JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY VOL. 74, NO. 3, 2019

PUBLISHED BY ELSEVIER

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

Enrico Ammirati, MD, PhD,[a] Giacomo Veronese, MD,[a,b] Michela Brambatti, MD, MS,[c] Marco Merlo, MD,[d] Manlio Cipriani, MD,[a] Luciano Potena, MD,[e] Paola Sormani, MD,[a] Tatsuo Aoki, MD, PhD,[f] Koichiro Sugimura, MD,[f] Akinori Sawamura, MD, PhD,[g] Takahiro Okumura, MD, PhD,[g] Sean Pinney, MD,[h] Kimberly Hong, MD,[c] Palak Shah, MD, MS,[i] Öscar Braun, MD, PhD,[j] Caroline M. Van de Heyning, MD, PhD,[k] Santiago Montero, MD,[l,m] Duccio Petrella, MD,[a] Florent Huang, MD,[m] Matthieu Schmidt, MD,[m] Claudia Raineri, MD,[n] Anuradha Lala, MD,[h] Marisa Varrenti, MD,[a,b] Alberto Foà, MD,[e] Ornella Leone, MD,[e] Piero Gentile, MD,[d] Jessica Artico, MD,[d] Valentina Agostini, PhD,[e] Rajiv Patel, MD,[i] Andrea Garascia, MD,[a] Emeline M. Van Craenenbroeck, MD, PhD,[k] Kaoru Hirose, MD,[o] Akihiro Isotani, MD,[o] Toyoaki Murohara, MD, PhD,[g] Yoh Arita, MD, PhD,[p] Alessandro Sionis, MD,[l] Enrico Fabris, MD,[d] Sherin Hashem, MD, PhD,[q] Victor Garcia-Hernando, MD,[l] Fabrizio Oliva, MD,[a] Barry Greenberg, MD,[c] Hiroaki Shimokawa, MD,[f] Gianfranco Sinagra, MD,[d] Eric D. Adler, MD,[c] Maria Frigerio, MD,[a,*] Paolo G. Camici, MD[r,*]

ABSTRACT

BACKGROUND Fulminant myocarditis (FM) is a form of acute myocarditis characterized by severe left ventricular systolic dysfunction requiring inotropes and/or mechanical circulatory support. A single-center study found that a patient with FM had better outcomes than those with acute nonfulminant myocarditis (NFM) presenting with left ventricular systolic dysfunction, but otherwise hemodynamically stable. This was recently challenged, so disagreement still exists.

OBJECTIVES This study sought to provide additional evidence on the outcome of FM and to ascertain whether patient stratification based on the main histologic subtypes can provide additional prognostic information.

METHODS A total of 220 patients (median age 42 years, 46.3% female) with histologically proven acute myocarditis (onset of symptoms <30 days) all presenting with left ventricular systolic dysfunction were included in a retrospective, international registry comprising 16 tertiary hospitals in the United States, Europe, and Japan. The main endpoint was the occurrence of cardiac death or heart transplantation within 60 days from admission and at long-term follow-up.

RESULTS Patients with FM (n = 165) had significantly higher rates of cardiac death and heart transplantation compared with those with NFM (n = 55), both at 60 days (28.0% vs. 1.8%, p = 0.0001) and at 7-year follow-up (47.7% vs. 10.4%, p < 0.0001). Using Cox multivariate analysis, the histologic subtype emerged as a further variable affecting the outcome in FM patients, with giant cell myocarditis having a significantly worse prognosis compared with eosinophilic and lymphocytic myocarditis. In a subanalysis including only adults with lymphocytic myocarditis, the main endpoints occurred more frequently in FM compared with in NFM both at 60 days (19.5% vs. 0%, p = 0.005) and at 7-year follow up (41.4% vs. 3.1%, p = 0.0004).

CONCLUSIONS This international registry confirms that patients with FM have higher rates of cardiac death and heart transplantation both in the short- and long-term compared with patients with NFM. Furthermore, we provide evidence that the histologic subtype of FM carries independent prognostic value, highlighting the need for timely endomyocardial biopsy in this condition. (J Am Coll Cardiol 2019;74:299–311) © 2019 by the American College of Cardiology Foundation.

Listen to this manuscript's audio summary by Editor-in-Chief Dr. Valentin Fuster on JACC.org.

From the [a]De Gasperis Cardio Center, Niguarda Hospital, Milano, Italy; [b]Department of Health Sciences, University of Milano-Bicocca, Monza, Italy; [c]Division of Cardiology, Department of Medicine, University of California San Diego, La Jolla, California; [d]Cardiothoracic Department, Azienda Sanitaria Universitaria Integrata (ASUITS), University of Trieste, Trieste, Italy; [e]Academic Hospital S. Orsola-Malpighi, Bologna, Italy; [f]Tohoku University Graduate School of Medicine, Sendai, Japan; [g]Nagoya University Graduate School of Medicine, Nagoya, Japan; [h]Icahn School of Medicine at Mount Sinai, New York, New York; [i]Inova Heart and Vascular Institute, Falls Church, Virginia; [j]Department of Cardiology, Clinical Sciences, Lund University and Skåne University Hospital, Lund, Sweden; [k]Department of Cardiology, Antwerp University Hospital, Edegem, Belgium; [l]Department of Cardiology,

ISSN 0735-1097/$36.00 https://doi.org/10.1016/j.jacc.2019.04.063

ABBREVIATIONS AND ACRONYMS

EM = eosinophilic myocarditis

EMB = endomyocardial biopsy

FM = fulminant myocarditis

GCM = giant cell myocarditis

HTx = heart transplantation

IQR = interquartile range

LM = lymphocytic myocarditis

LVEF = left ventricular ejection fraction

LVSD = left ventricular systolic dysfunction

MCS = mechanical circulatory support

NFM = nonfulminant myocarditis

Acute myocarditis is an inflammatory disease of the myocardium most often resulting from a viral infection or autoimmune disorders (1,2). Among the other potential causes, myocarditis may be due to hypersensitivity reactions (e.g., clozapine) (3), or to the inhibition of immune checkpoints by novel antitumor drugs (e.g., antibodies targeting program death receptor) (4–6). Endomyocardial biopsy (EMB) represents the gold standard for the diagnosis (2,7), although its sensitivity may be limited by patchy distribution of the inflammatory infiltrate (8–11).

SEE PAGE 312

The relationship between the clinical presentation and outcome in patients with myocarditis is still debated (12–14). A single-center, retrospective study published in the year 2000 including 147 patients with biopsy-proven lymphocytic myocarditis (15) showed that patients with hemodynamic compromise requiring inotropes and/or mechanical circulatory support (MCS), a condition known as fulminant myocarditis (FM) (16), had better outcome than did patients with nonfulminant myocarditis (NFM), presenting with left ventricular systolic dysfunction (LVSD), but who were otherwise hemodynamically stable (15). By contrast, a recent report on 187 patients with a diagnosis of acute myocarditis confirmed by EMB or cardiac magnetic resonance demonstrated that patients with FM had a higher rate of cardiac death or need for heart transplantation (HTx) than did patients with NFM (17). As observed by Cooper in the accompanying editorial (18), the heterogeneity of that patient series and the low risk profile of patients with NFM (of whom only 8% were biopsy-proven and 36% had LVSD) could explain the differences in outcome compared with earlier reports.

The present study, based on data derived from a multicenter, international registry, was undertaken to overcome these limitations and to provide more definitive data on the prognosis of patients with histologically proven acute myocarditis and LVSD, with fulminant or nonfulminant presentation. Furthermore, we ascertain whether patient stratification, based on the main histologic subtypes—lymphocytic myocarditis (LM), giant cell myocarditis (GCM), and eosinophilic myocarditis (EM)—can provide additional prognostic information.

