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ORIGINAL RESEARCH ARTICLE

Natural History of Patients With Histologically Proven Acute Eosinophilic Myocarditis

Enrico Ammirati, MD, PhD; Matteo Palazzini, MD; Jukka Lehtonen, MD; Luciano Potena, MD; Mikko I. Mäyränpää, MD, PhD; Johanna Rågback, MD; Alberto Foà, MD; Aitor Uribarri, MD; Holger Thiele, MD; María Vidal-Burdeus, MD; Anne Freund, MD; Finn Gustafsson, MD, DSc; Carsten Tschöpe, MD; Ahmed Elsanhoury, PhD; Joshua Ihle, MD; Wolf-Stephan Rudi, MD; Ulrich Grabmaier, MD; Marco Merlo, MD; Vojtěch Melenovský, MD; Ivana Weislova, MD; Stefanie Jellinghaus, MD; Axel Linke, MD; Chiara Baldovini, MD, PhD; Rachele Adorisio, MD; Petr Kuchynka, MD; Tomáš Paleček, MD; Jan Krejčí, MD, PhD; Hana Poloczková, MD; Anna Laura Caterino, MD; Nisha A. Gilotra, MD; Jana P. Lovell, MD; Elaine P. Macomb, ARPN; Jeffrey Shih, MD; Kimberly Hong, MD; Valentina A. Rossi, MD; Frank Ruschitzka, MD; Claudio Cavallini, MD; Clara Riccini, MD; Mohamed Kamal, MD; Florent Huang, MD; Matthieu Groh, MD; Piero Gentile, MD; Andrea Garascia, MD; Anuradha Lala, MD; Hiroaki Shimokawa, MD, PhD; Christophe Vandenbriele, MD; Alessandro Sionis, MD, PhD; Matthieu Schmidt, MD, PhD; Aurelia Grosu, MD; Entela Bollano, MD; Annalisa Turco, MD; Maria G. Crespo-Leiro, MD; David Couto-Mallon, MD, PhD; Antonio Cannatà, MD; Daniel I. Bromage, MD, PhD; Maria Lucia Narducci, MD; Vincenzo Cicchitti, MD; Umberto Ianni, MD; Leonardo De Luca, MD; Raffaella Mistrulli, MD; Simone Frea, MD; Claudia Raineri, MD; Jan W. Schroeder, MD; Anibal Martin Arias, MD; Michele Emdin, MD; Marco Corda, MD; Daniele Pasqualucci, MD; Simon Greulich, MD; Meinrad Gawaz, MD; Tatiana Manuylova, MD; Manuel Martínez-Sellés, MD, PhD; Francisco José Hernández Pérez, MD, PhD; Alba Martín Centellas, MD; Fernando Domínguez, MD, PhD; Antoine Gaillet, MD; Nicoletta D'Alessandris, MD; Cory Trankle, MD; Marc K. Halushka, MD, PhD; Francesco Moroni, MD; Antonio Abbate, MD, PhD; Cristina Basso, MD, PhD; Gianfranco Sinagra, MD; Giacomo Veronese, MD; Paolo G. Camici, MD; Eric D. Adler, MD; Davide P. Bernasconi, PhD; Karin Klingel, MD*; Leslie T. Cooper Jr, MD*

BACKGROUND: No large registries of patients with acute eosinophilic myocarditis (EM) are available. However, EM is perceived as a cardiac disease with high mortality, affecting mainly young and middle-aged adults according to small series and case reports. Awareness of the clinical presentation, associated systemic conditions, treatments, and outcomes of this uncommon condition is an unmet need.

METHODS: In this international, multicenter, retrospective cohort study, 53 centers screened 193 patients with histologically proven acute EM between 1992 and 2023. After the exclusion of patients with insufficient data (n=10), symptoms lasting >30 days (n=19), or histological diagnosis not confirmed after review (n=8), 156 patients were included.

RESULTS: Median age at presentation was 48 years (first to third quartile, 34–59 years) with male predominance (67.3%), and only 2 were pediatric cases (≤16 years of age; 1.3%). The main signs and symptoms at presentation were dyspnea (75.6%), fever (61.3%), and chest pain (53.2%). Unexpectedly, peripheral eosinophilia was reported in only 57.4% of cases, with a median cell count of 630 eosinophils/μL. The median left ventricular ejection fraction at presentation was 32% (first to third quartile, 25%–48%). The disorders most frequently associated with EM were eosinophilic granulomatosis with polyangiitis (22.4% of cases) and hypersensitivity forms (14.1%). Idiopathic/undefined forms accounted for 44.9% of cases, and miscellaneous causes accounted for 18.6%. In-hospital death or need for heart transplantation (HTx) occurred in 23 patients (14.7%; 22 deaths and 1 HTx), despite 43.6% being treated with temporary mechanical circulatory support and 92.9% being treated with immunosuppressive agents. Estimated rates of death or HTx at 1 and 3 years were 19.0% and 23.8%. Increased age, decreased left ventricular ejection fraction on admission, and no immunosuppressive therapy

Correspondence to: Enrico Ammirati, MD, PhD, "De Gasperis" Cardio Center and Transplant Center, ASST Grande Ospedale Metropolitano Niguarda, Piazza Ospedale Maggiore 3, 20162 Milan, Italy. Email enrico.ammirati@ospedaleniguarda.it
*K. Klingel and L.T. Cooper Jr contributed equally.
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during hospitalization were independent predictors of death or HTx. A nonsignificant higher occurrence of deaths or HTx was observed in the hypersensitivity form (46.1%) compared with the eosinophilic granulomatosis with polyangiitis–associated form (13.1%) at 3 years (P=0.15).

CONCLUSIONS: Acute EM can often present without peripheral eosinophilia, and rates of in-hospital and midterm mortality or HTx are high. Endomyocardial biopsy is required to reach the final diagnosis of EM because relying on peripheral eosinophilia can lead to missing diagnosis. In-hospital immunosuppression is associated with HTx-free survival, although tailored immunosuppressive therapies are needed to improve outcomes.

REGISTRATION: URL: https://www.clinicaltrials.gov; Unique identifier: NCT06447935.

Key Words: biopsy ■ Churg-Strauss syndrome ■ eosinophilia ■ hypersensitivity ■ myocarditis ■ treatment outcome

ORIGINAL RESEARCH ARTICLE

Clinical Perspective

What Is New?

- Acute eosinophilic myocarditis can present without peripheral eosinophilia in up to 42.6% of cases.
- Eosinophilic granulomatosis with polyangiitis in 22.4% and hypersensitivity in 14.1% of cases are the disorders most frequently associated with eosinophilic myocarditis.
- Ulcerative colitis is a previously unrecognized associated cause of eosinophilic myocarditis in ≈5% of patients.
- Rates of death or heart transplantation at 1 and 3 years are 19.0% and 23.8%, without significant differences among different types.
- Increased age, reduced left ventricular ejection fraction, and immunosuppressive therapy during hospitalization are associated with long-term outcomes.

What Are the Clinical Implications?

- Endomyocardial biopsy is required to reach the final diagnosis of eosinophilic myocarditis because relying on peripheral eosinophilia can lead to missing diagnosis.
- In-hospital immunosuppression is associated with heart transplantation–free survival.

Nonstandard Abbreviations and Acronyms

CMRI	cardiac magnetic resonance imaging
EF	ejection fraction
EGPA	eosinophilic granulomatosis with polyangiitis
EM	eosinophilic myocarditis
EMB	endomyocardial biopsy
HES	hypereosinophilic syndrome
HF	heart failure
HR	hazard ratio
HTx	heart transplantation
IBD	inflammatory bowel disorder
IL	interleukin
LGE	late gadolinium enhancement
LV	left ventricular
OR	odds ratio
Q1–Q3	first to third quartile
t-MCS	temporary mechanical circulatory support

Among patients admitted for clinically suspected acute myocarditis, those who develop a high-risk clinical syndrome unresponsive to standard medical therapy have a recommendation for endomyocardial biopsy (EMB).[1–3] Myocarditis with fulminant presentation characterized by hemodynamic instability or acute heart failure (HF) can be caused by eosinophilic myocarditis (EM) in ≈15% of cases.[4,5] EM is characterized by eosinophilic infiltration, generally accompanied by lymphocytic and macrophagic infiltration and different degrees of myocardial necrosis. No large registries of patients with EM are currently available.[6] According to a review of published clinical cases and small series, the most frequent conditions associated with EM were allergic reactions to drugs (hypersensitivity forms; 34.1%) and eosinophilic granulomatosis with polyangiitis (EGPA; 12.8%), followed by hypereosinophilic syndromes (HES), parasitic infections, and solid cancers.[7] In 35.7% of patients, a causative condition could not be found or identified (idiopathic or undefined forms).[7] Suspicion of an eosinophilic disorder and consequent myocardial involvement can be supported by peripheral eosinophilia, although lack of eosinophilia has been described in 24.1% of patients with histologically proven EM,[7] and under these circumstances, EMB becomes mandatory for diagnosis and treatment. However, clinicians can reach a suspect diagnosis by relying on troponin, eosinophilia, and cardiac magnetic resonance imaging (CMRI), which often has a typical subendocardial late gadolinium enhancement (LGE) in EM, even if other localizations can be found.[3,7] Conversely, in the setting of new-onset HF and severe

systolic dysfunction, demonstration of eosinophilia could justify EMB.[2,3,8,9] High in-hospital mortality, 22.3% among 179 published cases, especially in allergic myocarditis (36.1%), has been reported,[7] even if publication bias of case reports or small case series could have led to an overestimation of mortality.[7] Because of the need for specific treatments for distinct types (ie, use of cyclophosphamide or interleukin [IL]-5 receptor antagonists in EGPA-related EM, albendazole in EM associated with *Toxocara canis* infection), identification of eosinophilic disorders related to EM is crucial.[3,7] There are neither clear evidence-based guidelines nor specific consensus statements for the treatment of idiopathic EM,[7] although expert consensus generally supports the usefulness of steroids.[1,3,8]

For this reason, an international registry that investigates and describes the clinical presentations, main associated systemic conditions, treatments, and outcomes can contribute to a better comprehension of EM. The potential clinical impact can translate into an early recognition of this potentially deadly condition.[1]

METHODS

Study Protocol

We conducted an international, multicenter, retrospective cohort study involving 53 hospitals in Europe (n=42), North America (n=7), South America (n=1), Asia (n=2), and Australia (n=1; Figure 1A). Table S1 provides a complete list of centers and recruited patients. The total number of centers that provided at least 1 suitable patient for the registry was 43. The Niguarda Hospital in Milano, Italy, acted as the coordinating center. This study complied with the Declaration of Helsinki, and the Institutional Review Board in Milano, Italy (Ethics Committee Milano Area 3) approved the study (718-16112021). Because of the retrospective nature of the study, written informed consent was deemed unnecessary. The study was registered at ClinicalTrials.gov with the identifier NCT06447935 and the study name Acute Eosinophilic Myocarditis International Registry.

To be included in our study, patients had to fulfill the following criteria: (1) presence of acute symptoms consistent with acute myocarditis (chest pain, dyspnea, palpitation, syncope, fatigue, or abdominal symptoms) presenting within 30 days from hospitalization and (2) histologically proven EM on EMB (performed surgically or percutaneously) or on explanted heart or postmortem examination. According to the Dallas criteria, borderline myocarditis (presence of inflammatory infiltrate) and active myocarditis (presence of inflammatory infiltrate plus myocardial necrosis) with evidence of eosinophils were considered histologically proven EM.[10] The study focused on acute myocarditis defined by a 30-day cutoff duration of symptoms before hospitalization following current expert consensus documents,[3,11] intending to provide data on a relatively homogeneous population. Chronic or subchronic forms of eosinophilic cardiomyopathies (eg, Loeffler cardiomyopathy) were excluded (>30 days). Patients with preexisting advanced HF (eg, on dobutamine infusion) or those who had an out-of-hospital death were not considered in this study. To standardize and harmonize data derived from multiple centers, 2 authors (E.A. and M.P.) centrally reviewed the inclusion and exclusion criteria to include the patients in the final analysis. Discrepancies were resolved by consensus or by a third author (L.T.C.) if necessary. The reasons why 10 patients were excluded because of incomplete data are detailed in Table S2. After central review of the pathology reports, an additional 8 patients were excluded because EM diagnosis was not confirmed by histology (Table S3), and 19 patients were excluded because of symptoms duration >30 days or unavailable onset of symptoms. The local centers reported the systemic conditions associated with EM, which were also centrally reviewed. This study adhered to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guideline for cohort studies (STROBE checklist is presented in the Supplemental Material).

