (17%) with Epstein – Barr virus and eosinophilic FM. Among patients with lymphocytic FM, 27 (22%) had a PCR-based viral genome search performed, yielding positive results in five patients (18%), with ***PVB19 identified in all positive cases***. Three cases had low viral titres of myocardial PVB19 genome equivalents per microgram of isolated nucleic acids, one case had high titre and in one case titre was not reported; two cases were treated with intravenous immunoglobulin. When comparing lymphocytic FM patients with and without a myocardium PCR-based viral search performed, there were no statistically significant differences in demographics, early management, including prevalence of use of immunosuppressive therapy, and 1-year outcome.

Viral genome search was performed in 22% of lymphocytic FM patients, with PVB19 being the only detected virus in all five positive cases. This is consistent with previous findings from cohorts of myocarditis patients, although not specifically addressing FM, where PVB19 was the most frequently identified virus. Of note, recent evidence suggests that immunosuppression does not seem to aggravate PVB19 replication in myocardium of patients with inflammatory cardiomyopathy and PVB19 persistence.

Available literature on the role of myocarditis management based on viral genome identification has been mostly derived from small studies in patients affected by chronic myocarditis or inflammatory dilated cardiomyopathy and the results obtained have been inconsistent. Our survey

Table 1 **Clinical presentation, initial diagnostic findings, in-hospital management and 1-year outcome of patients admitted with histologically proven lymphocytic fulminant myocarditis comparing cases with vs. those without a polymerase chain reaction-based viral search performed in myocardium**

	No. of patients with available data	Lymphocytic fulminant myocarditis ($n = 120$)		
		Viral genome search not performed ($n = 93$)	Viral genome search performed ($n = 27$)	*P*-value
Demographics				
Age, years, median (Q1–Q3)	120	38 (23–53)	34 (23–50)	0.517
Female sex, *n* (%)	120	50 (53.7)	11 (40.7)	0.278
Presenting symptoms, *n* (%)				
Dyspnoea	119	63 (68.4)	21 (77.7)	0.115
Chest pain	117	27 (30.0)	13 (48.1)	0.106
Syncope	117	19 (21.1)	2 (7.4)	0.153
Prodromal symptoms, *n* (%)	120	76 (81.7)	20 (74.0)	0.417
Autoimmune diseases, *n* (%)	115	11 (12.3)	2 (7.7)	0.729
ECG at admission, *n* (%)				
Normal	115	6 (6.8)	0 (0.0)	0.333
ST-segment elevation	115	33 (37.5)	9 (33.3)	0.820
Other ST-T segment abnormalities	115	27 (30.6)	12 (44.4)	0.245
QRS >120 ms	108	36 (43.9)	4 (15.4)	0.001
Life-threatening arrhythmias[a], *n* (%)				
Cardiac arrest	116	21 (23.6)	7 (25.9)	0.801
VT/VF	68	18 (37.5)	9 (45.0)	0.537
Advanced AV block	120	6 (6.4)	2 (7.4)	1.000
Admission laboratory tests, *n* (%)				
Increased CRP	109	72 (87.8)	19 (70.3)	0.069
Increased troponin T/I or CK-MB	114	77 (88.5)	21 (77.7)	0.204
Echocardiography at admission				
LVEF, %, median (Q1–Q3)	120	20 (15–30)	25 (20–35)	0.054
LVEDD, mm, median (Q1–Q3) (patients ≥15 years)	93	48 (43–55)	52 (46–60)	0.096
Pericardial effusion, *n* (%)	114	45 (51.7)	13 (48.1)	0.827
Immunosuppressive therapy, *n* (%)	119	54 (58.7)	17 (62.9)	0.824
Steroids		46 (50.0)	13 (48.1)	1.000
Immunoglobulin		29 (31.5)	6 (22.2)	0.473
Other		9 (9.7)	5 (18.5)	0.305
Temporary MCS devices, *n* (%)	120	64 (68.8)	13 (48.1)	0.103
IABP		53 (56.9)	9 (33.3)	
Days, median (Q1–Q3)		6 (3–9)	3 (2–12)	0.147
Only		16 (17.2)	3 (11.1)	
With other MCS		37 (39.7)	6 (22.2)	
MCS other than IABP		44 (51.6)	10 (37.0)	
1-year outcome, *n* (%)	120			
Cardiac death or HTx		30 (32.2)	7 (25.9)	0.530
HTx		5 (5.3)	3 (11.1)	
Cardiac death		25 (26.8)	4 (14.8)	
Alive		63 (67.8)	20 (74.1)	

AV, atrioventricular; CRP, C-reactive protein; ECG, electrocardiogram; HTx, heart transplant; IABP, intra-aortic balloon pump; LVEDD, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; MCS, mechanical circulatory support; Q, quartile; VF, ventricular fibrillation; VT, ventricular tachycardia.
[a]Defined as ventricular arrhythmias or cardiac arrest requiring resuscitation manoeuvres that took place during the acute phase of the disease.

is limited by its retrospective nature, a relatively small sample size, the lack of systematic viral genome search in the whole cohort, and the presence of heterogeneity in the techniques used for viral search analysis, based on local standards. Notwithstanding this, it provides unique information about

the frequency of use of PCR-based viral genome identification in myocardium of FM patients. Whether a routine viral genome search in myocardial tissue, a time-consuming procedure, improves patient management guiding immunosuppression therapy in patients with FM remains to be proven. In acute myocarditis, especially in FM, where early immunosuppression may be crucial, initiation of immunosuppressive treatment (e.g. pulse steroid therapy) before obtaining PCR results might represent a reasonable approach. Decisions on cessation or implementation of a tailored immuno-suppression may be procrastinated after final histopathological characterization and eventual virus detection. Large prospective studies are warranted to address the role of viral genome identification in acute and fulminant myocarditis.

6. Prevalence and outcome of patients with acute myocarditis and positive viral search on nasopharyngeal swab.

Viral infections are believed to be associated with AM and indeed typical prodromic symptoms/signs (i.e. fever, flu-like symptoms, sore throat) are frequently reported in AM patients.

Respiratory viruses, such as influenza and corona viruses, identified with real-time polymerase chain reaction (RT-PCR) from nasopharyngeal swabs, have been increasingly recognized as AM triggers. Nevertheless, no systematic study ever investigated the presence of respiratory viruses in the upper respiratory airways in AM patients.

We conducted a single-center, prospective study to ascertain the prevalence of respiratory viruses in nasopharyngeal swabs in consecutive adult patients (≥16 years) with AM admitted to the Niguarda Hospital between January 2018 and October 2020 . We further evaluated differences in clinical presentation, management and prognosis between those who tested positive vs. negative (6).