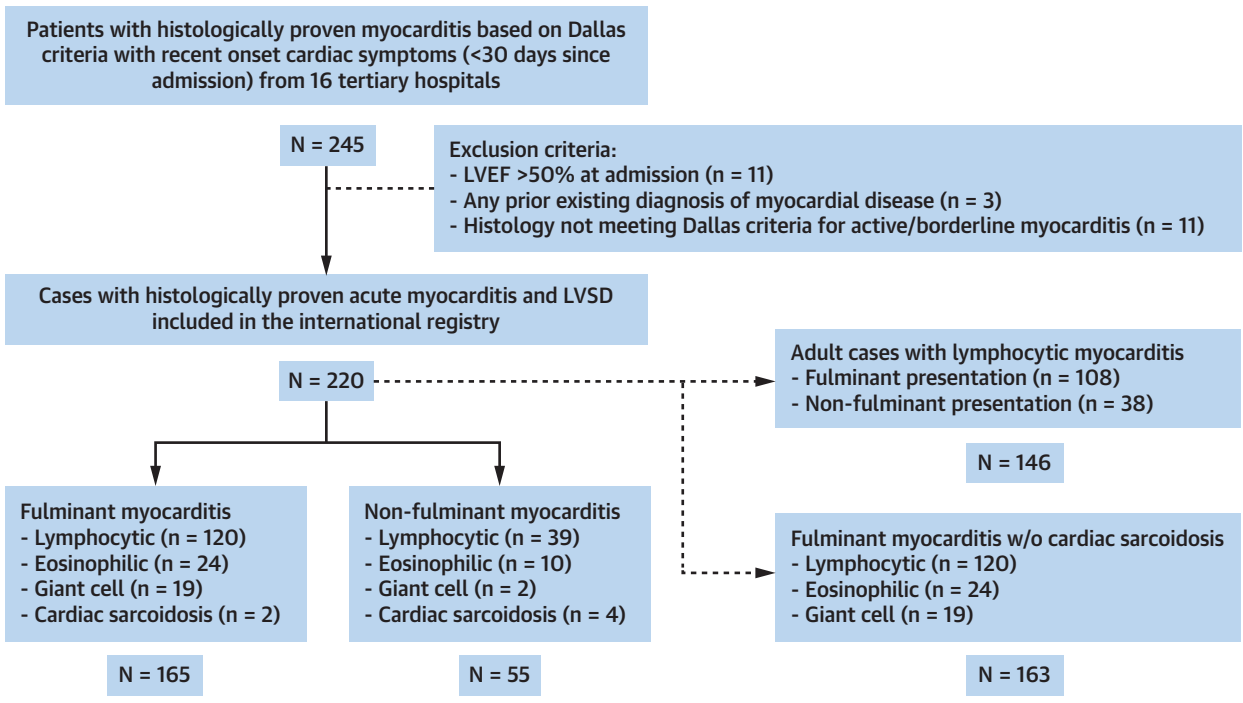
METHODS

This is a retrospective, international, multicenter cohort study. Sixteen tertiary hospitals (13 [81.3%] with an HTx program) across the United States (n = 3), Europe (n = 9), and Japan (n = 4) contributed to the registry (the complete list of participating centers is available in the Online Appendix). The Niguarda Hospital in Milan, Italy, acted as coordinating center. The Institutional Review Board in Milan (Ethics Committee Milano Area 3) approved the study during the session of April 20, 2018 (identifier 169-042018). The participating centers obtained local institutional review board approval for the collection of retrospective anonymous data. The study was conducted according to the Declaration of Helsinki and the principles of good clinical practice. All consecutive patients with a diagnosis of histologically proven myocarditis (from EMB, explanted heart, specimen of the myocardium at the time of implantation of LV assist device or at autopsy) were searched from the local pathology database from January 1, 2001, onward. Deadline for data entry was March 31, 2018. The researchers at each participating center manually reviewed the charts to extract the data, following the indications of the coordinating center. Data were uploaded on the Research Electronic Data Capture (REDCap, Vanderbilt University, Nashville, Tennessee), a secure web-based application for building online database managed by M.B. from the University of California at San Diego. E.A. and G.V. centrally checked the data quality and, when needed, local investigators were contacted for clarifications or further details.

Hospital de la Santa Creu i Sant Pau, Biomedical Research Institute IIB Sant Pau, CIBER-CV, Universitat Autònoma de Barcelona (UAB), Barcelona, Spain; [m]Sorbonne Université, Assistance Publique-Hôpitaux de Paris, Pitié-Salpêtrière Hospital, Medical Intensive Care Unit, Paris Cedex 13, France; [n]Istituto di Ricovero e Cura a Carattere Scientifico Policlinico San Matteo, Pavia, Italy; [o]Kokura Memorial Hospital, Kitakyushu, Japan; [p]Japan Community Healthcare Organization, Osaka Hospital, Osaka, Japan; [q]Department of Pathology, University of California, San Diego, La Jolla, California; and the [r]Vita Salute University and San Raffaele Hospital, Milano, Italy. *Drs. Frigerio and Camici share senior authorship. Dr. Pinney is a consultant for Abbott, CareDx, and Medtronic. Dr. Shah has received grant support from Abbott, Medtronic, and Merck; and is a consultant for NuPulse CV and Ortho Clinical Diagnostics. Dr. Schmidt has received lecture fees from Getinge, Drager, and Xenios. Dr. Adler is a consultant for Abbott and Medtronic. Dr. Camici is a consultant for Servier. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

Manuscript received March 11, 2019; revised manuscript received April 23, 2019, accepted April 29, 2019.

FIGURE 1 Inclusion Criteria and Patient Selection



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.

Inclusion criteria were as follows: 1) histologically proven borderline (presence of inflammatory infiltrate) or active (presence of inflammatory infiltrate plus myocardial necrosis) myocarditis according to the Dallas criteria (9); 2) acute presentation, defined by the onset of cardiac symptoms within 30 days before admission; and 3) LVSD at admission, defined as a left ventricular ejection fraction (LVEF) <50% at first echocardiogram. Patients with any prior diagnosis of myocardial disease were excluded. FM was defined in accordance with previously published reports (15–17,19), as a low cardiac output syndrome requiring inotropes and/or MCS, whereas NFM was defined by hemodynamic stability without need for inotropes or MCS. The primary outcome of the study was the composite of cardiac death and HTx at 60 days and at long-term follow-up.

Subanalyses were carried out as follows: 1) on the subgroup of adult patients (age >15 years) with lymphocytic histology, applying the same criteria used by McCarthy et al. (15); and 2) on the 3 main histologic subtypes of FM (i.e., LM, EM, and GCM), excluding 2 patients with cardiac sarcoidosis due to the scarce representability of this histologic type.

A total of 41 patients from the Niguarda Hospital in Milano, Italy (n = 37) and the San Matteo Hospital in Pavia, Italy (n = 4) of the 220 patients (18.6%) included in the international registry on myocarditis were previously reported in another study (17).