Quality Control of the Histological Diagnosis of EM

Furthermore, to provide a centralized review of the histologic diagnosis of EM during the review process, the centers were asked to provide at least 1 histology image that supported the diagnosis of EM. The available photos (116/156, 74.4%) were sent. Further details on the central review process and interobserver variability in the reading of the pathology images are presented in the Supplemental Methods. The central confirmation of EM occurred in at least 3 of 4 expert pathologist reviewers in 99.1% of the analyzed images (Figures S1–S3). Table S4 shows the interrater reliability of the histopathologic diagnosis of EM.

Study Population

Among the 193 patients identified by the contributing centers, 156 (80.8%) fulfilled the prespecified criteria and were included in the final analysis (Figure 1B and Table S1). Further details are presented in the Supplemental Methods. Four groups were further identified according to cause or associated systemic disorders: idiopathic/unclassified, EGPA, hypersensitivity, or miscellaneous forms. Miscellaneous forms included different causes that individually accounted for <15 cases. Only 1 case was admitted before 2000; the remaining cases were admitted between 2000 and 2023, of whom 127 patients (81.4%) were hospitalized between 2010 and 2023, reflecting a contemporary population of patients with acute EM.

Data Collection

Details on data collection are reported in the Supplemental Material.

Comparator Group With Lymphocytic Acute Myocarditis

To contextualize the outcomes of patients with EM in our series, we compared the mortality and need for heart transplantation (HTx) with a comparator group of patients with histologically confirmed lymphocytic acute myocarditis. This subgroup was derived from the international registry of histologically proven myocarditis,[4] restricted to patients enrolled at the same centers participating in the EM registry and with age ≥10 years (Figure S4 and Table S11).

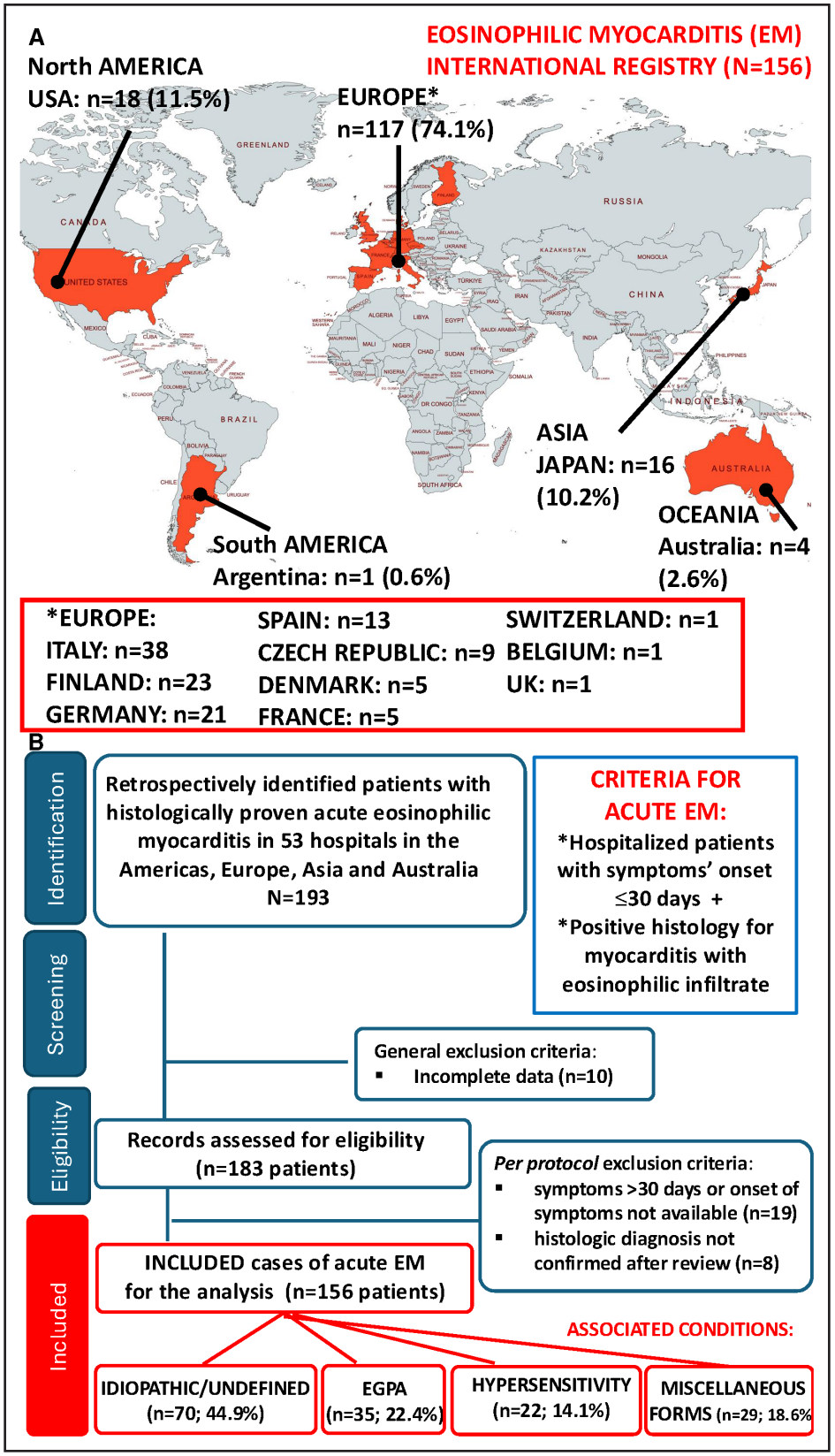

Figure 1. EM international registry.
A, Geographical distribution of cases of histologically proven eosinophilic myocarditis (EM). The countries where at least 1 case has been included in the final analysis are shown in red. Most cases are from Europe, North America, and Japan. **B**, Study selection flow diagram. The identification, screening, and inclusion process led to the inclusion of 156 clinical cases of EM in the study. Four groups are presented: 70 patients (44.9%) classified as having idiopathic or undefined EM, 35 cases of EM (22.4%) associated with eosinophilic granulomatosis with polyangiitis (EGPA), 22 (14.1%) cases due to hypersensitivity, and 29 cases (18.6%) with miscellaneous causes.

Statistical Analysis

The distribution of continuous variables was summarized with median and first to third quartile (Q1–Q3) and compared across type groups with the Kruskal-Wallis test (post hoc pairwise comparisons were performed with Mann-Whitney test with correction for multiple comparisons performed with the Holm method). Categorical variables were reported as absolute and relative frequencies and compared across type groups with the χ^2 test (post hoc pairwise comparisons were performed with the χ^2 test with the Holm correction for multiple comparisons).

The association of variables at admission with in-hospital death or HTx was assessed with a univariable logistic regression model, and the association with overall death or HTx was assessed with univariable Cox regression models. The Kaplan-Meier method was used to estimate the cumulative incidence of death or HTx in time (both on the overall sample and stratified by type groups, compared with the log-rank test). Details on the strategy for the multivariable analysis are presented in the Supplemental Methods.[12] Comparisons with values of $P<0.05$ were considered statistically significant. R (version 4.2.0) and GraphPad Prism (version 10.2.0, Software Inc, La Jolla, CA) were the software packages used for the statistical analysis.

Data Sharing

Anonymized participant data may be available after the time of publication. Appropriate institutional data transfer agreements will be required. Requests should be emailed to the corresponding author, along with an analysis proposal.

RESULTS

Causes

Of the 156 patients diagnosed with acute EM, an associated systemic disorder was identified in 86 (55.1%), whereas in the remaining 70 (44.9%), the type of EM was classified as idiopathic or undefined. The disorders most frequently associated with EM were EGPA (formerly Churg-Strauss syndrome) in 35 (22.4%), followed by 22 cases of hypersensitivity (14.1%) and 29 cases (18.6%) of miscellaneous causes. Among the miscellaneous causes, HES accounted for 12 cases (7.7% of the total cases of EM), inflammatory bowel disorder (IBD) for 9 cases (5.7%; 8 ulcerative colitis, 1 Crohn disease), lymphomas for 3 cases (1.9%), and parasitic infections for 2 cases (1.3%); celiac disease, lung cancer, and systemic lupus erythematosus were found in the remaining 3 cases (Figure 2A and 2B).

Table S5 lists drugs or vaccines more frequently associated with hypersensitivity EM and patients' characteristics. Antibiotics were the most commonly reported (n=7/17 with available data on the agent related to hypersensitivity, 41.2%, mainly amoxicillin), followed by central nervous system agents (n=3/17, 17.6%), vaccines (n=2/17, 11.8%), anticancer agents (n=2/17, 11.8%), and other agents or substances (n=3/17, 17.6%). Data on drugs potentially involved were not available in 5 of all 22 cases (22.7% of the hypersensitivity EM).

Clinical Characteristics and Diagnostic Findings

Table 1 reports the main characteristics of the overall population and the 4 groups of idiopathic/undefined EM, EGPA-associated EM, hypersensitivity EM, and miscellaneous forms of EM. Among the 156 patients with EM, the median age on admission was 48 years (Q1–Q3, 34–59 years); 32.7% were female, with a predominance of White patients (74.1%). Only 2 were pediatric cases (age ≤16 years; 1.3%). The median time from cardiac symptom onset to hospitalization was 3 days (2–10 days). Patients presented with a median systolic blood pressure of 103 mm Hg with a heart rate of 100 bpm. The most frequent symptom at presentation was dyspnea (n=118/156, 75.6% of patients), followed by chest pain (n=83/156, 53.2%). In addition, 123 patients (78.8%) had prodromal symptoms, with fever being the most common prodromal sign in 95 (of 155 with available data, 61.3%). Groups differed in female prevalence and White ethnicity, with the lowest prevalence in the idiopathic/undefined group. History of asthma was observed in 50 patients (of 103, 48.5%) with EM, and the EGPA-associated group, as expected, had the highest prevalence of asthma (75.0%) compared with the hypersensitivity group (21.4%; $P<0.05$, EGPA versus hypersensitivity group).

Electrocardiographic and laboratory examinations are summarized in Table 1 and presented in the Supplemental Results.

Echocardiographic Examination

Median left ventricular (LV) ejection fraction (EF) on admission was 32% (Q1–Q3, 25%–48%), with the lowest LVEF during hospitalization of 28% (16%–44%). The LV was not dilated, confirming the acuity of the presentation with a median LV end-diastolic diameter of 50 mm (Q1–Q3, 43–55 mm). An LV restrictive filling pattern was observed in 34 patients (of 122 with available data, 27.9%), with the highest proportion in the hypersensitivity group (50.0%) and the lowest in the idiopathic/undefined group (10.9%; $P<0.05$ comparing idiopathic/undefined and hypersensitivity groups). Other findings are summarized in Table 1 and presented in the Supplemental Results.

Coronary Angiogram

A coronary angiogram was performed in 109 patients (70.8%) and showed an associated coronary artery disease in 1 patient (0.9%, presenting an EM associated with an acute coronary syndrome).

Endomyocardial Biopsy

The diagnosis of EM was reached by EMB in 149 patients (95.5%), and by postmortem examination or on the explanted heart in the remaining 7 patients (4.5%).