A control group of 36 consecutive patients admitted for other acute cardiac disorders was used as comparator to assess the prevalence of positive viral genome in nasopharyngeal swabs in patients without AM. Fifty consecutive patients with clinically suspected AM and onset of symptoms within 30 days were enrolled, including patients with all forms of clinical presentation from isolated chest pain to cardiogenic shock (i.e. fulminant myocarditis). All had high-sensitivity troponin T elevation upon admission (median, 903 ng/L, normal value <14 ng/L) and final AM diagnosis was confirmed either by endomyocardial biopsy (EMB) or cardiac magnetic resonance imaging (CMRI). Median age at presentation was 34 years, female prevalence was 24.0% (**Table 1**). A total of 49 (98.0%) patients underwent CMRI during hospitalization. Right ventricular EMB was performed in 28 patients (56.0%), after a median time of 2 days since admission and histologic evidence of myocarditis based on Dallas criteria was found in 19/28 (67.9%), whereas the diagnosis of

myocarditis based on the European Society of Cardiology (ESC) criteria was confirmed in 26/28 cases (92.9%). Patients without histology or who did not reach Dallas/ESC criteria for AM had positive criteria on CMRI; one patient who did not perform CMRI had AM confirmed by histology.

All 50 patients underwent nasopharyngeal swabbing within a median time of 1 day from hospitalization and the specimens were tested for the following respiratory viruses by RT-PCR: coronavirus (subtypes 229E, NL63, OC43 and severe acute respiratory syndrome coronavirus 2 [SARS-CoV-2] from March 2020), influenza A and B, metapneumovirus, parainfluenza (subtypes 1 to 4), bocavirus (subtypes 1 to 4), rhinovirus A, B and C, syncytial respiratory virus (SRV) A and B, adenovirus and enterovirus. Nine (18.0%) patients tested positive for a virus on nasopharyngeal swab. The following viruses were identified: rhinovirus in 4 patients (in 1 case associated with influenza B), coronavirus in 3 patients (2 subtype 0C43, and 1 subtype 229E associated with SRV A positivity), parainfluenza virus subtype 2 in 1 case and adenovirus in the other case. None of the 36 (0%) patients admitted with acute cardiac disorders other than AM tested positive for a virus on nasopharyngeal swab as opposed to 9/50 (18.0%) in the AM group (p=0.009). In 12/28 patients with AM (42.9%) undergoing EMB, myocardium RT-PCR-based viral genome search was performed, yielding positive results in 5 (41.7%) patients, with parvovirus (PV) B-19 identified in all cases (2 cases with a viral load >500 gEq/µg). Differences between patients who tested positive vs. negative on nasopharyngeal swab are reported in **Table 1**. Coherently with the presence of respiratory viruses in the nasopharyngeal mucosa, patients with positive nasopharyngeal swab had a higher prevalence of prodromal respiratory symptoms/signs compared with patients with negative nasopharyngeal swab, 88.9% vs. 36.6%, respectively (p=0.008). *Positive patients were more likely to be females* (55.6% vs. 17.1% in negative patients, p=0.03) *and to present with fulminant forms* (55.6% vs 17.1%, p=0.03), *defined as requiring temporary mechanical circulatory supports* (t-MCS) *and/or inotropes*. Accordingly, positive patients were more likely to receive a t-MCS compared with negative patients

(44.4% vs. 9.7%; p=0.02). There were no significant differences when comparing other clinical characteristics including type of presentation, treatment, use of immunosuppressive therapy, and mortality. Lymphocytic AM was the most common histologic type in both groups. Of interest, all patients with a virus detected on nasopharyngeal swab had a lymphocytic AM; while detection of PVB-19 genome in the myocardium was not significantly different between the 2 groups.

In conclusion, in the cohort of AM patients, the prevalence of viral identification on nasopharyngeal swab was 18.0%, with rhinoviruses and coronaviruses detected in the majority of patients. Nevertheless, delays in swabbing relative to the onset of symptoms could have potentially underestimated the proportion of patients with a viral induced AM. Nasopharyngeal swab may thus be a valuable tool to identify viral triggers in AM. To reinforce the proposed association between viral findings on nasopharyngeal swab and AM, none of the patients with acute cardiac disorders other than AM tested positive for a virus. Our findings suggest that virus-triggered immune-mediated reactions can play a major role in determining cardiac injury in a susceptible host with a permissive genetic background. Acquired knowledge on myocardial injury in severe acute respiratory coronavirus (SARS-COV)-2 infection supports this hypothesis. SARS-COV-2 may induce an immune-mediated systemic inflammatory response sustaining the associated cardiac injury and possibly explaining the benefits from corticosteroid therapy. Of note, immunosuppression was used in 66.6% of our cases who finally tested positive for a virus on nasopharyngeal swab and appeared safe. Furthermore, in line with another recent report, PVB-19 was the only detected virus in myocardial specimens, supporting the hypothesis that PVB-19 could be a bystander in the heart rather than the virus causing myocarditis. The absence of PVB-19 genome in the blood of all patients having a PVB-19 positive EMB ruled out a systemic PVB-19 infection. The Identification of a specific trigger associated with AM may have an etiological relevance. The presence of specific viruses, such as influenza virus, could lead to specific treatments (i.e. oseltamivir) to eradicate the virus.

Respiratory viruses are not generally found in the EMB. Thus, it is more plausible that these viruses do not cause a direct cytolytic effect on the myocardium, although they might trigger an immune response against the heart in predisposed individuals.