STATISTICAL ANALYSIS. The baseline characteristics of the population were tabulated using standard descriptors of central tendency and variability (mean ± SD or median [interquartile range (IQR)], as appropriate). We then tabulated pre-specified data according to the clinical presentation (FM vs. NFM) in the overall population, in the adult patients with LM, and in patients with FM according to the main histological subtype (LM, GCM, EM). Differences between groups were analyzed using parametric and nonparametric tests, as appropriate. Estimations of the incidence of cardiac death or HTx at 60 days and in the long term were computed through Kaplan-Meier analysis and were compared with the use of the log-rank statistic. We also assessed the associations among the clinical presentation (FM vs. NFM), the histological subtype, and other clinically relevant variables, with cardiac death or HTx at 60 days and in the long term using Cox regression, both univariate

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.

and multivariate, in the overall population. Similarly, Cox regression analyses were performed in the adult population with LM and in the FM population. Factors showing a statistically significant association with cardiac death or HTx at the univariate analysis ($p < 0.05$) were included in the multivariate model. Sample size calculation was computed on the expected cardiac death or HTx among adult patients with acute LM. A 25% difference in the occurrence of cardiac death or HTx between FM and NFM was hypothesized assuming a 5% rate of cardiac death or HTx in the NFM group at 1 year. Thus, the minimum sample size needed was 37 in the NFM and 111 in the FM group (alpha = 0.05 2-sided, power: 0.9, FM/NFM = 3). All analyses were performed using Stata (version 12 SE, StataCorp, College Station, Texas) and GraphPad Prism version 6 (GraphPad Software Inc., San Diego, California).

RESULTS

STUDY POPULATION. Figure 1 shows the study inclusion criteria and the patients' disposition used for main analysis and subanalyses. The overall population included 220 patients (FM = 165, NFM = 55), of whom 141 were from Europe (64%), 35 from the United States (16%), and 44 from Japan (20%). There were 146 adult patients with lymphocytic histology (FM = 108, NFM = 38) that entered the first subanalysis aimed to assess the outcome in adults with LM. 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 significantly 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 fibrillation, and sustained ventricular tachycardia occurred more frequently in FM patients. With regard to the histologic subtypes, GCM was more

TABLE 2 In-Hospital Management of Acute Myocarditis Patients Comparing FM Versus NFM Cases

	Acute Myocarditis		
	NFM	FM	p Value
Overall	55	165	
Immunosuppressive therapy	31/53 (58.5)	109/163 (66.8)	0.321
Single treatment	15 (28.3)	53 (32.5)	
Steroids	15 (28.3)	40 (24.5)	
Oral	9 (16.9)	7 (4.2)	
Intravenous	6 (11.3)	33 (20.2)	
IgG	0 (0.0)	12 (7.3)	
Other	0 (0.0)	1 (0.6)	
Combination treatment	16 (30.1)	56 (34.3)	
Steroids + IgG	0 (0.0)	24 (14.7)	
Steroids + IgG + others	0 (0.0)	9 (5.5)	
Steroids + others (no IgG)	16 (30.1)	23 (14.1)	
Thymoglobulin	0 (0.0)	5 (3.0)	
Azathioprine	13 (24.5)	9 (5.5)	
Cyclosporine	1 (1.8)	8 (4.9)	
Methotrexate	1 (1.8)	1 (0.6)	
Cyclophosphamide	1 (1.8)	4 (2.4)	
MMF	0 (0.0)	1 (0.6)	
Other medical treatment			
NSAID	19/54 (35.1)	40/159 (25.1)	0.298
ACE-inhibitors/ARB	43/54 (79.6)	87/157 (55.4)	0.002
MRA	23/53 (43.4)	42/156 (26.9)	0.038
Beta-blockers	41/53 (77.3)	87/157 (55.4)	0.005
Amiodarone	8/53 (15.0)	27/155 (17.4)	0.833
Inotropes	0 (0.0)	165 (100.0)	
Days		10 (6–17)	
Epinephrine	0 (0.0)	71 (43.0)	
Norepinephrine	0 (0.0)	68 (41.2)	
Dobutamine	0 (0.0)	97 (58.7)	
Dopamine	0 (0.0)	57 (34.5)	
Phosphodiesterase inhibitors	0 (0.0)	35 (21.2)	
Levosimendan	0 (0.0)	9 (5.4)	
Other*	0 (0.0)	12 (7.2)	
Temporary MCS devices	0 (0.0)	114/165 (69.0)	
IABP	0 (0.0)	91 (55.1)	
Days		6 (3–11)	
Only	0 (0.0)	30 (18.1)	
With other MCS	0 (0.0)	61 (36.9)	
MCS other than IABP	0 (0.0)	84 (50.9)	
Days		9 (5–15)	
va-ECMO	0 (0.0)	73 (44.2)	
Peripheral	0 (0.0)	51 (30.9)	
Central	0 (0.0)	9 (5.4)	
Peripheral and central	0 (0.0)	7 (4.2)	
Central + Impella	0 (0.0)	1 (0.6)	
Peripheral + Impella	0 (0.0)	5 (3.0)	
Impella	0 (0.0)	2 (1.2)	
Other†	0 (0.0)	9 (5.4)	

Continued in the next column

TABLE 2 Continued

	Acute Myocarditis		
	NFM	FM	p Value
Other supports			
Mechanical ventilation	0 (0.0)	106/161 (65.8)	
Days		10 (6–17)	
CVVH	0 (0.0)	46/147 (31.2)	
Days		15 (5–25)	

Values are n, n/n available (%), n (%), or median (interquartile range). *Including 4 patients on vasopressin, 2 patients on phenylephrine, 2 patients on isoprenaline, and 4 patients with unspecified inotropes. †Including 1 patient on left and right Impella devices (Abiomed, Danvers, Massachusetts), 3 patients on extracorporeal biventricular support, 1 patient on Medos paracorporeal support (Xenios, Heilbronn, Germany), 1 patient on Impella and Medos paracorporeal support, and 3 patients with unspecified supports.

ACE = angiotensin-converting enzyme; ARB = angiotensin II receptor blocker; CVVH = continuous veno-venous hemofiltration; IABP = intra-aortic balloon pump; IgG = immunoglobulin G; MCS = mechanical circulatory support; MMF = mycophenolate mofetil; MRA = mineralocorticoid receptor antagonist; NSAID = nonsteroidal anti-inflammatory drugs; va-ECMO = veno arterial-extracorporeal membrane oxygenation; other abbreviations as in Table 1.

common in FM patients and cardiac sarcoidosis in NFM patients. Similar findings were obtained in the subanalysis focusing on adult patients with LM (Online Table 1). 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. In-hospital management of patients with FM and NFM is detailed in the Table 2. 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