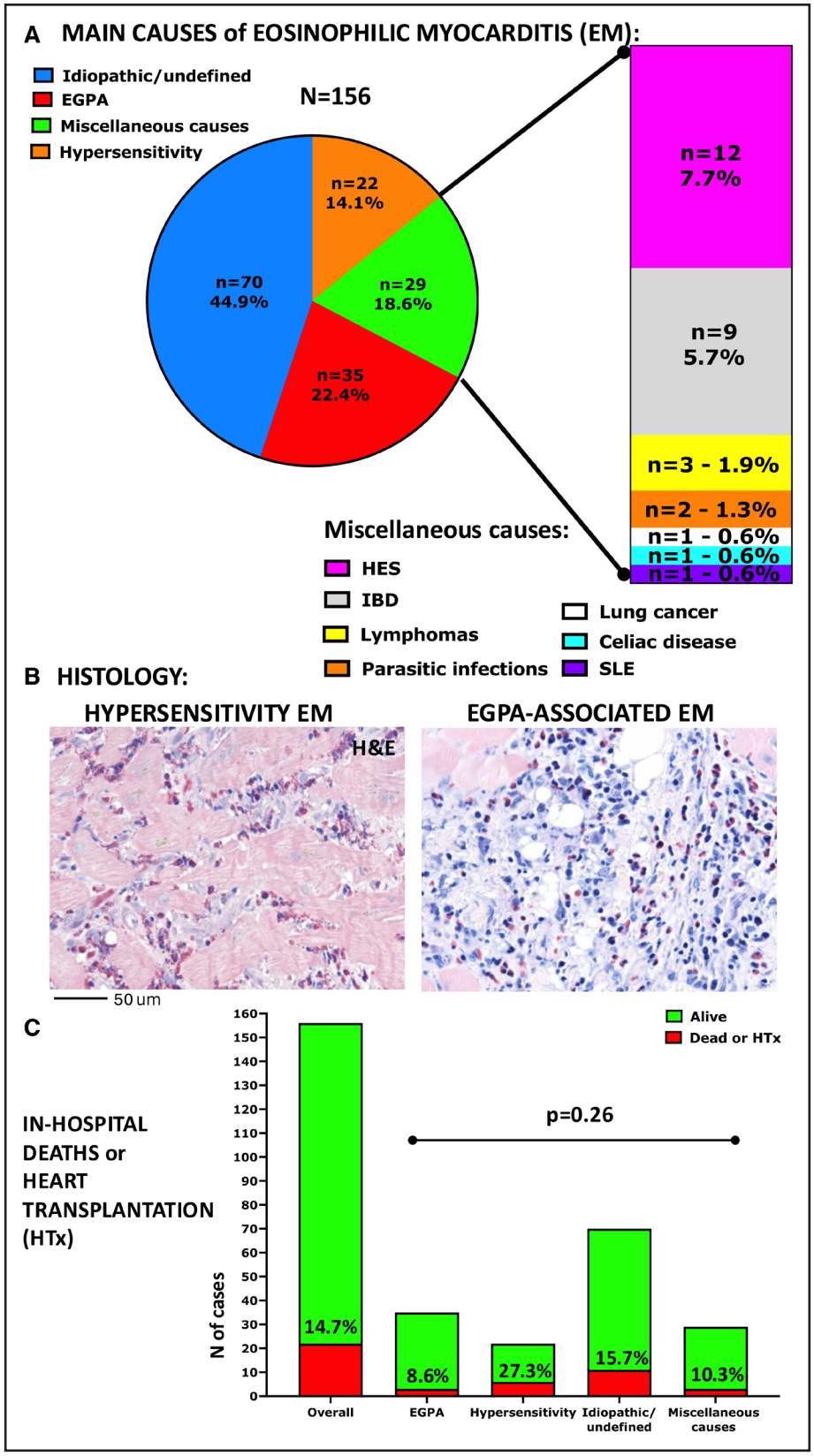

Figure 2. Prevalence of main causes of EM and impact of cause on in-hospital death or need for HTx.
A, Prevalence of eosinophilic myocarditis (EM)–associated conditions. **B**, Histologies from 2 patients in the registry with hypersensitivity EM (**left**) and eosinophilic granulomatosis with polyangiitis (EGPA)–associated EM (**right**). **C**, The proportion of patients who died or received heart transplantation (HTx) during hospitalization (red) compared with those who survived free of HTx in the overall population and the different groups of EM. Hypersensitivity EM showed a higher proportion of death or HTx (27.3%), but the differences among the groups were not statistically significant.

Table 1. Clinical, Laboratory, and Diagnostic Findings of Patients With Acute EM in the OVERALL population and the 4 Groups With Specific Causes

	Patients with available data	Overall (N=156)	EGPA (n=35, 22.4%)	Hypersensitivity (n=22, 14.1%)	Idiopathic/ undefined (n=70, 44.9%)	Miscellaneous causes (n=29, 18.6%)	*P* value for overall comparison/significant pairwise comparisons
Age, y	156	48 (34–59)	50 (36–58)	48 (38–59)	48 (34–61)	40 (31–50)	0.311
Female	156	51 (32.7)	15 (42.9)	11 (50.0)	15 (21.4)	10 (34.5)	0.033*
Age <16 y	156	2 (1.3)	0	1 (4.5)	1 (1.4)	0	0.441
White race	143	106 (74.1)	27 (84.4)	15 (83.3)	41 (61.2)	23 (88.5)	0.011*
Comorbidities							
Any associated condition	156	70 (44.9)	35 (100)	4 (18.2)	4 (5.7)	27 (93.1)	<0.001* <0.001† <0.001‡ <0.001¶ <0.001#
Autoimmune disorder	156	52 (33.3)	35 (100)	3 (13.6)	3 (4.3)	11 (37.9)	<0.001* <0.001† <0.001‡ <0.001§ <0.001#
Hematologic disorder	156	14 (9.0)	0 (0)	0 (0)	0 (0)	14 (48.3)	<0.001* <0.001§ <0.001¶ <0.001#
Infective condition	156	2 (1.3)	0 (0)	0 (0)	1 (1.4)	1 (3.4)	0.609
Solid cancer	156	2 (1.3)	0 (0)	1 (4.5)	0 (0)	1 (3.4)	0.232
Clinical presentation							
Time between symptoms onset and hospitalization, d	156	3 (2–10)	10 (3–14)	4 (1–5)	3 (2–8)	2 (1–7)	0.107
Systolic blood pressure, mm Hg	147	103 (90–120)	102 (90–120)	110 (89–122)	103 (88–115)	105 (93–124)	0.784
Heart rate, bpm	144	100 (82–116)	104 (90–117)	100 (84–125)	100 (78–115)	100 (84–119)	0.555
Chest pain	156	83 (53.2)	16 (45.7)	13 (59.1)	38 (54.3)	16 (55.2)	0.760
Dyspnea	156	118 (75.6)	26 (74.3)	19 (86.4)	51 (72.9)	22 (75.9)	0.636
Syncope	156	16 (10.3)	4 (11.4)	1 (4.5)	10 (14.3)	1 (3.4)	0.317
Prodromal symptoms	156	123 (78.8)	28 (80.0)	18 (81.8)	55 (78.6)	22 (75.9)	0.960
Fever	155	95 (61.3)	20 (57.1)	12 (54.5)	44 (63.8)	19 (65.5)	0.784
Sore throat	148	20 (13.4)	6 (17.6)	3 (15.8)	6 (8.7)	5 (18.5)	0.467
Gastrointestinal symptoms	156	46 (29.5)	4 (11.4)	7 (31.8)	25 (35.7)	10 (34.5)	0.066
Pneumonia	156	21 (13.5)	5 (14.3)	3 (15.8)	10 (14.3)	3 (10.3)	0.959
Asthma	103	50 (48.5)	21 (75.0)	3 (21.4)	17 (44.7)	9 (39.1)	0.003* 0.012†
ECG on presentation	149						
Normal	149	20 (13.4)	3 (9.1)	0	14 (20.9)	3 (10.7)	0.066
ST-segment elevation	149	42 (28.2)	4 (12.1)	7 (33.3)	26 (38.8)	5 (17.9)	0.021*
ST-segment depression/abnormalities	149	38 (25.5)	16 (48.5)	4 (19.0)	11 (16.4)	7 (25.0)	<0.001* <0.001‡ 0.011#
T-wave inversion	149	30 (20.1)	6 (18.2)	7 (33.3)	6 (9.0)	11 (39.3)	0.003* 0.008#
QRS duration >120 ms	149	18 (10.1)	4 (12.1)	3 (14.3)	10 (14.9)	2 (7.1)	0.769
LBBB	149	4 (2.7)	1 (3.0)	0 (0)	3 (4.5)	0 (0)	
RBBB	149	5 (3.4)	2 (6.1)	2 (9.5)	0 (0)	1 (3.6)	
Third-degree atrioventricular block	149	2 (1.3)	0 (0)	0 (0)	2 (3.0)	0 (0)	

(*Continued*)

Table 1. Continued

	Patients with available data	Overall (N=156)	EGPA (n=35, 22.4%)	Hypersensitivity (n=22, 14.1%)	Idiopathic/ undefined (n=70, 44.9%)	Miscellaneous causes (n=29, 18.6%)	*P* value for overall comparison/significant pairwise comparisons
Ventricular tachycardia	149	8 (5.4)	1 (3.0)	1 (4.8)	5 (7.5)	1 (3.6)	
Laboratory findings							
Peripheral eosinophilia based on cell count (≥500 cells/μL) or if not available on ≥5%*‡	136	78 (57.4)	23 (74.2)	12 (57.1)	24 (42.1)	19 (70.4)	0.003* 0.021‡
Peripheral eosinophilia only based on cell count (≥500 cells/μL)	125	67 (53.6)	21 (72.4)	7 (36.8)	22 (41.5)	17 (70.8)	0.007*
Eosinophils, cells/μL	125	630 (200–3260)	3290 (430–5500)	330 (185–1515)	370 (150–1520)	1335 (353–3198)	0.003* 0.015† 0.008‡
Eosinophilic percentage ≥10%	125	51 (40.8)	19 (67.9)	6 (30.0)	13 (25.0)	13 (52.0)	<0.001* 0.002‡
Eosinophilic percentage ≥5%	125	69 (55.2)	21 (75.0)	11 (55.0)	20 (38.5)	17 (68.0)	0.007* 0.015‡
Eosinophilic percentage, %	125	6.0 (1.5–26.3)	28.5 (4.9–38.2)	5.7 (1.2–19.1)	3.7 (1.2–9.8)	10.4 (1.7–26.3)	0.004* 0.005‡
Increased CRP on admission	146	133 (91.1)	31 (93.9)	19 (95.0)	60 (88.2)	23 (92.0)	0.702
First available CRP value (× fold URL)	91	10.2 (4.6–23.1)	8.4 (2.9–14.4)	17.0 (9.2–22.6)	14.2 (5.1–27.0)	7.9 (4.6–22.3)	0.104
Increased troponin T or troponin I or CK-MB on admission	149	143 (96.0)	34 (97.1)	19 (90.5)	62 (95.4)	28 (100)	0.861
Troponin increase on admission, × fold URL	110	82.2 (25.0–203.5)	154.5 (33.1–250.1)	66.7 (46.7–173.1)	45.3 (9.2–178.3)	95.7 (44.9–371.9)	0.802
Troponin increase peak, × fold URL	110	84.3 (14.0–248.4)	184.9 (32.1–321.2)	67.9 (41.3–213.2)	40.7 (8.3–203.8)	97.9 (28.8–381.6)	0.217
BNP, pg/mL	32	638 (261–944)	613 (577–1050)	1520 (1196–1843)	631 (319–869)	615 (238–1263)	0.517
NT-proBNP, pg/mL	75	8499 (2333–14 698)	7191 (2516–10 077)	10 451 (4258–27 286)	7943 (1875–1 3632)	9053 (8021–15 680)	0.356
Increased liver enzymes	150	99 (66.0)	18 (52.9)	14 (63.6)	48 (71.6)	19 (70.4)	0.282
Increased creatinine	153	62 (40.5)	15 (42.9)	8 (36.4)	29 (42.0)	10 (37.0)	0.932
Echocardiography							
LVEF on admission	156	32 (25–48)	30 (25–49)	28 (20–39)	35 (20–48)	34 (25–50)	0.502
Lowest LVEF during hospital	149	28 (16–44)	29 (25–45)	25 (16–39)	26 (11–43)	30 (25–45)	0.415
IVS thickness on admission, mm	110	11 (10–12)	11 (10–12)	11 (9–12)	11 (9–13)	11 (10–14)	0.772
LVEDD on admission, mm	128	50 (43–55)	50 (44–57)	52 (43–56)	49 (43–55)	48 (44–52)	0.885
LVEDV on admission, mL	68	106 (84-135)	119 (89–153)	130 (77–146)	100 (84–129)	96 (77–117)	0.261
At least moderate mitral regurgitation	137	33 (24.1)	10 (30.3)	6 (30.0)	12 (20.3)	5 (20.0)	0.623
LV restrictive filling pattern*‖	122	34 (27.9)	12 (35.3)	9 (50.0)	5 (10.9)	8 (33.3)	0.006* 0.013‖
Pericardial effusion at presentation*†	142	68 (47.9)	21 (61.8)	4 (19.0)	29 (46.8)	14 (56.0)	0.016* 0.030†
RV-TAPSE on admission, mm	82	16 (12–20)	18 (15–20)	13 (12–18)	16 (13–20)	16 (11–20)	
Coronary angiogram performed	154	109 (70.8)	25 (71.4)	16 (72.7)	51 (73.9)	17 (60.7)	0.627
Coronary artery disease	109	1 (0.9)	0	1 (6.3)	0	0	
Histology							
EMB	156	149 (95.5)	34 (97.1)	19 (86.4)	68 (97.1)	28 (96.6)	0.080