Table 1 **Clinical presentation and initial diagnostic findings in 50 patients admitted with clinically suspected acute myocarditis undergoing nasopharyngeal swab investigation for the detection of respiratory viruses by real-time polymerase chain reaction**

	N. of patients with available data	Acute myocarditis			*P*-value
		All	Virus positive NP swab	Virus negative NP swab	
Patients, *n*		50	9	41	
Age, years, median (Q1–Q3)	50	34 (23–46)	33 (18–48)	35 (24–46)	0.52
Age <15 years, *n* (%)	50	0 (0)	0 (0)	0 (0)	–
Female sex, *n* (%)	50	12 (24.0)	5 (55.6)	7 (17.1)	0.03
Caucasian ethnicity, *n* (%)	50	43 (86.0)	7 (77.8)	36 (87.8)	0.59
Clinical presentation, *n* (%)					
Dyspnoea	50	12 (24.0)	3 (33)	9 (21.9)	0.67
Chest pain	50	31 (62.0)	5 (56.5)	26 (63.4)	0.71
Syncope	50	4 (8.0)	1 (11)	3 (7.3)	0.56
Fulminant presentation[a]	50	12 (24.0)	5 (55.6)	7 (17.1)	0.03
Duration of presenting symptoms <1 month, *n* (%)	50	50 (100)	9 (100)	41 (100)	–
Time to admission after symptom onset, days, median (Q1–Q3)	50	4 (2–7)	6 (3–9)	4 (1–7)	0.24
Fever, *n* (%)	50	27 (54.0)	5 (55.6)	22 (53.7)	>0.99
Prodromal symptoms/signs, *n* (%)	50	37 (74.0)	7 (77.8)	30 (73.2)	>0.99
Sore throat or respiratory tract symptoms, *n* (%)	50	23 (46.0)	8 (88.9)	15 (36.6)	0.008
Sore throat, *n* (%)	50	14 (28.0)	5 (55.6)	9 (22.0)	*0.09*
Respiratory tract symptoms *n* (%)	50	9 (18.0)	3 (33)	6 (14.6)	0.33
Gastrointestinal disorders, *n* (%)	50	21 (42.0)	2 (22)	19 (46.3)	0.27
Patients with associated autoimmune disorders, *n* (%)	50	5 (10.0)	0 (0.0)	5 (12.2)	0.57
Previous myocarditis, *n* (%)	50	10 (20.0)	2 (22.2)	8 (19.5)	>0.99
ECG at admission, *n* (%)					
Normal	50	8 (16.0)	2 (22.2)	6 (14.6)	0.62
ST segment elevation	50	14(28.0)	2 (22.2)	12 (29.3)	>0.99
Other ST-T segment abnormalities	50	20 (40.0)	2 (22.2)	18 (43.9)	0.17
Bundle branch block	50	8 (16.0)	3 (33.3)	5 (12.2)	0.14
Any AV block	50	5 (10.0)	1 (11.1)	4 (9.76)	>0.99
Laboratory findings					
Increased CRP at admission, *n* (%)	50	44 (88.0)	9 (100)	35 (85.4)	0.57
Increased troponin T on admission, *n* (%)	50	50 (100)	9 (100)	41 (100)	–
Hs-troponin T levels on admission, ng/mL, median (Q1–Q3)	48	903 (241–2116)	1100 (257–4617)	896 (202–1604)	0.46
Peak hs-troponin T levels, ng/mL, median (Q1–Q3)	48	1561 (406–3633)	2043 (409–10 482)	1189 (403–3562)	0.46
ESR levels on admission, mm/1 h, median (Q1–Q3)	21	41 (10–63)	44 (6–82)	41 (11–56)	0.87
Presence of autoantibodies, *n* (%)	45	11 (24.4)	1 (12.5)	10 (27)	0.66
NP swab performed	50	50 (100)	9 (100)	41 (100)	–
Time to swab after symptom onset, days, median (Q1–Q3)	50	6 (4–9)	8 (3–10)	6 (4–9)	0.61
Time to swab after admission, days, median (Q1–Q3)	50	1 (1–4)	1 (1–3)	1 (1–4)	0.39
Echocardiography on admission					
LVEF, %, median (Q1–Q3)	50	50 (34–58)	25 (19–58)	50 (35–58)	0.08
LVEDD, mm, median (Q1–Q3)	42	48 (46–52)	48 (43–52)	48 (46–52)	0.75
RV-TAPSE <18 mm or evidence of visual dysfunction, *n* (%)	50	11 (22.0)	4 (44.4)	7 (17.1)	0.08
Presence of pericardial effusion, *n* (%)	50	11 (22.0)	3 (33.3)	8 (19.5)	0.39
Coronary angiography or CT angiography performed, *n* (%)	50	22 (44.0)	4 (44.4)	18 (43.9)	>0.99
Evidence of haemodynamically significant CAD, *n* (%)	22	0 (0)	0 (0)	0 (0)	–
EMB performed – *n* (%)	50	28 (56.0)	5 (55.6)	23 (56.1)	>0.99
Time to EMB after admission, days, median (Q1–Q3)	28	2 (0–4)	2 (0–3)	2 (0–5)	0.67
Active myocarditis based on ESC criteria among patients with EMB, *n* (%)	28	26 (92.9)	5 (100)	21 (91.3)	>0.99
Active myocarditis based on Dallas criteria among patients with EMB, *n* (%)	28	19 (67.9)	5 (100)	14 (60.9)	0.14
Presence of moderate to severe infiltrate (>1R based on ISHLT grading score used for cellular heart transplantation), *n* (%)	28	11 (39.3)	3 (60.0)	8 (34.8)	0.35
Histologic findings, *n* (%)					
Lymphocytic myocarditis	28	17 (60.7)	5 (100)	12 (52.2)	0.12
Giant cell myocarditis	28	0 (0)	0 (0)	0 (0)	–
Cardiac sarcoidosis	28	1 (3.6)	0 (0)	1 (4.4)	>0.99
Eosinophilic myocarditis	28	1 (3.6)	0 (0)	1 (4.4)	>0.99
Viral search on histology	28	12 (42.9)	2 (40.0)	10 (43.5)	>0.99
Presence of virus in the heart[b]	12	5 (41.7)	1 (50.0)	4 (40.0)	>0.99
CMR performed, *n* (%)	50	49 (98.0)	9 (100)	40 (97.6)	>0.99
Time to CMRI after admission, days, median (Q1–Q3)	49	4 (2–7)	7 (4–23)	4 (2–7)	0.02
LVEF, %, median (Q1–Q3)	48	59 (45–63)	62 (42–68)	58 (45–63)	0.45
LVEDVi, mL/m^2, median (Q1–Q3)	48	78 (67–89)	74 (65–105)	80 (67–89)	0.67
Positive T2w-STIR, *n* (%)	48	43 (89.6)	7 (77.8)	36 (92.3)	0.23
Presence of LGE, *n* (%)	46	45 (97.8)	8 (100)	37 (97.4)	>0.99
Diffuse LGE, *n* (%)	45	43 (95.6)	7 (87.5)	36 (97.3)	0.33
Septal LGE, *n* (%)	45	2 (4.4)	1 (12.5)	1 (2.7)	0.33

Table 1 (Continued)