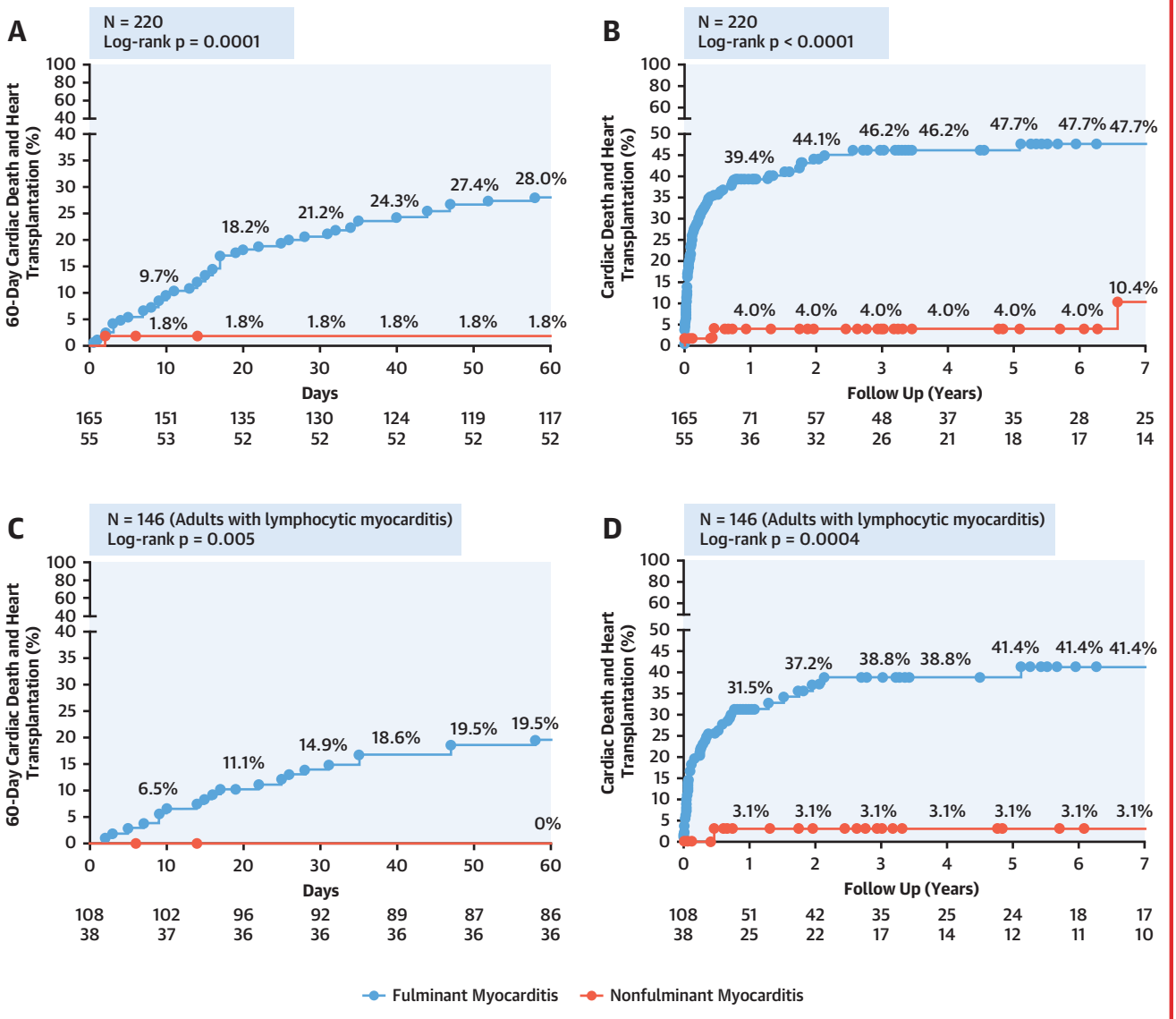
TABLE 3 Outcome at 60-Day and at Long-Term Follow-Up in FM and NFM Patients

	Acute Myocarditis		
	NFM (n = 55)	FM (n = 165)	p Value
60-day outcome			
Cardiac death or HTx	1 (1.8)	46 (27.8)	<0.0001
HTx	0 (0.0)	7 (4.2)	
t-MCS as BTT	0 (0.0)	5 (3.0)	
LVAD as BTT*	0 (0.0)	2 (1.2)	
Cardiac death	1 (1.8)	39 (23.6)	
On t-MCS before exitus	0 (0.0)	23 (13.9)	
On LVAD before exitus†	0 (0.0)	8 (4.8)	
Alive	54 (98.2)	119 (72.1)	
Recovery with t-MCS	0 (0.0)	41 (24.8)	
Alive with t-MCS	0 (0.0)	2 (1.2)	
Alive with LVAD	0 (0.0)	14 (8.4)	
t-MCS to LVAD	0 (0.0)	8 (4.8)	
Long-term outcome			
Cardiac death or HTx	5 (9.0)	71 (43.0)	<0.0001
HTx	1 (1.8)	24 (14.5)	
Cardiac death	4 (7.2)	47 (28.4)	
Noncardiac death	1 (1.8)	2 (1.2)	

Values are n (%). *1 patient underwent t-MCS before LVAD implantation. †6 cases underwent t-MCS before LVAD implantation.

BTT = bridge to transplant; HTx = heart transplant; LVAD = left ventricle assist device; t-MCS = temporary mechanical circulatory support (intra-aortic balloon pump not included); other abbreviations as in Table 1.

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.

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.

OUTCOME. Table 3 reports the 60-day and the long-term occurrence of cardiac death or HTx in FM and NFM. 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%

TABLE 4 Univariate and Multivariate Analysis of Factors Associated With the Occurrence of Cardiac Death and HTx in the Overall Population

		HR (95% CI) for Cardiac Mortality or HTx			
		60-Day Follow-Up		Long-Term Follow-Up	
Overall (N = 220)	Patients With Available Data	Univariate	Multivariate	Univariate	Multivariate
Fulminant presentation	220	17.14 (2.36–124.3)	14.52 (1.67–126.2)*	5.95 (2.40–14.77)	5.08 (1.65–15.68)*
Female	220	0.92 (0.52–1.64)	–	0.80 (0.51–1.26)	–
Age	220	1.01 (0.99–1.03)	–	1.01 (0.99–1.02)	–
Histologic subtypes	220				
Lymphocytic		1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Eosinophilic		1.34 (0.55–3.28)	1.91 (0.70–5.17)	1.33 (0.67–2.65)	1.76 (0.84–3.66)
GCM		4.48 (2.35–8.53)	3.24 (1.41–7.44)*	3.75 (2.18–6.45)	3.48 (1.81–6.70)*
Sarcoidosis		1.07 (0.14–7.94)	–	0.61 (0.08–4.43)	–
Admission LVEF ≤30%	220	1.80 (0.89–3.63)	–	2.05 (1.17–3.62)	1.62 (0.87–3.04)
Immunosuppression	216	0.94 (0.52–1.74)	–	0.78 (0.48–1.24)	–
ECG findings					
QRS interval >120 ms	198	2.62 (1.35–5.05)	2.25 (1.09–4.62)*	2.26 (1.37–3.72)	2.49 (1.44–4.28)*
ST-segment elevation	208	0.79 (0.29–1.30)	–	0.82 (0.49–1.38)	–
Cardiac arrest†	213	3.41 (1.86–6.24)	1.13 (0.49–2.61)	2.68 (1.64–4.37)	1.32 (0.73–2.40)
Advanced AV block†	220	2.49 (1.05–5.89)	1.49 (0.47–4.75)	1.73 (0.75–4.00)	–
Prodromal symptoms	219	0.90 (0.49–1.64)	–	0.72 (0.45–1.15)	–
Year of admission	220		–		–
2001–2010	70	1.00 (reference)	–	1.00 (reference)	–
2011–2018	150	1.34 (0.69–2.59)	–	1.40 (0.85–2.33)	–

Values are n unless otherwise indicated. Dashes indicate that variables were not included in the multivariate model. *Significant results at multivariate analysis. †During the acute phase of the disease.

CI = confidence interval; HR = hazard ratio; GCM = giant cell myocarditis; other abbreviations as in Tables 1 and 3.

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 (Table 4), 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 (Online Table 2), the only variable that was associated with cardiac death or HTx in the long term at multivariate analysis was fulminant presentation.