(*Continued*)

Table 1. Continued

	Patients with available data	Overall (N=156)	EGPA (n=35, 22.4%)	Hypersensitivity (n=22, 14.1%)	Idiopathic/ undefined (n=70, 44.9%)	Miscellaneous causes (n=29, 18.6%)	*P* value for overall comparison/significant pairwise comparisons
Postmortem examination/ explanted heart	156	7 (4.5)	1 (2.9)	3 (13.6)	2 (2.8)	1 (3.4)	
Moderate to severe fibrosis	152	22 (14.5)	5 (14.7)	0	11 (16.4)	6 (20.7)	0.184
Presence of giant cells	156	9 (5.8)	1 (2.9)	1 (4.5)	5 (7.1)	2 (6.9)	0.387
Presence of granuloma	156	3 (1.9)	0	0	2 (2.9)	1 (3.4)	0.441
Viral search in the myocardium performed	116	40 (34.5)	8 (25.8)	8 (53.3)	17 (32.7)	7 (38.9)	0.701
If viral search performed, positive result	40	7 (17.5)	0 (0)	0 (0)	5 (29.4)	2 (28.6)	0.571
CMRI							
CMRI performed*‡§	156	84 (53.8)	27 (77.1)	13 (59.1)	33 (47.1)	11 (37.9)	0.007* 0.033‡ 0.021§
Time between hospitalization and first CMRI if performed within 60 d, d	82	6 (2–11)	6 (3–11)	4 (1–9)	5 (2–12)	5 (0–11)	0.626
LVEF, %	84	45 (35–55)	41 (33.5–55)	48 (36–54)	46 (40–63)	45 (30–50)	0.305
LV-EDV indexed, mL/m^2	70	91 (68–117)	108 (72–137)	88 (76–101)	90 (77–123)	65 (50–92)	0.567
RV-EDV, indexed, mL/m^2	47	75 (58–90)	57 (50–81)	76 (62–87)	76 (66–94)	75 (59–96)	0.221
RVEF, %	55	52 (43–60)	55 (43–60)	49 (44–59)	52 (44–60)	52 (39–53)	0.676
LGE presence	84	64 (76.2)	22 (84.6)	8 (57.1)	24 (75.0)	10 (83.3)	0.243
Main LGE pattern	31	31 (100)	14	4	10	3	
Transmural LGE		6/31 (19.4)	4/14 (28.6)	0	2 (20.0)	0	
Subendocardial LGE		18/31 (58.1)	9/14 (64.3)	1/4 (25.0)	2/10 (20.0)	1/3 (33.3)	
Subepicardial LGE*		7/31 (22.6)	1/14 (7.1)	3/4 (75.0)	6/10 (60.0)	2/3 (66.7)	
Edema on T2-weighted images	81	43 (53.1)	16 (59.3)	6 (46.2)	15 (51.7)	6 (50.0)	0.866

Values are number (percent) or median (quartile 1–3) unless otherwise indicated.

BNP indicates B-type natriuretic peptide; CK-MB, creatine kinase myocardial band; CMRI, cardiac magnetic resonance imaging; CRP, C-reactive protein; EDD, end-diastolic diameter; EDV, end-diastolic volume; EF, ejection fraction; EGPA, eosinophilic granulomatosis with polyangiitis; EM, eosinophilic myocarditis; EMB, endomyocardial biopsy; IVS, interventricular septum; LBBB, left bundle-branch block; LGE, late gadolinium enhancement; LV, left ventricular; NT-proBNP, N-terminal pro-B-type natriuretic peptide; RBBB, right bundle-branch block RV, right ventricular; TAPSE, tricuspid annular plane systolic excursion; and URL, upper reference limit.

*Overall *P* value (χ^2 test) was <0.05 for these variables.

Pairwise χ^2 test with Holm correction *P*<0.05: †comparing EGPA with hypersensitivity, ‡comparing EGPA with idiopathic/undefined, §comparing EGPA with miscellaneous causes, ‖comparing hypersensitivity with idiopathic/undefined, ¶comparing hypersensitivity with miscellaneous causes, and #comparing idiopathic/undefined with miscellaneous causes.

Moderate to severe fibrosis was observed in 14.5% of the histologies. In 9 patients (5.8%), giant cells were reported; in 3 patients (1.9%), granulomas were reported. In these cases, the local pathologists did not assign the diagnosis of giant-cell myocarditis or cardiac sarcoidosis because of a large amount of eosinophilic infiltrate. Other findings are summarized in Table 1 and presented in the Supplemental Results. Histological findings of a representative case of EGPA-associated EM are reported in Figure S5A through S5D.

Cardiac Magnetic Resonance Imaging

A baseline CMRI performed within 60 days of the initial hospitalization was available in 84 patients (53.8%) with a median time since admission of 6 days (2–11 days) and a median LVEF of 45% at the time of CMRI. LGE was reported in 76.2% of patients with available data, with a predominance of subendocardial LGE pattern (58.1%) in the 31 patients with LGE pattern data available. No differences were observed in the CMRI findings among groups except the subepicardial LGE pattern, which was observed in only 7.1% of the patients with EGPA-associated forms compared with the highest in the hypersensitivity forms of 75.0% (Table 1). A representative case is shown in Figure S5E and S5F.

In-Hospital Treatment and Outcome

The median hospital stay was 19 days (Q1–Q3, 11–30 days), and 76.9% of patients required admission to the intensive care unit, with a median stay in the intensive care unit of 9 days (Q1–Q3, 4–19 days; Table S6).

Hemodynamic instability requiring inotropic support occurred in 80 patients (51.3%), and in 68 cases (43.6%), a temporary mechanical circulatory support (t-MCS) was positioned with a median time on support of 6 days (Q1–Q3, 1–10 days). A t-MCS was placed in the first 24 hours after hospitalization in 55 of 68 patients (80.9%). Venoarterial extracorporeal membrane oxygenation (n=47) was the most common t-MCS (Table 2 and Table S7). One patient was treated with HTx, and 4 patients received a long-term LV assist device, of whom 3 patients died during hospitalization (Table 2).

In-hospital death or need for HTx occurred in 23 patients (14.7%; 22 deaths and 1 HTx), although 92.9% (n=145) were treated with immunosuppressive agents (Table 2 and Table S7). There were no differences in terms of mortality among the different groups, although a nonsignificant numerically higher occurrence was observed in the hypersensitivity group (n=6/22; 27.3%) compared with the EGPA-associated group (n=3/35, 8.6%; Figure 2C). On admission or during hospitalization, sustained ventricular arrhythmias occurred in 28 patients (17.9%). On admission or during hospitalization, episodes of atrial fibrillation or embolic complications occurred in 13 patients (8.3%) and 12 patients (9.2%), respectively, with evidence of intraventricular thrombus in 16 (11.9%) and cardiac tamponade in only in 2 (1.3%). A temporary pacemaker was required in 7 patients (4.5%) because of a third-grade atrioventricular block. Only 4 patients were treated with an implantable cardioverter defibrillator. No significant differences were observed in the abovementioned in-hospital events among the groups (Table 2).

In-Hospital Medications

All but one patient treated with immunosuppression received corticosteroids (n=144/145), and a second

Table 2. In-Hospital Events and Postdischarge Events in the Overall Population and the 4 Groups With Specific Causes

	Patients with available data, n	Overall (N=156)	EGPA (n=35)	Hypersensitivity (n=22)	Idiopathic/ Undefined (n=70)	Miscellaneous causes (n=29)	*P* value for overall comparison/ significant pairwise comparisons
In-hospital events							
All deaths	156	22 (14.1)	3 (8.6)	6 (27.3)	10 (14.3)	3 (10.3)	0.343
Cardiac deaths	156	18 (11.5)	3 (8.6)	4 (18.2)	8 (11.4)	3 (10.3)	0.224
HTx	156	1 (0.6)	0 (0)	0 (0)	1 (1.4)	0 (0)	0.744
LVAD	156	4 (2.6)	0 (0)	1 (4.5)	3 (4.3)	0 (0)	0.414
t-MCS	156	68 (43.6)	15 (42.9)	7 (31.8)	35 (50.0)	11 (37.9)	0.424
Sustained ventricular arrhythmias (on admission, or during hospital stay)	156	28 (17.9)	4 (11.4)	4 (18.2)	14 (20.0)	6 (20.7)	0.715
Third-grade atrioventricular block requiring temporary pacemaker (on admission, or during hospital stay)	156	7 (4.5)	1 (2.9)	1 (4.5)	5 (7.1)	0 (0)	0.376
Atrial fibrillation	156	13 (8.3)	1 (2.9)	3 (13.6)	7 (10.0)	2 (6.9)	0.472
Cardiac tamponade	156	2 (1.3)	0 (0)	1 (4.5)	0 (0)	1 (3.4)	0.232
LV/RV thrombus	135	16 (11.9)	4 (12.5)	1 (4.8)	10 (17.5)	1 (4.0)	0.234
Embolic complications	131	12 (9.2)	2 (6.5)	1 (4.8)	8 (14.0)	1 (4.8)	0.414
ICD implantation	156	4 (2.6)	0 (0)	1 (4.5)	2 (2.9)	1 (3.4)	0.741
Postdischarge events							
	Patients with available data	**Overall (N=133)**	**EGPA (n=32)**	**Hypersensitivity (n=16)**	**Idiopathic/ Undefined (n=59)**	**Miscellaneous causes (n=26)**	
All deaths	133	12 (9.0)	3 (9.4)	2 (12.5)	4 (6.8)	3 (11.5)	0.837
Cardiac deaths	133	6 (4.5)	1 (3.1)	1 (6.3)	3 (5.1)	1 (3.8)	0.955
HTx	133	4 (3.0)	0 (0)	0 (0)	2 (3.4)	2 (7.7)	0.322
LVAD	133	1 (0.8)	0 (0)	0 (0)	1 (1.7)	0 (0)	>0.999
Sustained ventricular arrhythmias/ cardiac arrest	133	3 (2.3)	1 (3.1)	0 (0)	2 (3.4)	0 (0)	0.574
HF hospitalizations	133	16 (12.0)	2 (6.3)	1 (6.3)	7 (11.9)	6 (23.1)	0.208
ICD implantation	133	8 (6.0)	3 (9.4)	0 (0)	3 (5.1)	1 (3.8)	0.749

Values are n (%) or median (quartile 1–3), unless otherwise indicated.