	N. of patients with available data	Acute myocarditis			*P*-value
		All	Virus positive NP swab	Virus negative NP swab	
Immunosuppressive therapy, *n* (%)	50	26 (52.0)	6 (66.6)	20 (48.8)	0.47
Corticosteroids	50	26 (52.0)	6 (66.6)	20 (48.8)	0.47
IVIG	50	5 (10.0)	2 (22.2)	3 (7.3)	0.23
Other	50	5 (10.0)	0 (0)	5 (12.2)	0.57
Oseltamivir, *n* (%)	50	1 (2.0)	1 (11.1)	0 (0)	0.15
In-hospital mortality, *n* (%)	50	0 (0)	0 (0)	0 (0)	–
In-hospital use of t-MCS, *n* (%)	50	8 (16.0)	4 (44.4)	4 (9.7)	0.02
In hospital use of IABP, *n* (%)	50	6 (12.0)	3 (33.3)	3 (7.3)	0.06
In-hospital use of VA-ECMO, *n* (%)	50	4 (8.0)	2 (22.2)	2 (4.9)	0.14
In-hospital HTx or LVAD, *n* (%)	50	0 (0)	0 (0)	0 (0)	–
Duration of follow-up, days, median (Q1–Q3)	44	357 (151–597)	91 (67–454)	370 (197–607)	0.04
Cardiac death during follow-up, *n* (%)	44	0 (0)	0 (0)	0 (0)	-
HTx or LVAD during follow-up, *n* (%)	44	0 (0)	0 (0)	0 (0)	-
Non-cardiac death during follow-up, *n* (%)	44	0 (0)	0 (0)	0 (0)	-

AV, atrio-ventricular; CAD, coronary artery disease; CMRI, cardiac magnetic resonance imaging; CRP, C-reactive protein; CT, computed tomography; EMB, endomyocardial biopsy; ESC, European Society of Cardiology; ESR, erythrocyte sedimentation rate; Hs, high-sensitivity; HTx, heart transplantation; IABP, intra-aortic balloon pump; IVIG, intravenous immunoglobulin; ISHLT, International Society for Heart and Lung Transplantation; LGE, late gadolinium enhancement; LVAD, left ventricular assist device; LVEDD, left ventricular end-diastolic diameter; LVEDV, left ventricular end-diastolic volume index; LVEF, left ventricular ejection fraction; NP, nasopharyngeal; Q1–Q3, first and third quartile; RV-TAPSE, right ventricular tricuspid annular plane systolic excursion; t-MCS, temporary mechanical circulatory support (IABP and/or VA-ECMO); T2w-STIR, T2-wieghted short tau inversion recovery; VA-ECMO veno-arterial extracorporeal membrane oxygenation.
[a]Fulminant presentation indicates patients with low cardiac output syndrome requiring inotropes and/or mechanical circulatory support.
[b]In all cases the identified virus was parvovirus B19.

It must be acknowledged that the small sample size of the group with virus-positive nasopharyngeal swab (N=9) is a limitation that might lead to potential statistical errors and thus this finding must be confirmed in larger studies. We further recognize that some patients could have a false-negative nasopharyngeal swab, or alternatively the virus could have disappeared by the nasopharyngeal mucosa at the time of swabbing. Furthermore, the case of acute myocarditis triggered by gastrointestinal virus has not been explored and thus a proportion of virus-negative nasopharyngeal swab acute myocarditis might have a viral etiology/trigger, that has not been assessed in the present study.

AIM OF THE WORK

The natural history of AM varies from complete recovery to persistence of inflammatory and evolution into dilated/hypokinetic cardiomyopathy.

There is evidence that the prognosis of patients with AM can be predicted on the basis of the clinical presentation: patients with left ventricular (LV) ejection fraction (EF) < 50% at first echocardiogram, and those with sustained ventricular arrhythmias, define as complicated AM, have a worse prognosis compared with uncomplicated AM with preserved LVEF and without arrhythmias.

Additionally, among the forms with complicated myocarditis we can distinguish fulminant myocarditis (FM) presenting with severely impaired LVEF (generally <40%), and with need for inotropes and/or temporary mechanical circulatory supports (t-MCS). As evidenced in our previous studies, FM are related to increased in-hospital mortality, and adverse events in long-term follow-up, compared to non-fulminant myocarditis.

In recent years, cardiac magnetic resonance imaging (CMRI) acquired a key role in the diagnosis of AM. The presence of late gadolinium enhancement (LGE) in this setting has a diagnostic and prognostic value but there is conflicting evidence on the association between the presence of septal LGE, compared with other LGE localizations, and the occurrence of major cardiac events at follow up (7,8).

The purpose of our work is to clarify the prognostic performance of cardiac magnetic resonance imaging parameters, especially LGE localization, compared to clinical presentation, in a subgroup of AM patients from the Lombardy Registry of myocarditis .

METHODS

Study population

The Lombardy Registry of myocarditis is a retrospective registry of 443 AM patients (onset of cardiac symptoms <30 days before admission), diagnosed either by endomyocardial biopsy (EMB) or increased troponin plus edema and non-ischemic LGE pattern on CMRI.

Of these, we considered 248 patients who performed a CMRI with LGE, collected between February 2006 and February 2017 from 5 hospitals.

We assessed the prognostic performance for the prediction of major cardiac events [*cardiac death*, *heart transplant*, *aborted ventricular arrhythmias*, *sustained ventricular tachycardia* or *hospitalization due to heart failure*] of the following parameters:

1] presence of septal LGE at basal CMR;

2] evidence of left ventricular ejection fraction (LVEF)<50% at basal CMRI;

3] complicated clinical presentation (CCP) of AM defined as a presence of sustained ventricular arrhythmias or a low cardiac output state at admission or the evidence of LVEF <50% at first echocardiogram performed after hospitalization.

Statistical methods

Continuous variables are reported as mean ± standard deviation (SD) or median and Q1-Q3, according to normal or non-normal distribution as per Shapiro-Wilk normality test. Unpaired Student's t test or Mann-Whitney U test were used as appropriate to compare continuous variables. Categorical variables were compared with Fisher's exact test and relative-risk (RR) was calculated. Kaplan–Meier (KM) curves were compared with use of the log-rank statistic.

Cox regression analysis was used to explore the impact of each variable in univariate analysis to predict the occurrence of cardiac events. Differences with p values <0.05 were considered statistically

significant. GraphPad Prism (version 9) and Rstudio were the Software packages used.

RESULTS

Our population included 248 patients admitted with a diagnosis of acute myocarditis in 5 Hospitals in Lombardy from February 2006 to April 2019.

The median age at presentation was 34 years (first to third quartile [Q1-Q3], 23-41 years) and female prevalence was 12.9 %.