STRATIFICATION OF FM ACCORDING TO HISTOLOGICAL SUBTYPES. The characteristics and outcome of FM patients according to main histological subtypes are summarized in Table 5. Patients with LM were significantly 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 stratified 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 (Table 6), 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

TABLE 5 Clinical Presentation and Initial Diagnostic Findings in Patients With FM Stratified According to the 3 Main Histologic Subtypes

	Patients With Available Data	Histologic Subtypes of Acute Myocarditis			p Value
		Lymphocytic	Giant Cell	Eosinophilic	
Overall	163	120	24	19	
Demographics					
Age, yrs	163	38 (23–52)	53 (46–67)	57 (34–61)	<0.0001
Female	163	61 (50.8)	12 (50.0)	8 (42.1)	0.815
Clinical presentation					
Dyspnea	161	84 (70.6)	18 (78.2)	16 (84.2)	0.589
Chest pain	159	40 (34.2)	5 (21.7)	6 (31.5)	0.530
Syncope	158	21 (17.9)	5 (21.7)	2 (11.1)	0.694
Prodromal symptoms	163	96 (80.0)	13 (54.1)	11 (57.9)	0.009
Fever	160	82 (69.5)	6 (26.1)	9 (47.3)	0.0001
GI symptoms	159	47 (40.1)	7 (30.4)	7 (36.8)	0.719
Respiratory symptoms	157	40 (34.8)	6 (26.1)	3 (15.8)	0.219
Autoimmune disorders*	156	13 (11.3)	3 (13.6)	10 (52.6)	<0.0001
ECG at admission					
Normal	154	6 (5.2)	2 (9.1)	1 (5.9)	0.722
ST-segment elevation	154	42 (36.5)	5 (22.7)	7 (41.1)	0.422
Other ST-T segment abnormalities	154	39 (33.9)	7 (31.8)	7 (41.1)	0.847
QRS interval >120 ms	144	40 (37.0)	8 (40.0)	6 (37.5)	0.958
Life threatening arrhythmias†					
Cardiac arrest	157	28 (24.1)	11 (50.0)	2 (10.5)	0.014
VT/VF	96	27 (39.7)	14 (82.3)	4 (36.3)	0.031
Advanced AV block	163	8 (6.6)	3 (12.5)	2 (10.5)	0.498
Admission laboratory tests					
Increased CRP	143	91 (83.5)	15 (93.7)	17 (94.4)	0.413
Increased troponin T/I or CK-MB	152	98 (85.9)	16 (84.2)	17 (89.4)	0.928
Increased creatinine	152	51 (45.1)	14 (70.0)	8 (42.1)	0.113
Increased transaminases	152	94 (82.4)	15 (75.0)	15 (83.3)	0.687
Echocardiography at admission					
LVEF, %	163	21 (15–30)	25 (12–35)	25 (20–30)	0.290
LVEDD in patients ≥15 yrs, mm	128	49 (45–57)	52 (48–57)	50 (43–54)	0.412
RV-TAPSE <18 mm or evidence of visual dysfunction	78	64 (75.3)	11 (91.6)	11 (84.6)	0.866
Pericardial effusion	153	58 (50.8)	5 (25.0)	11 (57.9)	0.070
Coronary angiogram	155	59 (51.7)	21 (95.4)	13 (68.4)	<0.0001

Values are n, median (interquartile range), or n (%). *In the lymphocytic myocarditis group: systemic lupus erythematosus, n = 2; ulcerative colitis and autoimmune thyroiditis, n = 1; mixed connective tissue disease, n = 1, Miller-Fisher disease, n = 1; myasthenia gravis, n = 1; Kawasaki disease, n = 1; rheumatoid arthritis, n = 1; thrombotic thrombocytopenic purpura, n = 1; scleroderma, n = 1; autoimmune thyroiditis, n = 2; eosinophilic granuloma (histiocytosis X), n = 1. In the giant cell myocarditis group: systemic lupus erythematosus and autoimmune hepatitis and ulcerative recto colitis, n = 1; vitiligo, n = 1; eosinophilic granulomatosis with polyangiitis, n = 1. In the eosinophilic group: eosinophilic granulomatosis with polyangiitis, n = 7; Crohn disease, n = 1; pernicious anemia and autoimmune thyroiditis, n = 1; IgA deficiency, n = 1. †Defined as ventricular arrhythmias or cardiac arrest requiring resuscitation maneuvers that took place during the acute phase of the disease.

Abbreviations as in Table 1.

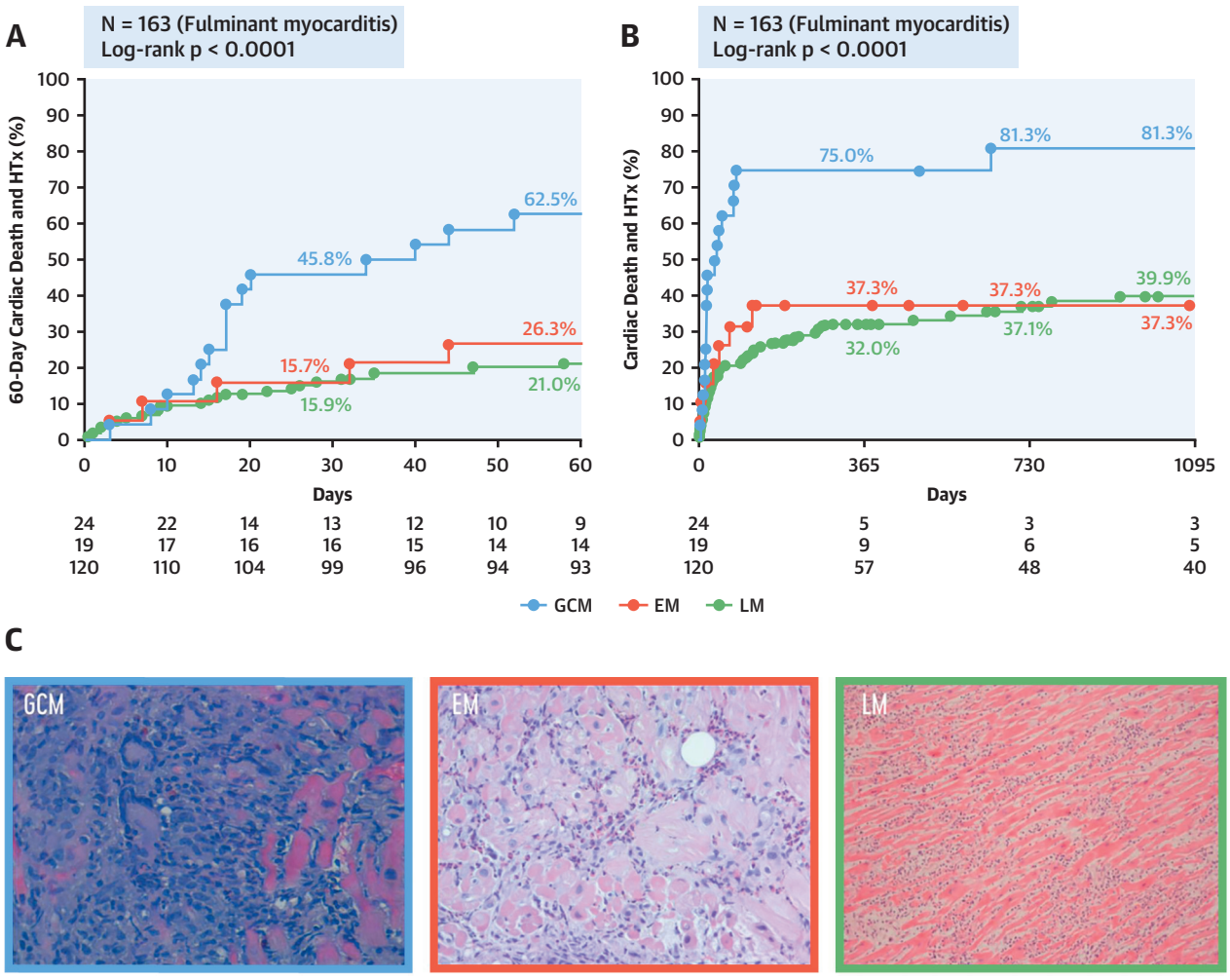
of outcome in the long term. Finally, as shown in Figures 3A and 3B, there was no significant difference in the incidence of cardiac death or HTx in the first time period (2001 to 2010) compared with more recent years (2011 to 2018) among patients with FM. During the first 60 days, MCS were more frequently used in patients from 2011 to 2018, when compared to their counterparts from 2001 to 2010 (62.0% vs. 23.4%, respectively) (Figure 3C). The characteristics of patients with FM stratified according to the time period are shown in the Online Table 3. Of note, the occurrence of cardiac arrest (31.3% vs. 11.9% in patients from 2001 to 2010; p = 0.014) and life-threatening arrhythmias (53.3% vs. 36.1% in patients from 2001 to 2010; p = 0.049) were significantly higher among the patients from 2011 to 2018.