EGPA indicates, eosinophilic granulomatosis with polyangiitis; HF, heart failure; HTx, heart transplantation; ICD, implantable cardioverter defibrillator; LV, left ventricular; LVAD, left ventricular assist device; RV, right ventricular; and t-MCS, temporary mechanical circulatory support.

agent was used during hospitalization in 34.6%. Other commonly used immunosuppressive drugs were intravenous immunoglobulins (n=22, 14.1%), azathioprine (n=22, 14.1%), cyclophosphamide (n=19, 12.2%), methotrexate (n=9, 5.8%), and IL-5 receptor blockers (n=8, 5.1%; mepolizumab in 4, benralizumab in 3, in 1 case not specified). The use of immunosuppressive agents differed significantly among the 4 groups, with a second agent, particularly cyclophosphamide and methotrexate, being more frequently used in EGPA-associated forms (Table S7).

Predictors of In-Hospital Outcome

Non-White, dyspnea on admission, presence of gastrointestinal symptoms, decreased systolic blood pressure, increased heart rate, raised creatinine levels, decreased LVEF, and LV restrictive filling pattern on first echocardiogram were all associated with in-hospital death or HTx in univariable analyses (Table 3). Reduced LVEF (odds ratio [OR], 0.940 per 1-unit increase in LVEF [95% CI, 0.899–0.984) on first echocardiogram and decreased systolic blood pressure (OR, 0.966 per 1–mm Hg increase [95% CI, 0.939–0.995]) remained significant in multivariable logistic regression analyses, whereas non-White race was a borderline variable associated with in-hospital death or HTx (OR, 2.981 [95% CI, 0.970–9.161]; Table 3). Abnormal ECG on admission and raised transaminases were findings observed only in patients who died or underwent HTx during hospitalization. It must be noted that, the folds of elevation of C-reactive protein and troponin above their upper reference limits at admission demonstrated a significant nonlinear association (P=0.016 and P=0.049, respectively; Table S8).

Analyses including in-hospital treatments showed that the use of inotropes, anticoagulants, and t-MCS was associated with in-hospital death or HTx in univariable analyses, whereas immunosuppressive agents were associated with a decrease in in-hospital death or HTx (Table S9). Non-White (OR, 2.593 [95% CI,0.837–8.039]), reduced LVEF (OR, 0.959 per 1-unit increase in LVEF [95% CI, 0.914–1.006]), decreased systolic blood pressure (OR, 0.974 per 1–mm Hg increase [95% CI, 0.947–1.003]), and use of inotropes (OR, 6.915 [95% CI, 0.743–64.396]) had a borderline significance at multivariable logistic regression analyses that included in-hospital treatments (Table S9). In the multivariable analyses, inotropes were used instead of t-MCS because all patients on t-MCS were on inotropes.

Long-Term Outcomes

Estimated rates of death or HTx (including in-hospital events) at 1 and 3 years were 19.0% and 23.8% (Figure 3A), without significant differences among different groups, although a nonsignificant numerically higher occurrence was observed in the hypersensitivity form (46.1%) compared with the EGPA-associated form (13.1%) at 3 years (P=0.15; Figure 3B). Incidence rates in terms of events per person-years for the long-term composite end point (death or HTx) in the overall sample and for the 4 groups are presented in Table S10. After a median follow-up of 22 months (Q1–Q3, 2–62 months), a further 12 patients died (9.0% of the 133 patients who were discharged without HTx), although only 6 of them (4.5%) died of a cardiac cause, without significant differences among the groups (Table 2). Another 4 patients were treated with HTx (3.0% of patients discharged without HTx), whereas 1 more received a long-term LV assist device. There were no significant differences in mortality or HTx after discharge based on the types. After discharge, HF relapses requiring hospitalization occurred in 16 patients (12.0%) patients, and ventricular arrhythmias or cardiac arrest occurred in 3 cases (2.3%; Table 2). An additional 8 patients received an implantable cardioverter defibrillator during the follow-up. With the exclusion of the 7 patients in whom the final diagnosis was reached after postmortem examination or on explanted heart after HTx, estimated rates of deaths or HTx at 1 and 3 years were 15.1% and 20.1%, without differences among the different types (Figure S6A and S6B). When patients with EM were compared with those with lymphocytic myocarditis, the overall rate of deaths or HTx was similar (23.8% versus 30.2% at 1080 days, respectively; P=0.76; Figure S7), although the clinical presentation was more severe in patients with lymphocytic myocarditis (Table S11 and Supplemental Results, which provides further details on the comparison of patients' characteristics). In addition, regional differences in clinical presentation, treatments, and outcomes of patients with EM from Europe (n=117), the United States (n=18), and Japan (n=16) are presented in Table S12. Patients from Japan more often presented with an idiopathic/undefined form and had a more severe clinical presentation and a higher number of deaths, HTx, or long-term LV assist device implantation (Table S12).

Immunosuppression After Discharge

In the long term, immunosuppression was continued in 72.5% of cases (79/109 with available data), and a second agent was used in 25.7% of cases (Table S13). Further details are presented in the Supplemental Results.

Predictors of Long-Term Outcome

Hypersensitivity versus EGPA type, increased age (per 10 years), non-White race, decreased systolic blood pressure, raised creatinine levels, elevated NT-proBNP (N-terminal pro-B-type natriuretic peptide) levels (per 1000 pg/mL), decreased LVEF (which had a time-dependent effect and thus its hazard ratio [HR] was estimated in 3 time windows: 60 days, 60 days–1 year, and 1–3 years since hospitalization), and LV restrictive filling pattern on first echocardiogram were all associated with overall death

Table 3. Univariable and Multivariable Logistic Regression Analyses to Assess the Association of Variables on Admission With In-Hospital Death or HTx

Variables	n	Univariable models		Multivariable model	
		OR (95% CI)	*P* value	OR (95% CI)	*P* value
Hypersensitivity vs EGPA		4.000 (0.883–18.112)	0.072		
Idiopathic vs EGPA	156	1.989 (0.517–7.650)	0.317		
Miscellaneous vs EGPA		1.231 (0.229–6.616)	0.809		
Age, per 10 y	156	1.280 (0.973–1.684)	0.078		
Male vs female sex	156	1.903 (0.664–5.457)	0.127		
Non-White vs White race	143	3.654 (1.425–9.369)	0.007*	2.981 (0.970–9.161)	0.059†
Any associated condition‡	156	0.759 (0.307–1.874)	0.550		
Autoimmune disorder	156	0.856 (0.328–2.230)	0.750		
Hematologic disorder	156	0.420 (0.052–3.372)	0.414		
Systolic blood pressure, per mm Hg	144	0.946 (0.920–0.973)	<0.001*	0.966 (0.939–0.995)	0.024†
Heart rate, per bpm	140	1.027 (1.006–1.048)	0.011*		
Dyspnea or syncope vs none	156	7.857 (1.021–60.476)	0.048*		
Dyspnea vs not	156	8.479 (1.103–65.182)	0.040*		
Syncope vs not	156	2.123 (0.620–7.267)	0.231		
Chest pain vs not	156	0.328 (0.127–0.850)	0.022*		
GI symptoms vs not	156	2.567 (1.039–6.342)	0.041*		
Fever vs not	156	1.562 (0.602–4.053)	0.359		
Prodromal symptoms vs not	156	1.325 (0.418–4.200)	0.633		
Initial ECG nonnormal vs normal	156	No events among patients with normal ECG	…		
Peripheral eosinophilia vs no	156	1.487 (0.602–3.671)	0.390		
Raised transaminases vs no	150	No events among patients with transaminases not raised	…		
Raised creatinine vs no	153	2.657 (1.070–6.602)	0.035*		
Fold of elevation of CRP above the URL at admission, fold URL	91	1.002 (0.966–1.039)	0.919		
Fold of elevation of troponin above the URL at admission, per 100-fold URL	108	1.008 (0.984–1.033)	0.506		
NT-proBNP, per 1000 pg/mL	75	1.018 (0.988–1.050)	0.248		
LVEF at admission, per % unit	155	0.923 (0.886–0.961)	<0.001*	0.940 (0.899–0.984)	0.008†
LVEDD at admission, per mL/m^2	128	0.989 (0.946–1.033)	0.609		
Interventricular septal thickness, per mm	110	1.032 (0.923–1.155)	0.576		
Pericardial effusion at admission vs no	142	0.987 (0.391–2.497)	0.979		
Mitral regurgitation moderate/severe vs no/mild	137	1.057 (0.317–3.532)	0.928		
LV restrictive filling pattern	137	3.760 (1.351–10.467)	0.011*		
RV TAPSE at admission, per mm	82	0.927 (0.829–1.037)	0.184		
Presence of moderate to severe fibrosis at first EMB vs no	152	1.383 (0.420–4.555)	0.594		
Giant cells vs no	156	1.714 (0.333–8.819)	0.519		
Viral search performed vs no	145	0.367 (0.102–1.316)	0.124		
Hospitalized before 2010 vs 2010 or after	156	2.207 (0.813-5995)	0.120		

CRP indicates C-reactive protein; EGPA indicates eosinophilic granulomatosis with polyangiitis; EMB, endomyocardial biopsy; GI, gastrointestinal; HTx, heart transplantation; LV, left ventricular; OR, odds ratio; LVEDD, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-B-type natriuretic peptide; OR, odds ratio; RV, right ventricular; TAPSE, tricuspid annular plane systolic excursion; and URL, upper reference limit.

*Variable significantly associated with in-hospital combined outcome of death or HTx in univariable logistic regression analysis.

†Variable selected with LASSO as an independent predictor of in-hospital combined outcome of death or HTx in multivariable logistic regression analysis.

‡Any associated condition includes autoimmune disorders, hematologic disorders, infective conditions, or solid cancer.

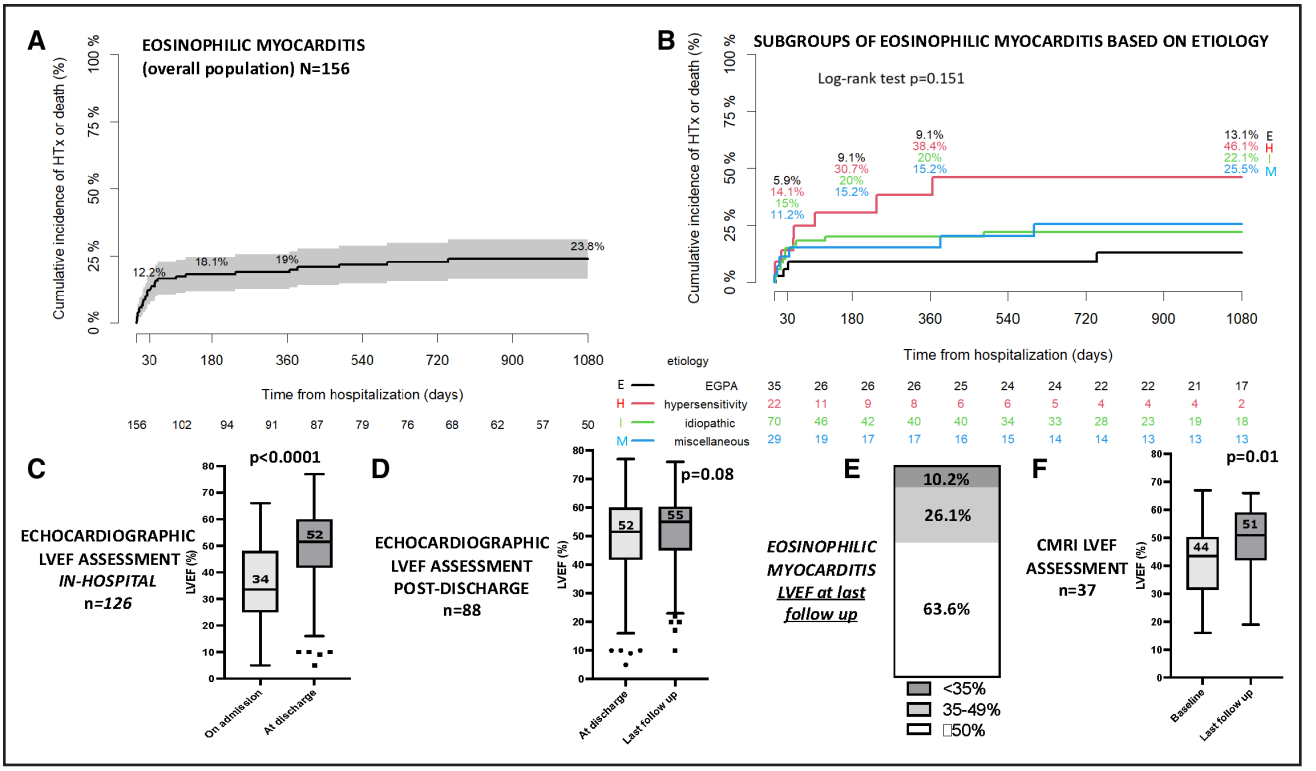

Figure 3. Estimated rates of death or HTx in the overall population with EM and in the subgroups with different causes and changes in LVEF.