All patients underwent cardiac MRI (CMRI), performed after a median time from admission of 6 days (Q1 - Q3, 4 - 9, days).

Out of the general population, 65 patients (26.2%) had a complicated clinical presentation, 31 patients (12.5 %) had an ejection fraction at baseline CMRI < 50% and 71 patients (28.6%) showed septal LGE at baseline CRMI. Table 1 shows the main characteristics of each group of patients.

TABLE 1. Clinical features and differences among the groups:

A) Complicated vs non complicated clinical presentation.

	No. of patients with available data	Acute myocarditis		P
		Complicated clinical presentation	No- Complicated clinical presentation	
No.	248	65	183	
Age, yr, *median(Q1-Q3)*	248	34 (20 – 42)	34 (24-40)	0.87
Age <15 yrs, n.(%)	248	3 (4.6)	6 (3.3)	0.7
Female, n.(%)	248	15 (23)	17 (9.3)	0.52
CLINICAL PRESENTATION				
Dyspnoea, n(%)	248	30 (46)	7 (3.8)	<0.001
Chest pain, n(%)	248	38 (58)	182 (99.5)	<0.001
Syncope, n(%)	248	8 (12)	1 (0.5)	0.001
Fulminant presentation*, n(%)	248	30 (46)	0 (0)	<0.001
ECHOCARDIOGRAPHY ON ADMISSION				
LVEF , median % (Q1-Q3)	243	35 (21-45)	60 (55-60)	<0.001
LVEF < 50%, n (%)	243	60 (100)	2 (1.1)	<0.001
HISTOLOGY				
Endomyocardial biopsy performed-*no.(%)*	248	31 (47.7)	8 (4.4)	<0.001
Active myocarditis based on Dallas criteria, *n (%)*	39	24 (80)	3 (37.5)	0.08
Lymphocytic myocarditis, n (%)	39	15 (50)	2 (25)	0.42
GMC, n (%)	39	2 (7)	0 (0)	0.99
Cardiac sarcoidosis, n (%)	39	2 (7)	0 (0)	0.99
Eosinophilic myocarditis, n(%)	39	1 (3)	1 (12.5)	0.37
CMRI				
Time to CMRI since admission (Q1-Q3) d, median	243	5 (2-15)	4.5 (3 – 6)	0.16
FE < 50 %	248	25 (38.5)	3 (1.6)	0.99
LVEF, median % (Q1-Q3)	246	54 (43 – 60)	63 (58 – 67)	<0.001
LV-EDV, median ml (Q1-Q3)	241	145 (122-167)	149 (130-168)	0.47
i-LVEDV (mL/m2), median (Q1-Q3)	238	77 (66-91)	78 (70 – 85)	0.7
Presence of STIR+, n (%)	248	55 (84.6)	173 (94.5)	0.02
Presence of LGE, n (%)	248	61 (94)	180 (98.4)	0.08
Septal LGE, n (%)	**248**	36 (55.4)	35 (19.1)	<0.001

LVEF=left ventriculare ejection fraction; CMRI=cardiac magnetic resonance; LV-EDV=left ventricular end diastolic volume; i-LVEDV=left ventricular end diastolic volume index; LGE=late gadolinium enhancement; GMC= giant cell myocarditis.

B) LVEF < 50% vs LVEF > 50% at first CMRI.

	No. of patients with available data	Acute myocarditis		
		LVEF < 50%	LVEF > 50%	P
No.	248	31	217	-
Age, yr, *median(Q1-Q3)*	248	36 (23 - 45)	33 (23 – 40)	0.14
Age <15 yrs, n.(%)	248	1 (3)	8 (4)	0.99
Female, n.(%)	248	9 (29)	23 (11)	0.008
CLINICAL PRESENTATION				
Dyspnoea, n(%)	248	16 (52)	24 (11)	<0.001
Chest pain, n(%)	248	14 (45)	204 (94)	<0.001
Syncope, n(%)	248	5 (16)	4 (2)	0.002
Fulminant presentation*, n(%)	248	14 (45)	16 (7)	<0.001
Clinical complicated presentation§ , n(%)	248	27 (87)	38 (17)	<0.001
ECHOCARDIOGRAPHY ON ADMISSION				
LVEF , median % (Q1-Q3)	**243**	40 (21 -45)	59 (52 – 6)	<0.0001
LVEF < 50%, n (%)		25 (81)	37 (6.4)	<0.0001
HISTOLOGY				
Endomyocardial biopsy performed-*no.(%)*	248	18 (58)	21 (9.7)	< 0.0001
Active myocarditis based on Dallas criteria, *n (%)*	39	15 (83)	15 (71)	0.46
Lymphocytic myocarditis, n (%)	39	6 (33)	8 (38)	0.99
GMC, n (%)	39	1 (6)	1 (5)	0.99
Cardiac sarcoidosis, n (%)	39	2 (11)	0 (0)	0.2
Eosinophilic myocarditis, n(%)	39	1 (6)	1 (5)	0.99
CMRI				
Time to CMRI since admission (Q1-Q3) d, median	243	3 (2 – 9)	6 (3 – 14)	0.02
FE < 50 %	248	-	-	
LVEF, median % (Q1-Q3)	246	41 (32 – 46)	60 (56 – 65)	<0.0001
LV-EDV, median ml (Q1-Q3)	241	150 (121 – 178)	135 (119 – 155)	0.07
i-LVEDV (mL/m2), median (Q1-Q3)	238	82 (64 – 100)	71 (65 – 79)	0.09
Presence of STIR+, n (%)	248	27 (87)	200 (92)	0.31
Presence of LGE, n (%)	248	28 (90)	212 (97)	0.06
Septal LGE, n (%)	248	18 (58)	53 (24)	0.0002

C) Presence vs absence of septal LGE at first MRI.