DISCUSSION

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. These findings contrast strikingly with the joint Scientific Statement on the role of EMB published in 2007 by the American Heart Association, the American College of Cardiology, and the European Society of Cardiology (7) that stated that "adults and pediatric patients who present with the sudden onset of severe left ventricular failure within 2 weeks of distinct viral illness and who have typical LM on EMB have an *excellent prognosis*." The European Society of Cardiology Position Statement on myocarditis (2) published in 2013 reflects a more cautious approach: "FM is said to differ from (sub)acute LM in its mode of onset, degree of hemodynamic compromise, and *better outcome*, but data are relatively scarce in adult patients." In fact, data from our registry, which includes patients from 16 centers from 3 different continents, demonstrate a risk of death or HTx at 60 days after admission as high as 19.5% in adults affected by histologically proven LM with fulminant presentation, in contrast to 0% in patients with nonfulminant presentation, despite the presence of LVSD in both groups. The striking difference with respect to the previous study by McCarthy et al. (15) could be explained by the selection criteria: their study included patients undergoing EMB as part of a diagnostic work-up for heart failure or unexplained ventricular arrhythmias up to 12 months after the onset of symptoms. Thus, high-risk FM were probably under-represented, because those who did not undergo EMB did not enter the study. This may have resulted in the exclusion of patients too unstable for biopsy (17).

In our study, a short temporal window between the onset of symptoms and hospitalization (<1 month) was set for both FM and NFM to identify patients with

FIGURE 2 Incidence of Cardiac Death and HTx Stratified According to Histologic Subtypes in Patients With FM



(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.

acute disease and characterize their course. Of note, in the present study, long-term mortality or HTx at 7 years was approximately 3% in adults with LM and nonfulminant presentation, whereas it was around 40% in the previous report by McCarthy et al. (15). Patients with NFM included in the study by McCarthy et al. (15) had a longer history of symptoms (up to 12 months before EMB) and persistence of an inflammatory infiltrate compared with NFM patients in our series that had a history of symptoms <1 month. This difference might be explained by a selection bias in favor of high-risk NFM patients, in other words, those with persistent LVSD and inflammatory infiltrate after the acute episode. It is also possible that patients included in our series could have benefitted from improvements in medical treatment for heart failure compared with approaches that were commonly used in the period between 1984 and 1997.

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

TABLE 6 Univariate and Multivariate Analysis of Factors Associated With the Occurrence of Cardiac Death and HTx in Patients With FM Excluding 2 Cases of Cardiac Sarcoidosis

FM Patients (n = 163)	Patients With Available Data	HR (95% CI) for Cardiac Mortality or HTx			
		60-Day Follow-Up		Long-Term Follow-Up	
		Univariate	Multivariate	Univariate	Multivariate
Female	163	0.87 (0.48–1.56)	–	0.76 (0.47–1.23)	–
Age	163	1.01 (0.99–1.02)	–	1.00 (0.99–1.02)	–
Histologic subtypes	163				
Lymphocytic		1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Eosinophilic		1.28 (0.49–3.36)	1.69 (0.62–4.63)	1.14 (0.51–2.53)	1.62 (0.71–3.72)
GCM		3.75 (1.97–7.14)	2.66 (1.31–5.41)*	3.43 (1.98–5.93)	3.03 (1.57–5.83)*
Admission LVEF ≤30%	163	1.06 (0.52–2.15)	–	1.39 (0.76–2.54)	–
Immunosuppression	161	0.95 (0.50–1.80)	–	0.73 (0.44–1.19)	–
ECG findings					
QRS interval >120 ms	144	1.94 (0.98–3.80)	–	1.87 (1.11–3.15)	1.74 (1.01–3.01)*
ST-segment elevation	154	0.54 (0.26–1.11)	–	0.78 (0.46–1.31)	–
Cardiac arrest†	157	2.61 (1.41–4.85)	1.85 (0.95–3.60)	2.18 (1.32–3.61)	0.98 (0.53–1.81)
Advanced AV block†	163	2.17 (0.91–5.13)	–	1.49 (0.64–3.46)	–
Prodromal symptoms	163	0.82 (0.43–1.54)	–	0.64 (0.39–1.06)	–
Autoimmune disease	156	1.07 (0.47–2.45)	–	0.63 (0.30–1.34)	–
Year of admission	163				–
2001–2010	47	1.00 (reference)	–	1.00 (reference)	–
2011–2018	116	1.23 (0.62–1.42)	–	1.21 (0.72–2.05)	–
Type of support	163		–		–
Inotropes only	50	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
IABP only	30	1.35 (0.41–4.44)	1.08 (0.32–3.67)	1.74 (0.79–3.83)	1.52 (0.57–4.05)
Other t-MCS	83	3.91 (1.64–9.33)	2.59 (1.04–6.44)*	3.08 (1.66–5.73)	3.27 (1.52–7.05)*

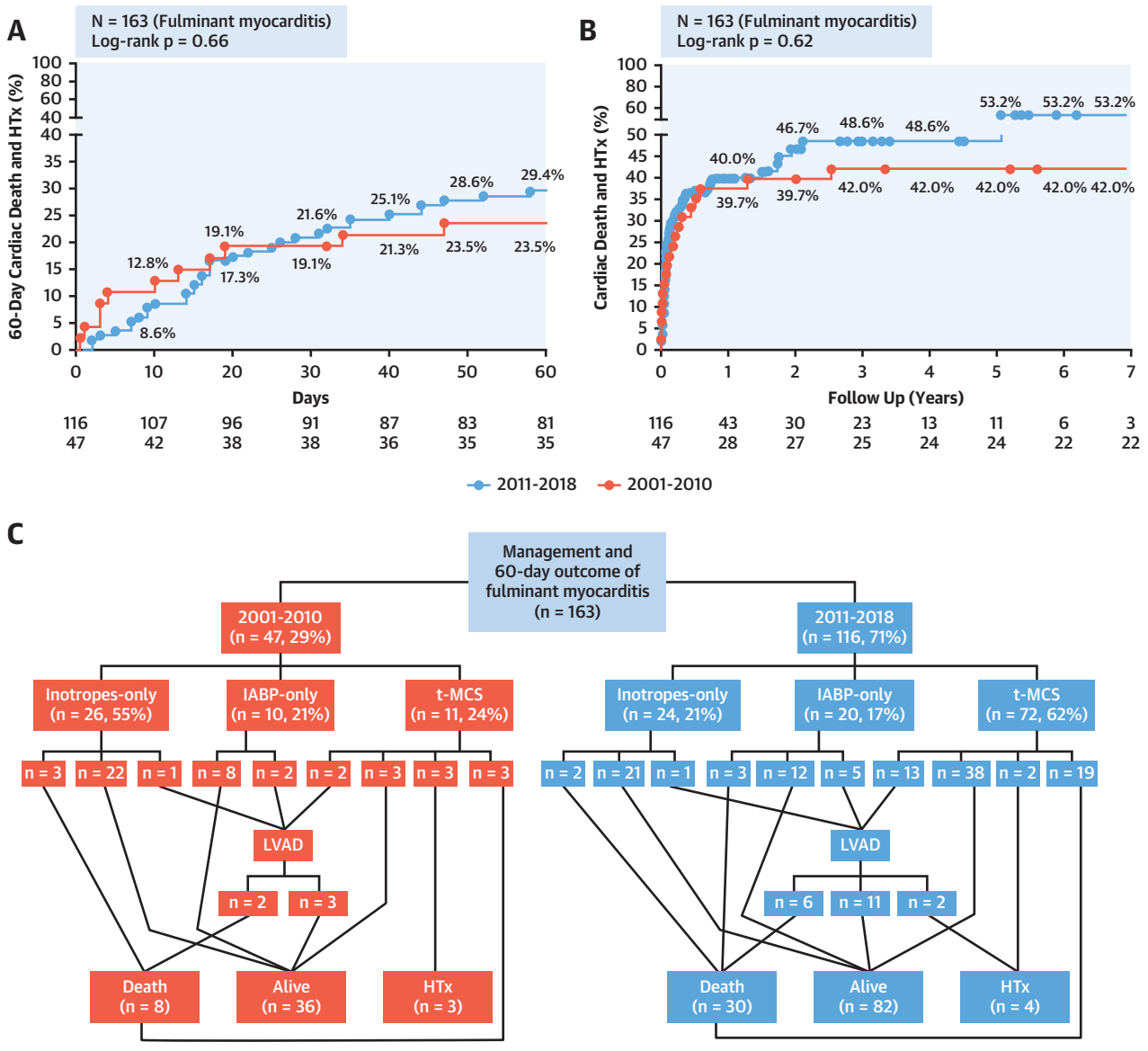
Values are n unless otherwise indicated. Dashes indicate that variables were not included in the multivariate model. *Patients with cardiac sarcoidosis were not included in the analysis (n = 2). †During the acute phase of the disease.