A, Estimated rates of death or heart transplantation (HTx; including in-hospital events) at 1 and 3 years in the overall population (**B**) and in the subgroups with different etiologies. No significant differences were observed, although a nonsignificant numerically higher occurrence was observed in the hypersensitivity form (46.1%) compared with eosinophilic granulomatosis with polyangiitis (EGPA)–associated EM (13.1%) at 3 years. **C**, Echocardiographic data of left ventricular ejection fraction (LVEF) on admission and discharge in the entire population of eosinophilic myocarditis (EM; available data, n=126). **D**, Echocardiographic data of LVEF at discharge and at the last available follow-up after a median time of 645 days (quartile 1–3 [Q1–Q3], 105–1088) among 88 patients with available data. **E**, Proportion of patients with LVEF <35%, 35% to 49%, and ≥50% and at the last available echocardiographic examination (n=88). **F**, LVEF data based on cardiac magnetic resonance imaging during hospitalization and at the last available follow-up after a median time of 298 days (Q1–Q3, 157–639) among 37 patients with available data. Dot-box plots are presented in Figure S11A through S11C. Wilcoxon matched-pair signed-rank test was used for comparisons.

or HTx in univariable analysis (Table 4). Increased age (per 10 years; HR, 1.420 [95% CI, 1.152–1.749]) and reduced LVEF (HR, 0.944 per 1-unit increase in LVEF in the first 60 days after hospitalization [95% CI, 0.907–0.983]) on first echocardiogram remained significant at multivariable Cox regression analyses, whereas LV restrictive pattern on first echocardiogram was a borderline variable associated with death or HTx (HR, 1.921 [95% CI, 0.948–3.893]; Table 4). Folds of elevation of C-reactive protein above the upper reference limit at admission, folds of elevation of troponin above the upper reference limit at admission, and right ventricular tricuspid annular plane systolic excursion at admission demonstrated a significant nonlinear association (P=0.033, P=0.032, and P=0.026, respectively; Table S8). The assessment of the linear effect of continuous covariates and the proportional hazards assumption for all covariates included in univariable and multivariable Cox models are reported in Tables S8 and S14 and Figures S8 through S10.

Analyses including in-hospital treatments showed that the use of inotropes and t-MCS was associated with overall death or HTx in univariable analysis, whereas immunosuppressive therapy was associated with a decrease in death or HTx (Table S15). Increased age (per 10 years; HR, 1.339 [95% CI, 1.083–1.654]), reduced LVEF (HR, 0.964 per 1-unit increase in LVEF [95% CI, 0.939–0.989]) on the first echocardiogram, and use of immunosuppressive therapy (use of immunosuppressive therapy was associated with a reduced risk with an HR of 0.315 [95% CI, 0.119–0.834]) remained significant in multivariable Cox regression analyses, whereas LV restrictive filling pattern on first echocardiogram was a borderline variable associated with overall death or HTx (HR, 2.140 [95% CI, 1.025–4.369]; Table S15).

Changes in LVEF During Hospitalization and in the Long-Term Follow-Up

Considering 126 patients with echocardiographic LVEF assessment on admission and at discharge, the median LVEF before discharge was 52% (Q1–Q3, 42%–60%), with a significant increase compared with LVEF on

Table 4. Univariable and Multivariable Cox Regression Analyses to Assess the Association of Variables on Admission With Overall Death or HTx

Variables	n	Univariable models		Multivariable model	
		HR (95% CI)	*P* value	HR (95% CI)	*P* value
Hypersensitivity vs EGPA		3.278 (1.124–9.556)	0.030*		
Idiopathic vs EGPA	156	1.637 (0.645–4.159)	0.300		
Miscellaneous vs EGPA		1.669 (0.577–4.831)	0.354		
Age, per 10 y	156	1.376 (1.120–1.690)	0.002*	1.420 (1.152–1.749)	0.002†
Male vs female sex	156	1.515 (0.746–3.069)	0.251		
Non-White vs White race	143	2.037 (1.018–4.076)	0.044*		
Any associated condition‡	156	0.842 (0.445–1.590)	0.595		
Autoimmune disorder	156	0.634 (0.308–1.303)	0.215		
Hematologic disorder	156	1.219 (0.468–3.176)	0.685		
Systolic blood pressure, per mm Hg	144	0.979 (0.965–0.992)	0.002*		
Heart rate, per bpm	140	1.011 (0.998–1.024)	0.098		
Dyspnea or syncope vs none	156	1.897 (0.794–4.536)	0.150		
Dyspnea vs not	156	1.982 (9.830–4.738)	0.124		
Syncope vs not	156	1.393 (0.490–3.961)	0.534		
Chest pain vs not	156	0.581 (0.304–1.111)	0.101		
GI symptoms vs not	156	1.424 (0.745–2.720)	0.284		
Fever vs not	156	0.787 (0.414–1.496)	0.464		
Prodromal symptoms	156	0.752 (0.370–1.528)	0.430		
Initial ECG nonnormal vs normal	156	1.715 (0.526–5.590)	0.371		
Peripheral eosinophilia vs no	156	1.165 (0.619–2.192)	0.635		
Raised transaminases vs no	150	2.120 (0.965–4.656)	0.061		
Raised creatinine vs no	153	2.779 (1.436–5.378)	0.002*		
Fold of elevation of CRP above the URL at admission, per fold URL	91	0.999 (0.972–1.027)	0.960		
Fold of elevation of Troponin above the URL at admission, per 100-fold URL	108	1.000 (0.981–1.019)	0.955		
NT-proBNP, per 1000 pg/mL	75	1.049 (1.025–1.074)	<0.001		
LVEF at admission, per % unit, from hospitalization–60 d	155	0.943 (0.914–0.974)	<0.001*	0.944 (0.907–0.983)	0.005†
LVEF at admission, per % unit, from 60 d–1 y		0.902 (0.804–1.013)	0.082	0.882 (0.775–1.004)	0.058
LVEF at admission, per % unit, from 1–3 y		0.936 (0.870–1.007)	0.076	0.924 (0.852–1.002)	0.055
LVEDD at admission, per mL/m^2	128	1.016 (0.979–1.055)	0.405		
Interventricular septal thickness, per mm	110	0.966 (0.873–1.070)	0.513		
Pericardial effusion at admission vs no	142	0.655 (0.333–1.291)	0.222		
Mitral regurgitation moderate/severe vs no/mild	137	1.515 (0.718–3.195)	0.276		
LV restrictive filling pattern	137	2.269 (1.125–4.575)	0.022*	1.921 (0.948–3.893)	0.080†
RV TAPSE at admission, per mm	82	0.966 (0.906–1.030)	0.291		
Presence of moderate to severe fibrosis at first EMB vs no	152	1.573 (0.687–3.603)	0.284		
Giant cells vs no	156	2.289 (0.810–6.471)	0.118		
Viral search performed vs no	145	0.991 (0.466–2.110)	0.982		
Hospitalized before 2010 vs 2010 or after	156	1.212 (0.555-2.650)	0.629		

CRP indicates C-reactive protein; EGPA, eosinophilic granulomatosis with polyangiitis; EMB, endomyocardial biopsy; GI, gastrointestinal; HTx, heart transplantation; LV, left ventricular; HR, hazard ratio; LVEDD, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-B-type natriuretic peptide; RV, right ventricular; TAPSE, tricuspid annular plane systolic excursion; and URL, upper reference limit.

*Variable significantly associated with overall death or HTx in univariable Cox regression analysis. LVEF at admission had a time-dependent effect; thus, its HR was estimated in 3 time windows.

†Variable selected using LASSO as an independent predictor of overall death or HTx in multivariable Cox regression analysis.

‡Any associated condition includes autoimmune disorders, hematologic disorders, infective conditions, or solid cancer.

admission. There was a median increase of 18% in LVEF during hospitalization, considering that 23 patients died or underwent HTx, and in 7 cases, data were unavailable (Figure 3C and Figure S11A). Further data on echocardiographic and CMRI findings at discharge and the last available follow-up are presented in Figure 3D through 3F, Figure S11B and S11C, Table S16, and the Supplemental Results.

DISCUSSION

This international registry of patients with histologically proven EM shows high mortality of this specific form of myocarditis. The in-hospital death or HTx rate is 14.7% (22 deaths and 1 HTx), with estimated mortality or need for HTx that increases to 19.0% at 1 year and 23.8% at 3 years. A nonsignificant higher occurrence in the hypersensitivity form (46.1%) was observed compared with the EGPA-associated form (13.1%) at 3 years. Although decreased systolic blood pressure, reduced LVEF on admission, and need for inotropes emerged as independent predictors of in-hospital death or HTx, age, reduced LVEF on admission, and use of immunosuppressive therapy were associated with the overall risk of death or HTx. Furthermore, other significant complications were frequently reported during hospitalization such as the need for t-MCS in 43.6%, sustained ventricular arrhythmias in 17.9%, and embolic complications in 9.2%. In patients with EM, although the clinical presentation was less severe than a comparator group of patients with histologically proven lymphocytic myocarditis, rates of estimated mortality or HTx were similar. A similar mortality rate or need for HTx in EM and lymphocytic myocarditis was in line with 2 previous registries that included 19 and 51 patients with EM.[4,5]

A 3-stage process of eosinophilic cardiac injury has been proposed, ranging from the initial inflammatory/necrotic phase of acute EM to the thrombotic phase and then the fibrotic remodeling of the endomyocardium, with overlap among the stages.[3,13] An acute, intense exposure to eosinophilia can cause an EM, which in some cases can be described as necrotizing due to extensive areas of cardiomyocyte necrosis. Even if the pathogenesis remains unclear, one explanation for peripheral eosinophilia may be bone marrow stimulation through IL-5 triggered by various factors (including concurrent infections, systemic conditions, and cancer). Alternatively, IL-5 could be produced by eosinophils in myocardial tissue, contributing to chemotaxis and degranulation, which might explain local injury without peripheral eosinophilia.[14] Compared with lymphocytic myocarditis, in which inflammatory infiltrates localize mainly in the epicardium or midwall, EM primarily involves the endocardium and is associated with a higher risk of intraventricular thrombus formation even with mildly reduced LVEF. The eosinophilic inflammatory phase can typically cause subendocardial and transmural injuries, which LGE identifies on CMRI.[15] The persistence of eosinophilic injury can evolve into the thrombotic and fibrotic stages, characterized by diffuse subendocardial fibrosis and apical thrombi, which are classic features of Loeffler cardiomyopathy. In this registry, apical thrombi have been reported in 11.9%, a figure that may be considered relatively low, although it is in line with the 13% to 18% found in previous studies.[7,15] However, it is worth noting that only patients with acute EM and symptom onset within 30 days were included. In contrast, including patients with a longer history of eosinophilia would have led to a higher proportion with apical thrombi. Anticoagulation appears to be a reasonable therapeutic option in patients with EM (used in 67% of patients in this registry), especially in patients with apical akinesia or severely depressed LVEF, because embolic complications were observed in 9.2% of cases.