	No. of patients with available data	Acute myocarditis		
		Septal LGE	No Septal LGE	P
No.	248	71	177	-
Age, yr, *median(Q1-Q3)*	248	36 (27 – 43)	33 (22 – 40)	0.16
Age <15 yrs, n.(%)	248	3 (4)	7 (4)	0.99
Female, n.(%)	248	16 (22)	17 (10)	0.01
CLINICAL PRESENTATION				
Dyspnoea, n(%)	248	22 (31)	16 (9)	<0.001
Chest pain, n(%)	248	53 (75)	167 (94)	<0.001
Syncope, n(%)	248	7 (9.8)	2 (1)	0.002
Fulminant presentation*, n(%)	248	19 (27)	11 (6)	<0.001
Clinical complicated presentation§ , n(%)	248	36 (51)	29 (16)	<0.001
ECHOCARDIOGRAPHY ON ADMISSION				
LVEF , median % (Q1-Q3)	**243**	50 (35 – 60)	58 (52 – 60)	<0.001
LVEF < 50%, n (%)	**243**	32 (45)	30 (17)	<0.001
HISTOLOGY				
Endomyocardial biopsy performed-*no.(%)*	248	26 (36)	13 (7)	<0.001
Active myocarditis based on Dallas criteria, *n (%)*	39	18 (69)	10 (77)	0.7
Lymphocytic myocarditis, n (%)	39	11 (42)	6 (46)	0.99
GMC, n (%)	39	3 (11)	0 (0)	0.54
Cardiac sarcoidosis, n (%)	39	1 (4)	0 (0)	0.99
Eosinophilic myocarditis, n(%)	39	2 (8)	0 (0)	0.54
CMRI				
Time to CMRI since admission (Q1-Q3) d, median	243	5 (2 – 10)	5 (3 – 7)	0.8
FE < 50 %	248	19 ()	11	
LVEF, median % (Q1-Q3)	246	59 (48-65)	61 (56 – 66)	**0.01**
LV-EDV, median ml (Q1-Q3)	241	146 (119-162)	147 (127 – 177)	0.3
i-LVEDV (mL/m2), median (Q1-Q3)	238	77 (64 -89)	79 (68 – 97)	0.5
Presence of STIR+, n (%)	248	66 (93)	161 (91)	0.8
Presence of LGE, n (%)	248	71 (100)	170 (96)	0.2
Septal LGE, n (%)	**248**	-	-	-

Among 248 patients, with a median follow-up time of 1709 days (Q1 - Q3, 999.8 - 2751), 13 patients (5.2%) experienced a major cardiac event after a median follow up of 144 days (Q1-Q3, 31 – 509 days).

Three patients experienced more than one event. Two patients died of extracardiac causes (suicide and traumatic event). One patient died of unknown causes. **Table 2** reports the characteristics of the 13 patients who had a major cardiac event at follow-up.

Overall, 16 events occurred:

- one sudden cardiac death preceded by hospitalization for acute HF associated with a supraventricular tachy-arrhythmias;
- one patient underwent a HTx preceded by hospitalization due to worsening HF;
- three patients experienced a resuscitated sudden cardiac arrest (in all cases before discharge);
- four patients had a hospitalization for heart failure, in one case due to rapid atrial fibrillation.
- five patients had an episode of sustained ventricular tachycardia in the follow-up.

The characteristics of patients with and without cardiac events are summarized in **Table 4.**

TABLE 2. Characteristics of the 13 patients with major cardiac events during follow up

N	Case	Event	CCP	LVEF<50%	Septal LGE	Notes
1	36y, M	Cardiac death	YES (FM)	YES	NO	-
2	29y, M	HTx, HFH	YES (FM)	YES	NO	-
3	34y, M	Cardiac arrest	YES (EF<50%)	YES	YES	DSP+
4	36y, M	Cardiac arrest	YES (FM)	YES	YES	EM - EGPA
5	20y, M	Cardiac arrest	YES (VA)	NO	YES	-
6	41y, F	SVT	NO	NO	YES	DSP+
7	47y, M	SVT	YES (FM)	YES	YES	sarcoidosis
8	48y, M	SVT	YES (VA/EF<50%)	YES	YES	sarcoidosis
9	39y, F	SVT, HFH (2)	YES (VA/EF<50%)	YES	YES	sarcoidosis
10	32y, M	SVT	YES (FM)	NO	YES	GCM
11	33y, F	HFH	YES (FM)	NO	YES	pheochromocytoma
12	16y, M	HFH (cAVB)	YES (FM)	NO	NO	-
13	51, F	HFH	YES (HF/EF<50%)	YES	YES	Systemic sclerosis

Abbreviations: CCP, complicated clinical presentation; FM, fulminant myocarditis; LVEF, left ventricular ejection fraction; HTX , heart transplantation; HFH, heart failure hospitalization; DSP, desmoplachin;

TABLE 3. Patients with major cardiac events in relation to complicated clinical presentation (CCP), or left ventricular ejection fraction (LVEF)<50% or septal late gadolinium enhancement (LGE) on first cardiac magnetic resonance imaging (CMRI).

	Acute myocarditis			
	All	**CCP**	**LVEF <50%**	**Septal LGE**
PATIENTS, n (%)	248	65 (26.2)	31 (12.5)	71 (28.6)
PATIENTS with ANY MAJOR EVENT, n (%)	13/248 (5.2)	12/65 (18.5)	8/31 (25.8)	10/71 (14.1)
Cardiac death, n (%)	1/248 (0.4)	1/65 (1.5)	1/31 (3.2)	0/71 (0)
HTx, n (%)	1/248 (0.4)	1/65 (1.5)	1/31 (3.2)	0/71 (0)
Cardiac arrest, n (%)	3/248 (1.2)	3/65 (4.6)	2/31 (6.5)	3/71 (4.2)
SVT, n (%)	5/248 (2.0)	4/65 (6.2)	3/31 (9.7)	5/71 (7.0)
HFH, n (%)	5*/248 (2.0)	5/65 (7.7)	3/31 (9.7)	1/71 (1.4)

In table 4 we reported the main characteristics of the patients who had a major cardiac event in the follow-up compared with the patients who had no event.