Abbreviations as in Tables 1 to 4.

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 (current recommendation: Class I, Level of Evidence: B) (7). However, even in patients with cardiac shock, EMB is rarely performed according to a nationwide survey carried in the Unites States of America (20). When GCM is confirmed at histology, proper immunosuppressive treatment, including anti-thymocyte globulins (21,22), should be initiated together with aggressive use of MCS support (23) and rapid screening for HTx.

At present, the specific risk profile of GCM is mainly based on the international registry published by Cooper et al. (24). In that seminal study, GCM cases recruited in the Multicenter GCM Study Group were compared with those with LM enrolled in the Myocarditis Treatment Trial (25). In the latter study, it is possible that a selection bias resulting in an overestimation of the relative risk of GCM compared with LM may have occurred because the 63 cases of GCM were collected retrospectively through an announcement launched in medical journals (24), whereas the 111 cases of LM were enrolled prospectively (25). Nevertheless, mortality or HTx rate was 89% in that study compared with 81.3% in our series, confirming the poor outcome of GCM that persists in the recent era despite wider use of MCS (26). In fact, a single-center retrospective study on 112 patients with histologically proven myocarditis did not show worse prognosis in patients with GCM or EM, but the number of cases was small (7 GCM and 7 EM) (27). On the other hand, a French series of 13 patients with GCM requiring veno-arterial extracorporeal membrane oxygenation showed 100% mortality or HTx at 1 year (28). A Finnish series of 46 patients with GCM reported a lower mortality or HTx (58% at 5 years) (29), but 60% of patients had mild symptoms of heart failure with a mean LVEF of 41% (29). These differences among studies could be explained by the fact that the use of temporary MCS is a marker of disease severity; in our study, indeed, temporary MCS other than intra-aortic balloon pump among patients with FM was an independent marker of poor prognosis in the short and long terms.

FIGURE 3 Incidence of Cardiac Death and HTx Stratified According to Different Time Periods in Patients With FM



(A) Incidence of cardiac death and HTx among patients with FM (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 did not show significant difference in the time periods from 2001 to 2010 versus from 2011 to 2018 both at 60 days **(A)** and at long-term follow-up **(B). (C)** Flow diagram of the management and 60-day outcome of patients with FM stratified by time periods from 2001 to 2010 versus from 2011 to 2018 (2 patients with fulminant presentation due to a sarcoid myocarditis were excluded). IABP = intra-aortic balloon pump; LVAD, left-ventricle assist device; t-MCS = temporary mechanical circulatory support; other abbreviations as in Figure 2.

EM was diagnosed in 29 patients in the present registry, of whom 19 had a fulminant presentation. Cardiac mortality at 60 days was 20.7%, in line with the 22.3% in-hospital mortality previously reported in 179 histologically proven EM cases (3).

In addition to the severity of heart failure on presentation, there are some baseline characteristics that were associated with prognosis. In the present study we found that a QRS interval >120 ms on electrocardiography emerged as an independent factor

associated with long-term prognosis with an adjusted hazard ratio of 2.49. This finding is in line with the results of 2 previous studies, the first on 186 cases of clinically suspected acute myocarditis (30) and the second on a cohort of 87 Japanese patients with suspected FM, including 57 with available histology (31). On the other hand, LVEF at admission, dichotomized as ≤30% versus 31% to 49%, did not correlate with short-term prognosis. Furthermore, LVEF is not useful to distinguish patients with LM versus GCM versus EM. Of note, FM patients with a GCM or EM were significantly older compared with those with an LM, and patients with LM more frequently reported prodromal symptoms and signs, in particular fever.

Based on this retrospective data, no significant difference was found in the incidence of cardiac death or HTx in the first time period (2001 to 2010) compared with more recent years (2011 to 2018) among patients with FM. Of note, the occurrence of cardiac arrest and life-threatening arrhythmias during the acute phase were significantly higher among patient in the period from 2011 to 2018, potentially reflecting the fact that efforts have been made to treat the most challenging patients, likely thanks to MCS, which were more extensively used in the early management of patients from 2011 to 2018 compared with the cohort from 2001 to 2010.

STUDY LIMITATIONS. Like most of the previous studies that focused on the outcome of acute myocarditis (15,27), this study suffers from ascertainment biases linked to its retrospective nature. It is worth noting that more than 80% of the participating hospitals had an HTx program, with experienced cardiac pathology units. Molecular analysis on the EMB specimens was performed only in a minority of cases. Viral genome analysis is recommended in the 2013 European Society of Cardiology Position Statement on myocarditis (2), but it is rarely performed in real-life clinical practice, and its usefulness in the acute setting has been questioned (14), because there is no evidence that the results can guide treatment. A possible role of viral genome analysis was indeed only reported in the setting of chronic inflammatory cardiomyopathy with at least 6 months of heart failure symptoms (32). A previous study showed no impact of the presence of viral genome on the prognosis of patients with histologically proven acute myocarditis (14). Furthermore, there was large variability in the timing, type, and dosage of immunosuppressant agents, thus precluding the interpretation of the impact of immunosuppression on patient outcomes. Finally, the timing of temporary MCS implantation was not available in this retrospective analysis and comparison between different times of implantation was not possible, even though, we believe that timely mechanical support in fulminant forms is of utmost importance to give a better chance of survival. This issue should be addressed in future prospective studies.

CONCLUSIONS

Our results challenge previous findings (15) in that they show that patients with FM have higher cardiac mortality and HTx rates than was previously recognized. Furthermore, our results support an important role of EMB in FM patients, because histologic subtypes are related to prognosis and may require specific treatment, with GCM portending the worst outcome. An urgent need for randomized trials or prospective registries testing the effectiveness of treatments in the context of FM is evident from these results. In particular, immunosuppressive regimens must be standardized, evaluated, and prospectively monitored in the acute setting.