A major novelty in our understanding of the clinical presentation and course of EM is that peripheral eosinophilia is present in only 57.4% of cases (Figure 4). Thus, physicians cannot rely on peripheral eosinophilia to reach this diagnosis; EMB is necessary.[16] High peripheral eosinophilic cells can suggest the association with eosinophilic conditions such as EGPA or idiopathic HES (the most common miscellaneous causes), with a median of 3290 and 1335 eosinophils/μL, respectively. In contrast, a relatively low increase of eosinophilic cells in the blood is more common in hypersensitivity and idiopathic forms (330 and 370 eosinophils/μL, respectively), making the diagnosis of EM even more challenging in these patients, often without the involvement of other organs. This finding was confirmed in a subanalysis of 115 patients for whom the date of immunosuppression administration was known. Peripheral eosinophilia was present in 53.0% of the patients without immunosuppression on admission (Table S17 provides further details). This finding provides additional evidence for the scientific statements that recommend EMB in the case of patients with clinically suspected severe myocarditis characterized by cardiogenic shock, advanced atrioventricular block, ventricular arrhythmias, or acute HF poorly responsive to medications.[2,3] The clinical ramification of EMB is identifying a specific histological form of myocarditis responsive to corticosteroids. This could explain why early EMB (<2 days after admission) can lead to a prognostic advantage in patients with fulminant myocarditis.[17,18]

Another relevant finding is that asthma was reported in 48.5% of cases. Thus, asthma in patients with suspected acute myocarditis could steer toward the suspicion of an eosinophilic form. Asthma was significantly higher in patients with EGPA (75.0%), in whom asthma is one of the main diagnostic features of EGPA.[19] In addition, asthma is observed in 44.7% of patients with idiopathic/undefined forms, suggesting that a final diagnosis of EGPA could have been missed in a proportion of patients classified as idiopathic. A practical clinical implication of this finding is that involving a rheumatologist or an internal

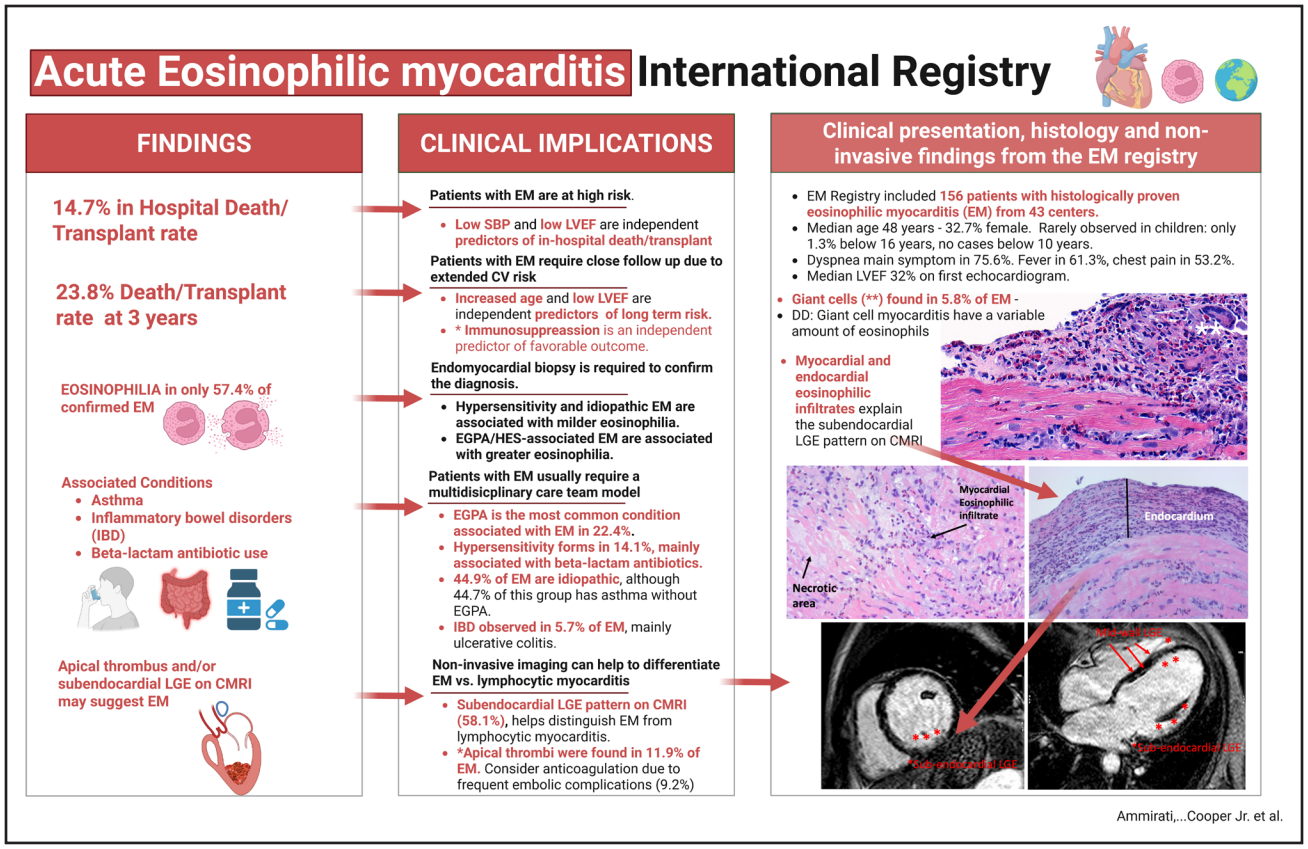

Figure 4. Summary of the major findings and clinical implications of the acute EM international registry.
CMRI indicates cardiac magnetic resonance imaging; DD, differential diagnoses; EGPA, eosinophilic granulomatosis with polyangiitis; EM, eosinophilic myocarditis; HES, hypereosinophilic syndromes; IBD, inflammatory bowel disorders; LGE, late gadolinium enhancement; LVEF, left ventricular ejection fraction; and SBP, systolic blood pressure. Figure created with BioRender.

medicine specialist in the management of a patient with a new diagnosis of EM should be preferable to reduce the likelihood of missing a concurrent diagnosis (Figure 4).

Another new finding is the association between EM and IBD, especially ulcerative colitis. IBD was associated with EM in 5.7% of patients, representing the fourth most common secondary condition. IBD is associated with other types of non–lymphocytic myocarditis such as giant-cell myocarditis, in which IBD was found in 7.9% of cases.[20] The association between IBD and EM was not previously clear, even if mesalazine, a salicylate drug commonly used in patients with IBD, was associated with hypersensitivity forms of myocarditis.[21] The local investigators did not report a potential association between the onset of EM in the setting of IBD and the use of mesalazine in our series. Another possible explanation for the association between IBD and EM can rely on the fact that colic involvement of EGPA could mimic IBD, and a misdiagnosis of IBD could have occurred.

Unexpectedly, the presence of a few giant cells in the setting of an EM was found in 9 patients (5.8%), without significant differences among subgroups, ranging from 2.9% in EGPA to 7.1% in idiopathic/undefined forms. Although various amounts of eosinophilic cells can be found in patients with giant-cell myocarditis,[3,20] in our cases, high numbers of eosinophilic cells were found and confirmed after an external review of the images (representative cases in Figures S12 and S13). The formation of giant cells can occur in EM, potentially being a histological marker of myocarditis severity. This finding may reflect a rare histological form of myocarditis with an overlap between EM and giant-cell myocarditis that was sporadically reported in case reports in the literature,[22,23] for which optimal immunosuppressive therapies must be defined.

This international registry confirms the poor prognosis of patients with acute EM, with an in-hospital mortality of 14.1%, in line with previous observations described in a review of published clinical cases and small series.[7] In that review, a potential publication bias, in which more striking and severe cases are more likely to be published, could have contributed to the higher in-hospital mortality rate of 22.3%.[7] In the current registry, the EGPA form was the most frequent condition associated with EM, observed in 22.4%, and the hypersensitivity forms were observed in 14.1%. Hypersensitivity EM was associated with the highest in-hospital mortality (27.3%), although this was not statistically significant. Antibiotics, especially β-lactam antibiotics, were the most common cause of hypersensitivity EM. Thus, in the case of myocarditis, a personal medical history of recent β-lactam antibiotic

administration could suggest a possible hypersensitivity EM, even in the absence of peripheral eosinophilia (Figure 4). Furthermore, EM associated with EGPA showed a lower in-hospital mortality rate of 8.5% compared with the previously reported 21.7%.[7] The observed lower mortality in EM associated with EGPA could reflect improved treatments for EGPA, including more frequent use of a combination of immunosuppressive agents. The most common association included steroids and cyclophosphamide, whereas IL-5 inhibitors emerged as new drugs used in combination with steroids. The use of immunosuppressive therapy is associated with improved survival; however, the exact mechanisms and optimal therapeutic approach remain unclear. Univariable analyses showed that a benefit on survival free of HTx can be observed both in patients who started immunosuppression in the first 5 days or beyond 5 days from hospitalization and in patients treated with azathioprine, although it was not observed with cyclophosphamide or intravenous immunoglobulins. A potential survival bias in a retrospective registry could explain why patients with a delayed start of immunosuppression still have a benefit compared with those who were not treated with immunosuppression. Too few patients were treated with IL-5 inhibitors to be included in the analysis; thus, the potential benefit of these new agents in EM remains to be assessed.

This registry provided, for the first time, predictors of death and HTx during index hospitalization or in the long term for patients with EM. Although factors such as reduced LVEF, decreased systolic blood pressure, or hemodynamic instability reflected by the use of inotropes or t-MCS can be expected predictors of in-hospital mortality or HTx in patients with acute myocarditis, likely not specific for EM,[24] non-White race emerged as a potential risk factor of in-hospital events (OR, 2.981; P=0.059). This study cannot address whether non-White race is a risk factor specific to EM. In recent research on predictors of outcome in patients with myocarditis supported with venoarterial extracorporeal membrane oxygenation, Asian ethnicity emerged as an independent risk factor with an OR of 1.47, but no data on histology were available.[25] Among the overall predictors of death or HTx, the protective role of immunosuppressive therapy emerged beyond increased age and LVEF on initial hospitalization. This is an important finding that can enhance the evidence for recommending the use of immunosuppressive therapies in the case of EM, which was previously based solely on expert consensus.[3,11] Immunosuppression has emerged as a relevant factor in the long-term outcome, so it will be crucial to establish the optimal immunosuppressive regimen in patients with EM in future trials. It may be worth testing the efficacy and safety of IL-5 inhibitors in patients with EM that are more specific against eosinophils and have fewer adverse events compared with steroids at higher doses or cyclophosphamide. Improving the best combination of immunosuppression therapies could also have an impact on the residual LV systolic dysfunction (LVEF <50%) that was reported in 36.3% of patients with an available echocardiogram after a median time of 645 days, of whom 10.2% had an LVEF<35%.