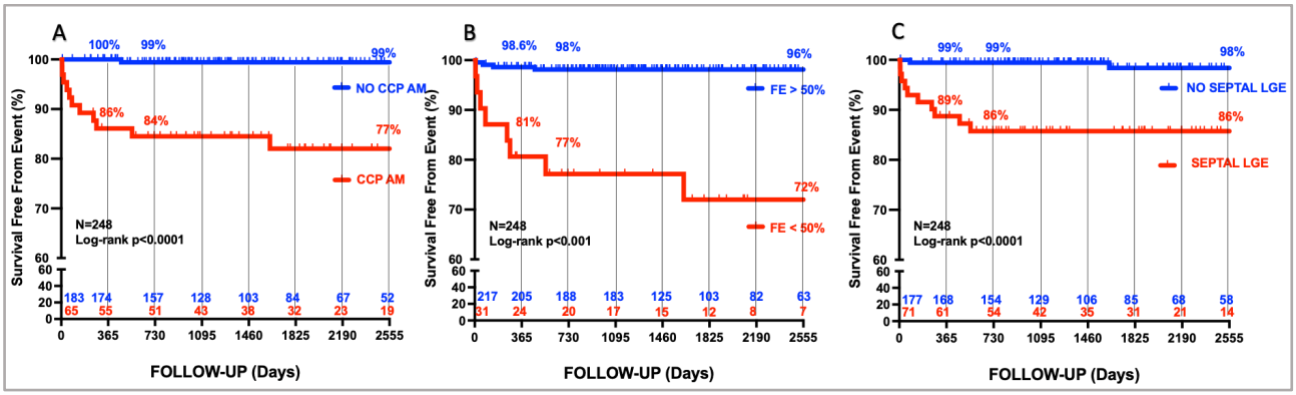
The two groups were similar in gender and age. Patients with events at follow-up had a more frequent complicated clinical presentation (92% vs 22%, p< 0.0001) with the fulminant form present in 46% of cases (vs 10% of the no-event group, p= 0.002). Regarding cardiac MRI data, although patients with events had MRI at a longer time interval than the non-event group (14 days vs 5 days, p=0.002), they had lower left ventricular function (44% vs 61%, p=0.0001). Patients with events had 77% septal localisation of the LGE (vs 26% of the non-event group, p=0.0003) and 30% had a histological diagnosis of cardiac sarcoidosis (vs 0% of the non-event group, p=0.013).

TABLE 4. Characteristics of patients with and without major cardiac events.

	No. of patients with available data	Acute myocarditis			
		All	Events	No-events	P
No.	248	248	13	235	-
Age, yr, *median(Q1-Q3)*	248	34 (23 – 41)	36 (30 - 44)	34 (23 - 41)	0.4
Age <15 yrs, n. (%)	248	8 (3.2)	0 (0)	8 (3.4)	> 0.99
Female, n. (%)	248	32 (12.9)	3 (23.1)	29 (12.3)	0.23
CLINICAL PRESENTATION					
Dyspnoea, n (%)	248	37 (14.9)	6 (46.1)	31 (13.2)	**0.006**
Chest pain, n (%)	248	220 (88.7)	5 (38.7)	215 (91.5)	**<0.0001**
Syncope, n (%)	248	9 (3.6)	4 (30.8)	5 (2.1)	**0.005**
Fulminant presentation*, n (%)	248	30 (12)	6 (46.1)	24 (10.2)	**0.002**
Clinical complicated presentation§, n (%)	248	65 (26)	12 (92)	53(22)	**<0.0001**
ECHOCARDIOGRAPHY ON ADMISSION					
LVEF, median % (Q1-Q3)	243	56 (48-60)	35 (21-47)	57 (50-60)	**<0.0001**
LVEF < 50%, n (%)	243	62 (25)	10 (77)	52 (22)	**<0.0001**
HISTOLOGY					
Endomyocardial biopsy performed-*no. (%)*	248	41 (16.5)	10 (76.9)	31 (13.2)	**<0.0001**
Active myocarditis based on Dallas criteria, *n (%)*	41	29 (70.7)	8 (80)	21 (67.7)	0.7
Lymphocytic myocarditis, n (%)	41	14 (34)	2 (20)	16 (51.6)	0.14
GMC, n (%)	41	2 (4.8)	1 (10)	1 (3.2)	0.44
Cardiac sarcoidosis, n (%)	41	3 (7.3)	3 (30)	0 (0)	**0.013**
Eosinophilic myocarditis, n(%)	41	3 (7.3)	1 (10)	2 (6.4)	>0.99
CMRI					
Time to CMRI since admission (Q1-Q3) d, median	243	6 (4-9)	14 (4 - 23)	5 (3– 7)	**0.002**
FE < 50 %	248	31 (12.5)	8 (61.5)	23 (9.7)	**<0.0001**
LVEF, median % (Q1-Q3)	246	61 (55-66)	44 (41 – 58)	61 (56 -66)	**0.0001**
LV-EDV, median ml (Q1-Q3)	241	147 (128 – 167)	151 (127 -176)	147 (128 – 167)	0.72
i-LVEDV (mL/m2), median (Q1-Q3)	238	78 (69 – 87)	86 (70 – 94)	78 (69 – 85)	0.3
Presence of STIR+, n (%)	248	227 (91.5)	12 (92.3)	215 (91.5)	>0.99
Presence of LGE, n (%)	248	240 (96.7)	13 (100)	228 (97)	>0.99
Septal LGE, n (%)	248	71 (28.6)	10 (76.9)	61 (26)	**0.0003**

Event-free survival, at 1 - 2 and 7 years, was respectively 86, 84 and 77% for patients with complicated clinical presentation (vs 100%, 99% and 99% for patients with uncomplicated presentation, log rank p > 0. 0001), 81% , 77 and 72% for patients with FE < 50% (vs 99, 98 and 96% in patients with FE > 50%) and 89, 86 and 86% for patients with LGE septal involvement (vs 99 - 99 and 98% in patients without LGE septal involvement, log rank p < 0.0001) (**Figure 1**).

Figure 1. Kaplan Mayer curves estimate event-free survival.



A] *Acute Myocarditis with complicated clinical presentation (CCP AM) vs non-complicated clinical presentation (NO CCP AM);* ***B]*** *FE > 50% vs FE < 50% at basal cardiac MRI;* ***C]*** *Presence of septal late gadolinium enhancemnet (LGE) vs no septal LGE on basal cardiac MRI.*

As shown in **Table 5**, on univariate analysis the CCP, FE < 50% and septal LGE variables are associated with an increased risk of a major cardiac event over time, with statistically significant difference within the different groups. Furthermore, we can see that this occurs for septal LGE but not for LGE present at other sites.