ADDRESS FOR CORRESPONDENCE: Dr. Enrico Ammirati, Niguarda Hospital, Piazza Ospedale Maggiore 3, 20162, Milano, Italy. E-mail: enrico.ammirati@ospedaleniguarda.it. Twitter: @ospniguarda. OR Dr. Eric D. Adler, Department of Cardiology, University of California San Diego, 9500 Gilman Drive, 0613K, La Jolla, California 92122. E-mail: eradler@ucsd.edu. Twitter: @ericadler17.

PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: Patients with FM, a form of acute myocarditis characterized by severe LVSD requiring inotropic and/or mechanical circulatory support, face high risks of mortality and often require HTx. Both histologic subtype and QRS prolongation are associated with adverse outcomes that are worse with GCM than EM or LM types.

TRANSLATIONAL OUTLOOK: Randomized trials evaluating treatments such as immunosuppressive drugs should target patients with FM.

REFERENCES

1. Cooper LT Jr. Myocarditis. N Engl J Med 2009; 360:1526–38.

2. Caforio AL, Pankuweit S, Arbustini E, et al. Current state of knowledge on aetiology, diagnosis, management, and therapy of myocarditis: a position statement of the European Society of Cardiology Working Group on Myocardial and Pericardial Diseases. Eur Heart J 2013;34. 2636–48a–d.

3. Brambatti M, Matassini MV, Adler ED, Klingel K, Camici PG, Ammirati E. Eosinophilic myocarditis: characteristics, treatment, and outcomes. J Am Coll Cardiol 2017;70:2363–75.

4. Johnson DB, Balko JM, Compton ML, et al. Fulminant myocarditis with combination immune checkpoint blockade. N Engl J Med 2016;375: 1749–55.

5. Postow MA, Sidlow R, Hellmann MD. Immune-related adverse events associated with immune checkpoint blockade. N Engl J Med 2018;378: 158–68.

6. Mahmood SS, Fradley MG, Cohen JV, et al. Myocarditis in patients treated with immune checkpoint inhibitors. J Am Coll Cardiol 2018;71: 1755–64.

7. Cooper LT, Baughman KL, Feldman AM, et al. The role of endomyocardial biopsy in the management of cardiovascular disease: a scientific statement from the American Heart Association, the American College of Cardiology, and the European Society of Cardiology. Endorsed by the Heart Failure Society of America and the Heart Failure Association of the European Society of Cardiology. J Am Coll Cardiol 2007;50:1914–31.

8. Chow LH, Radio SJ, Sears TD, McManus BM. Insensitivity of right ventricular endomyocardial biopsy in the diagnosis of myocarditis. J Am Coll Cardiol 1989;14:915–20.

9. Aretz HT. Myocarditis: the Dallas criteria. Hum Pathol 1987;18:619–24.

10. Trachtenberg BH, Hare JM. Inflammatory cardiomyopathic syndromes. Circ Res 2017;121: 803–18.

11. Baughman KL. Diagnosis of myocarditis: death of Dallas criteria. Circulation 2006;113:593–5.

12. Ammirati E, Cipriani M, Moro C, et al., for the Registro Lombardo delle Miocarditi. Clinical presentation and outcome in a contemporary cohort of patients with acute myocarditis. Circulation 2018;138:1088–99.

13. Caforio AL, Calabrese F, Angelini A, et al. A prospective study of biopsy-proven myocarditis: prognostic relevance of clinical and aetiopathogenetic features at diagnosis. Eur Heart J 2007; 28:1326–33.

14. Kindermann I, Kindermann M, Kandolf R, et al. Predictors of outcome in patients with suspected myocarditis. Circulation 2008;118:639–48.

15. McCarthy RE 3rd., Boehmer JP, Hruban RH, et al. Long-term outcome of fulminant myocarditis as compared with acute (nonfulminant) myocarditis. N Engl J Med 2000;342:690–5.

16. Ginsberg F, Parrillo JE. Fulminant myocarditis. Critic Care Clin 2013;29:465–83.

17. Ammirati E, Cipriani M, Lilliu M, et al. Survival and left ventricular function changes in fulminant versus nonfulminant acute myocarditis. Circulation 2017;136:529–45.

18. Cooper LT Jr. When lightning strikes: fulminant myocarditis in the realm of inflammatory cardiomyopathies. Circulation 2017;136:546–8.

19. Ammirati E, Veronese G, Cipriani M, et al. Acute and fulminant myocarditis: a pragmatic clinical approach to diagnosis and treatment. Curr Cardiol Rep 2018;20:114.

20. Singh V, Mendirichaga R, Savani GT, et al. Comparison of utilization trends, indications, and complications of endomyocardial biopsy in native versus donor hearts (from the Nationwide Inpatient Sample 2002 to 2014). Am J Cardiol 2018; 121:356–63.

21. Cooper LT Jr., Hare JM, Tazelaar HD, et al. Usefulness of immunosuppression for giant cell myocarditis. Am J Cardiol 2008;102:1535–9.

22. Kandolin R, Lehtonen J, Salmenkivi K, Raisanen-Sokolowski A, Lommi J, Kupari M. Diagnosis, treatment, and outcome of giant-cell myocarditis in the era of combined immunosuppression. Circ Heart Fail 2013;6:15–22.

23. Ammirati E, Oliva F, Belli O, et al. Giant cell myocarditis successfully treated with antithymocyte globuline and extracorporeal membrane oxygenation for 21 days. J Cardiovasc Med (Hagerstown) 2016;17 Suppl 2:e151–3.

24. Cooper LT Jr., Berry GJ, Shabetai R. Multicenter Giant Cell Myocarditis Study Group Investigators. Idiopathic giant-cell myocarditis—natural history and treatment. N Engl J Med 1997; 336:1860–6.

25. Mason JW, O'Connell JB, Herskowitz A, et al., for the Myocarditis Treatment Trial Investigators. A clinical trial of immunosuppressive therapy for myocarditis. N Engl J Med 1995;333:269–75.

26. Asaumi Y, Yasuda S, Morii I, et al. Favourable clinical outcome in patients with cardiogenic shock due to fulminant myocarditis supported by percutaneous extracorporeal membrane oxygenation. Eur Heart J 2005;26:2185–92.

27. Magnani JW, Danik HJ, Dec GW Jr., DiSalvo TG. Survival in biopsy-proven myocarditis: a long-term retrospective analysis of the histopathologic, clinical, and hemodynamic predictors. Am Heart J 2006;151:463–70.

28. Montero S, Aissaoui N, Tadié J-M, et al. Fulminant giant-cell myocarditis on mechanical circulatory support: management and outcomes of a French multicentre cohort. Int J Cardiol 2018; 253:105–12.

29. Ekstrom K, Lehtonen J, Kandolin R, Raisanen-Sokolowski A, Salmenkivi K, Kupari M. Long-term outcome and its predictors in giant cell myocarditis. Eur J Heart Fail 2016;18:1452–8.

30. Ukena C, Mahfoud F, Kindermann I, Kandolf R, Kindermann M, Bohm M. Prognostic electrocardiographic parameters in patients with suspected myocarditis. Eur J Heart Fail 2011;13: 398–405.

31. Sawamura A, Okumura T, Ito M, et al., for the CHANGE PUMP Investigators. Prognostic value of electrocardiography in patients with fulminant myocarditis supported by percutaneous venoarterial extracorporeal membrane oxygenation: analysis from the CHANGE PUMP Study. Circ J 2018;82:2089–95.

32. Frustaci A, Russo MA, Chimenti C. Randomized study on the efficacy of immunosuppressive therapy in patients with virus-negative inflammatory cardiomyopathy: the TIMIC study. Eur Heart J 2009;30:1995–2002.

KEY WORDS acute myocarditis, endomyocardial biopsy, eosinophilic myocarditis, fulminant myocarditis, giant cell myocarditis, outcome

APPENDIX For supplemental methods and tables, please see the online version of this paper.