Study Limitations

The retrospective nature of this registry may have introduced potential bias. This registry lacked a centralized review of echocardiography or CMRI data, even if the pathology images from 74.4% of cases were externally reviewed and validated by 4 experienced cardiac pathologists. Most of the patients were White (74.1%); thus, granular data from non-White groups affected by EM cannot be provided in this study. The systemic condition associated with EM relied on the diagnosis of the local investigators. Thus, nonhomogeneous criteria were used in this registry to classify EM caused by EGPA, hypersensitivity, or HES. Furthermore, the large subgroup of idiopathic or undefined EM could include some patients who later reached a diagnosis of a systemic eosinophilic disorder or in whom a systemic condition was missed. In addition, screening for vasculitis was based on site investigator standards. We did not specify screening criteria for this registry, and the management of patients with EM may have varied significantly over >2 decades among the 43 centers that contributed cases, potentially introducing bias. Data on cardiomyopathic gene variants were not collected in this registry because genetic testing is not a current standard in this patient group. Cardiomyopathy-associated variants are generally associated with lymphocytic myocarditis and rarely with cardiac sarcoidosis but have not been associated with EM.[26–28] Still, these factors can reflect the real-world practice of managing patients with suspected EM; thus, the results of this registry can be generalizable. This registry introduced a methodological bias because it included only patients admitted to the hospital with histologically proven EM, primarily from tertiary referral centers. Patients with milder cases who did not undergo EMB were likely missed; thus, mortality related to EM could be higher in this registry than the actual mortality rate of EM. Nevertheless, our approach appears methodologically sound because peripheral eosinophilia alone is unreliable in identifying histological cases of EM. In addition, EM more frequently associated with chronic forms such as HES was by definition, not represented in this study of acute EM. Moreover, there were no centers from sub-Saharan Africa, where chronic restrictive cardiomyopathy and parasite infection, presenting late as endomyocardial fibrosis after EM, are relatively common.[29] The distribution of sites outside Africa may have led to an underrepresentation of parasite-related endomyocardial disease, although it must be acknowledged that EMB is rarely performed in these areas. In addition, only 2 patients (1.3%; 10 and 14 years of age) were below the age of 16 years; thus, no conclusions can be drawn on EM

in the pediatric population, even if this finding supports the concept that EM is a rare entity among children and young adolescents, for whom most cases are lymphocytic myocarditis. Last, the finding that immunosuppression is associated with improved survival without HTx is compelling, but it cannot establish causality.

Conclusions

Acute EM can often present without peripheral eosinophilia, and rates of in-hospital and midterm mortality or HTx are high. Although noninvasive tools and clinical findings can raise suspicion of EM, EMB remains the gold standard for definitive diagnosis. Relying solely on peripheral eosinophilia is not sufficient and can lead to missed or delayed diagnoses. However, in cases in which EMB is not feasible or carries high risk, a probable diagnosis may still be based on a combination of clinical (older age at presentation compared with lymphocytic myocarditis, presence of associated conditions such as asthma), laboratory (previous episodes or current peripheral eosinophilia, evidence of parasitic infections such as *T canis*), and imaging (presence of ventricular apical thrombi even with nearly normal LVEF or subendocardial LGE pattern on CMRI compared with the classic epicardial LGE pattern of lymphocytic myocarditis; Figure 4) findings. In-hospital immunosuppression is associated with improved HTx-free survival, although tailored immunosuppressive therapies are necessary to further improve outcomes.

ARTICLE INFORMATION

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Affiliations

De Gasperis Cardio Center, Niguarda Hospital, Milan, Italy (E.A., M.P., P.G., A.G.). School of Medicine and Surgery, University of Milano-Bicocca, Monza, Italy (E.A., P.G.). Heart and Lung Center, Helsinki University Hospital, Finland (J.L.). Heart Failure and Transplant Unit, IRCCS Azienda Ospedaliero-Universitaria di Bologna, Italy (L.P., A. Foà). Department of Pathology, University of Helsinki, and Diagnostic Center, Helsinki University Hospital, Finland (M.I.M.). Internal Medicine, Helsinki University Hospital and University of Helsinki, Finland (J.R.). Cardiology Department, Hospital Universitari Vall d'Hebron, Barcelona, Spain (A.U., M.V.-B.). Heart Center Leipzig at Leipzig University and Leipzig Heart Science, Germany (H.T., A. Freund). Department of Cardiology, Rigshospitalet, Copenhagen, Denmark (F.G.). Department of Cardiology, Angiology, and Intensive Medicine (CVK), German Heart Center at Charité (DHZC); and German Center for Cardiovascular Research (DZHK), partner site Berlin, Germany (C.T.). Berlin Institute of Health at Charité (BIH), Charité Universitätsmedizin Berlin, BIH Center for Regenerative Therapies (BCRT), Germany (C.T., A.E.). Intensive Care Unit, Alfred Hospital, Melbourne, Australia (J.I., M.K.). Medizinische Klinik und Poliklinik I, Klinikum der Universität, Ludwig-Maximilians-Universität, Munchen, Germany (W.-S.R., U.G.). Cardiothoracovascular Department, Division of Cardiology, Azienda Sanitaria Universitaria Giuliano Isontina, University of Trieste, Italy, member of European Reference Network for Rare, Low-Prevalence, or Complex Diseases of the Heart (ERN GUARD-Heart) (M.M., G.S.). Department of Cardiology, Institute for Clinical and Experimental Medicine, Prague, Czech Republic (V.M., I.W.). Department of Internal Medicine and Cardiology, Heart Centre Dresden, University Hospital, Technische Universität Germany (S.J., A.L.). Pathology Unit, IRCCS Azienda Ospedaliero-Universitaria di Bologna, Italy (C.B.). Advanced Cardiovascular Therapy Unit, Bambino Gesù Children's Hospital, IRCCS, Rome, Italy (R.A.). Second Department of Medicine, Department of Cardiovascular Medicine, First Faculty of Medicine, Charles University in Prague and General University Hospital in Prague, Prague, Czech Republic (P.K., T.P.). St. Anne's University Hospital and Faculty of Medicine, Masaryk University, Brno, Czech Republic (J.K., H.P.). Azienda ULSS Numero 2 Treviso, Italy (A.L.C.). Department of Medicine, Johns Hopkins University School of Medicine, Baltimore, MD (N.A.G., J.P.L.). Department of Cardiovascular Medicine, Mayo Clinic, Jacksonville, FL (E.P.M., J.S., L.T.C.). Department of Cardiology, University of California San Diego, La Jolla (K.H., E.D.A.). University Heart Center, University Hospital Zurich and University of Zurich, Switzerland (V.A.R., F.R.). Center for Translational and Experimental Cardiology, Department of Cardiology, University Hospital Zurich, University of Zurich, Schlieren, Switzerland (V.A.R., F.R.). Division of Cardiology, Hospital S. Maria della Misericordia, Perugia, Italy (C.C., C.R.). ACTION Study Group, Sorbonne Université, Assistance Publique-Hôpitaux de Paris, La Pitié-Salpêtrière Hospital, Department of Cardiology, France (F.H.). Université de Versailles St-Quentin-en-Yvelines, Montigny-le-Bretonneux, France (M.G). Deparment of Internal Medicine, Clinical Immunology and Hematology, National Reference Center for Hypereosinophilic Syndrome (CEREO), Hôpital Foch, Suresnes, France (M.G.). Mount Sinai Fuster Heart Hospital, Icahn School of Medicine, New York, NY (A.L.). Tohoku University Graduate School of Medicine, Sendai, Japan (H.S.). Cardiology and Cardiac Intensive Care, Heart Center, OLV Hospital Aalst, Belgium (C.V.). Department of Intensive Care, Harefield Hospital, Royal Brompton and Harefield Hospitals, Guy's & St Thomas' NHS Foundation Trust, London, UK (C.V.). Cardiology Department, Hospital de la Santa Creu I Sant Pau, IIB-SantPau, Universidad Autónoma de Barcelona, Spain (A.S.). Centro de Investigación Biomédica en Red Enfermedades Cardiovasculares (CIBER-CV), Madrid, Spain (A.S., M.G.C.-L., D.C.-M., M.M.-S., F.D.). Sorbonne Université, UMRS 1166, Institute of Cardiometabolism and Nutrition, Service de Médecine Intensive-Réanimation, Institut de Cardiologie, Assistance Publique-Hôpitaux de Paris, Hôpital Pitié-Salpêtrière, France (M.S.). Azienda Socio-Sanitaria Territoriale Papa Giovanni XXIII, Bergamo, Italy (A.G.). Sahlgrenska University Hospital, Gothenburg, Sweden (E.B.). Division of Cardiology, Fondazione IRCCS Policlinico San Matteo, Pavia, Italy (A.T., L.D.L.). Department of Cardiology, Hospital Universitario A Coruña (CHUAC), Spain (M.G.C.-L., D.C.-M.). British Heart Foundation Centre of Research Excellence, School of Cardiovascular and Metabolic Medicine & Sciences, King's College London, UK (A.C., D.I.B.). Cardiology Department, King's College Hospital NHS Foundation Trust, London, UK (A.C., D.I.B.). Department of Cardiovascular and Thoracic Sciences, Fondazione Policlinico Universitario A. Gemelli IRCCS, Rome, Italy (M.L.N.). Intensive Cardiac Care unit and Cardiology Unit, Heart Department, SS. Annunziata Hospital, Chieti, Italy (V.C., U.I.). Division of Cardiology, A.O. San Camillo-Forlanini, and Department of Clinical and Molecular Medicine, Sapienza University of Rome, Rome, Italy (R.M.). Division of Cardiology, Cardiovascular and Thoracic Department Città della Salute e della Scienza Hospital, Turin, Italy (S.F., C.R.). Unit of Allergology and Immunology, Niguarda Hospital, Milan, Italy (J.W.S.). Servicio de Cardiología, Hospital Italiano de Buenos Aires, Argentina (A.M.A.). Cardiothoracic Department, Fondazione Toscana Gabriele Monasterio, Pisa, Italy (M.E.). Cardiology Division, Azienda di Rilievo Nazionale e Alta Specializzazione "G. Brotzu," Cagliari, Italy (M.C., D.P.). Department of Cardiology and Angiology (S.G., M.G.) and Cardiopathology, Institute for Pathology (T.M., K.K.), University Hospital Tübingen, Germany. Cardiology Department, Hospital General Universitario Gregorio Marañón, Instituto de Investigación Sanitaria Gregorio Marañón, Universidad Europea, Universidad Complutense, Madrid, Spain (M.M.-S). Department of Cardiology, Hospital Universitario Puerta de Hierro, Madrid, Spain (F.J.H.P., A.M.C., F.D.). Medical Intensive Care Unit, Hôpitaux Universitaires Henri Mondor, Assistance Publique Hôpitaux de Paris, Créteil, France (A.G.). Department of Woman and Child's Health and Public Health Sciences, Fondazione Policlinico Universitario A. Gemelli IRCCS, Rome, Italy (N.D.). Division of Cardiology, Pauley Heart Center, Virginia Commonwealth University, Richmond, VA (C.T.). Institute of Pathology and Laboratory Medicine, Cleveland Clinic, OH (M.K.H.). Division of Cardiology, and Berne Cardiovascular Research Center, School of Medicine, University of Virginia, Charlottesville (F.M., A.A.). Cardiovascular Pathology Unit, Azienda Ospedaliera, Department of Cardiac, Thoracic, Vascular Sciences and Public Health, University of Padua, Italy (C.B.). Pediatric Intensive Care Unit, ASST Papa Giovanni XXIII, Bergamo, Italy (G.V.). Department of Cardiothoracic Surgery, Heart and Vascular Centre, Maastricht University Medical Centre, the Netherlands (G.V.). IRCCS San Raffaele Hospital, Milano, Italy (P.G.C.). Bicocca Bioinformatics Biostatistics and Bioimaging (B4) Center, School of Medicine and Surgery, University of Milano-Bicocca, Monza, Italy (D.P.B.). Clinical Research and Innovation, Niguarda Hospital, Milan, Italy (D.P.B.).

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Dr Ammirati is a consultant for Lexeo and has served as a consultant for Hotgen Health Inc. Dr Abbate has served as a consultant to Kiniksa, MonterosaTx, and Novo Nordisk. Dr Gustafsson reports advisory fees from Abbott, Fineheart, Corwave, AdjuCor, Alnylam, Ionis, AstraZeneca, Pfizer, and Bayer and speaking fee from Novartis. Dr Vandenbriele reports speaking and travel fees from Medtronic, as well as research grants, speaking fees, and consultancy fees from Abiomed. Dr Adler is the Chief Scientific Officer: Lexeo Therapeutics and consultant for Kiniksa, serves in the advisory board and shareholder of Rocket Pharmaceuticals, scientific board of ResQue Therapeutics, and scientific Founder of Papillion Therapeutics. The other authors report no conflicts.

Supplemental Material

Supplemental Methods
Supplemental Results
Tables S1–S17
Figures S1–S13
STROBE checklist

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