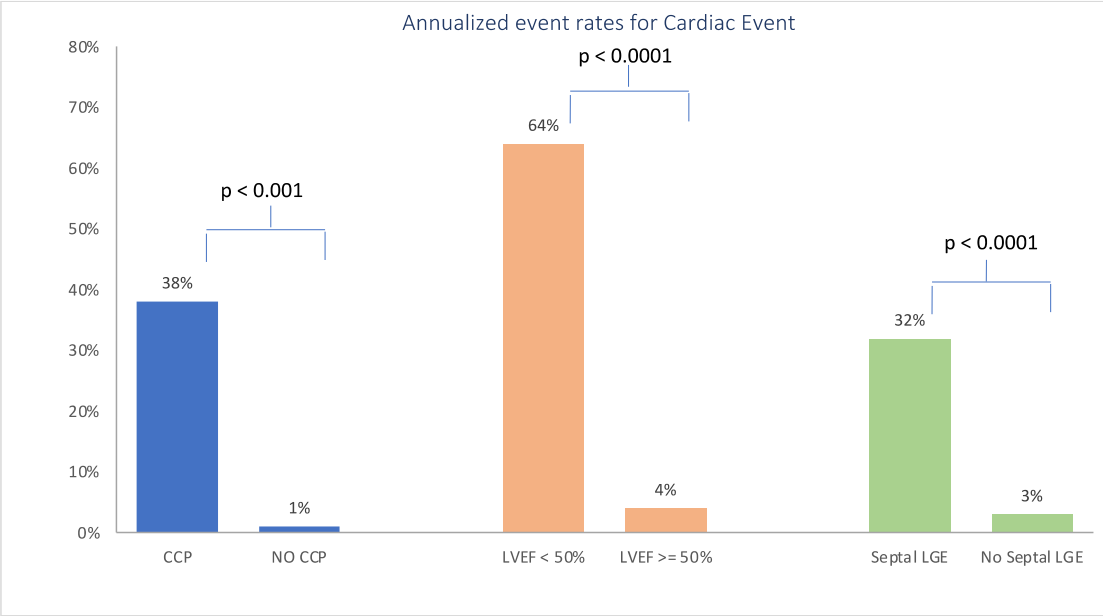
The best performance for these prognostic markers was the negative predictive value (NPV) ranging between 0.98 and 0.99 for CCP, while predictive positive value was low, ranging between 0.14 and 0.25 for LVEF<50% (**Table 6**).

Potential Predictor	Major Cardiac Event		
	HR (95% CI)	P Value	C index
Age, yrs	1.014 (0.976;1.054)	0.475	0.583
Female	2.135 (0.586;7.773)	0.250	0.558
CCP	35.672 (4.638;274.373)	0.001	0.836
LVEF <50%	12.442 (4.068;38.059)	<0.001	0.762
Septale LGE	9.156 (2.514;33.353)	0.001	0.786
Anterior LGE	1.426 (0.312;6.520)	0.647	0.539
Inferior-Lateral LGE	0.890 (0.197;4.019)	0.880	0.504
LVEF %	0.921 (0.888;0.955)	<0.001	0.816
LVEDV (mL)	1.008 (0.995;1.022)	0.236	0.567
LVEDVi (mL/m2)	1.023 (1.001;1.047)	0.042	0.644

Table 5. Univariable Association for Major Cardiac Event

CCP: complicated clinical presentation; LVEF < 50%: left ventricular ejection fraction <50% on first cardiac magnetic resonance imaging (CMRI); Septale LEG: septal late gadolinium enhancement on first CMRI.

Figure 2. Annualized event rates X 1000 patients by factors (with 95% CI)



Factors	Events	Person-years	Incidence rate X 1000 person-years (95%CI)
CCP yes (n=65)	12	313.111	38.325 (19.803 ; 66.946)
CCP no (n=183)	1	968.846	1.032 (0.026 ; 5.751)
LVEF <50% (n=31	8	124.112	64.458 (27.828 ; 127.008)
LVEF ≥50% (n=217)	5	1157.845	4.318 (1.402 ; 10.078)
Septal LGE (n=7)	10	310.921	32.162 (15.423 ; 59.148)
No septal LGE (n=241)	3	971.036	3.089 (0.637 ; 9.029)

CCP: complicated clinical presentation; LVEF < 50%: left ventricular ejection fraction <50% on first cardiac magnetic resonance imaging (CMRI); Septale LEG: septal late gadolinium enhancement on first CMRI.

Table 6. Prognostic Performance of Complicated Clinical Presentation, LVEF < 50% and Septal Late Gadolinium Enhancement (LGE) at basal Cardiac Magnetic Resonance (CMRI).

	ACUTE MYOCARDITIS		
	COMPLICATED CLINICAL PRESENTATION	LVEF < 50%	SEPTAL LGE
SENSITIVITY (95% CI)	0.92 (0.66-0.99)	0.62 (0.35-0.82)	0.78 (0.49-0.91)
SPECIFICITY (95% CI)	0.77 (0.72-0.82)	0.90 (0.85 – 0.9)	0.67 (0.59-0.7)
POSITIVE PREDICTIVE VALUE (PPV) (95% CI)	0.18 (0.11-0.29)	0.25 (0.14-0.4)	0.14 (0.08-0.24)
NEGATIVE PREDICTIVE VALUE (NPV) (95% CI)	0.99 (0.97-0.99)	0.98 (0.95-0.99)	0.98 (0.93-0.99)
INCIDENCE RATE X 1000 PERSON-YEARS (95% CI) *	38.325 (19.803; 66.946)	64.458 (27.828; 127.008)	32.162 (15.423; 59.148)
HR (95% CI) §	35.672 (4.638; 274.373)	12.442 (4.068; 38.059)	9.156 (2.514; 33.353)
P value	0.001	<0.001	0.001
C index	0.836	0.762	0.786

*Annualized event rates X 1000 patients by factors (with 95% CI)
§ Univariable Cox model for time to Major Cardiac Event

DISCUSSION AND CONCLUSION

According to previous data in the literature, we saw that clinical presentation is a predictor of outcome in patients with acute myocarditis. As highlighted by the Lombardy Myocarditis Registry, clinical presentation in patients with AM is associated with a worse outcome. Indeed, the main finding of this multicenter study is that cardiac mortality and HTx in both short and long term occurred exclusively in patients with complicated AM, presenting at admission with LVEF <50% on the first echocardiogram, sustained VAs, or hemodynamic instability (2).

The same finding was confirmed by comparing FM versus NFM, which showed that overall patients with FM have an increased mortality and need for HTx compared with those with NFM (3,4).

According to Grani and Aquaro, also in our work, cardiac MRI and LGE data are associated with the clinical risk of having an adverse event in the follow-up. In detail, we prove how a FE < 50%, the presence of septal LGE and CCP, identify a population at risk of a major cardiac event at follow-up. Regarding prognostic performance, the most relevant finding is the high negative predictive power (NPV) of these markers to identify patients without events after an AM.

This observation is very useful for practical purposes and can help the clinician to monitor the patient Follow-up.

Furthermore within 13 patients with event, 11 had more than one marker between CCP, FE < 50 and septal LGE. One patient with major cardiac event in follow-up, had only septal LGE at cardiac MRI and the following analysis showed desmoplakin gene mutation. This finding supports the hypothesis that septal LGE may deserve additional investigations such as EBM or genetic investigation with the aim of detecting other cardiac diseases (i.e sarcoidosis, autoimmune diseases, arrhythmogenic ventricular cardiomyopathy, ..).

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