ESC European Society of Cardiology

European Heart Journal (2024) **45**, 2548–2569
https://doi.org/10.1093/eurheartj/ehae169

CLINICAL RESEARCH
Heart failure and cardiomyopathies

Endomyocardial biopsy: safety and prognostic utility in paediatric and adult myocarditis in the European Society of Cardiology EURObservational Research Programme Cardiomyopathy and Myocarditis Long-Term Registry

Alida L. P. Caforio [1]*†, Juan P. Kaski[2], Juan R. Gimeno[3†], Perry M. Elliott[4], Cecile Laroche[5], Luigi Tavazzi[6], Michal Tendera[7], Michael Fu[8], Simone Sala[9], Petar M. Seferovic[10], Tiina Heliö[11†], Leonardo Calò[12], Olga Blagova[13], Ahmad Amin[14], Ingrid Kindermann[15], Gianfranco Sinagra[16†], Andrea Frustaci[17], Daniel Bonnet[18†], Philippe Charron[19†], and Aldo P. Maggioni[5,20]; on behalf of the CMY Registry Investigators‡

[1]Cardiology, Department of Cardiological, Thoracic and Vascular Sciences and Public Health, University of Padova, Via N Giustiniani, 2, Padova 35100, Italy; [2]Cardiology, University College London and Great Ormond Street Hospital for Children, London, UK; [3]Cardiac Department, Hospital Clínico Universitario Virgen de la Arrixaca, Murcia, Spain; [4]Institute of Cardiovascular Science, University College London and St. Bartholomew's Hospital, London, UK; [5]European Society of Cardiology, EURObservational Research Programme, Biot, France; [6]GVM Care& Research, Maria Cecilia Hospital, Cotignola, Italy; [7]Department of Cardiology and Structural Heart Disease, School of Medicine in Katowice, Medical University of Silesia, Katowice, Poland; [8]Section of Cardiology, Department of Medicine, Sahlgrenska University Hospital/Östra Hospital, Gothenburg University, Gothenburg, Sweden; [9]Myocarditis Unit, Department of Cardiac Electrophysiology and Arrhythmology, IRCCS San Raffaele Scientific Institute, Milan, Italy; [10]Serbian Academy of Sciences and Arts, Heart Failure Center, Faculty of Medicine, Belgrade University Medical Center, Belgrade, Serbia; [11]Heart and Lung Center, Helsinki University Hospital and University of Helsinki, Helsinki, Finland; [12]Department of Cardiology, Policlinico Casilino, Roma, Italy; [13]V.N. Vinogradov Faculty Therapeutic Clinic, I.M. Sechenov First Moscow State Medical University (Sechenov University), Moscow, Russian Federation; [14]Department of Heart Failure and Transplantation, Rajaie Cardiovascular Medical and Research Center, Iran University of Medical Sciences, Tehran, Iran; [15]Department of Internal Medicine III (Cardiology, Angiology and Intensive Care), Saarland University Medical Center, Saarland University, Homburg/Saar, Germany; [16]Cardiothoracovascular Department, University of Trieste, Trieste, Italy; [17]IRCCS San Raffaele, Rome, Italy; [18]M3C-Necker Enfants Malades, AP-HP, Université de Paris Cité, Paris, France; [19]Sorbonne Université, Centre de Référence des Maladies Cardiaques Héréditaires ou Rares, Assistance Publique-Hôpitaux de Paris, ICAN, Inserm UMR1166, Hôpital Pitié-Salpêtrière, Paris, France; and [20]ANMCO Research Center, Florence, Italy

Received 9 August 2023; revised 19 January 2024; accepted 27 February 2024; online publish-ahead-of-print 10 April 2024

See the editorial comment for this article 'Myocarditis diagnosis: harnessing order amongst heterogeneity through collaboration', by T.S. Kafil and P.P. Liu, https://doi.org/10.1093/eurheartj/ehae220.

Abstract

Background and Aims Contemporary multicentre data on clinical and diagnostic spectrum and outcome in myocarditis are limited. Study aims were to describe baseline features, 1-year follow-up, and baseline predictors of outcome in clinically suspected or biopsy-proven myocarditis (2013 European Society of Cardiology criteria) in adult and paediatric patients from the EURObservational Research Programme Cardiomyopathy and Myocarditis Long-Term Registry.

Methods Five hundred eighty-one (68.0% male) patients, 493 adults, median age 38 (27–52) years, and 88 children, aged 8 (3–13) years, were divided into 3 groups: Group 1 ($n = 233$), clinically suspected myocarditis with abnormal cardiac magnetic resonance; Group 2 ($n = 222$), biopsy-proven myocarditis; and Group 3 ($n = 126$) clinically suspected myocarditis with normal

* Corresponding author. Tel: +39 049 8212348, Fax: +39 049 8211802, Email: alida.caforio@unipd.it
† These authors are members of the European Reference Network for rare, low prevalence, and complex diseases of the heart (ERN GUARD-Heart).
‡ A complete list of the CMY Registry Investigators is provided in the Appendix.

or inconclusive or no cardiac magnetic resonance. Baseline features were analysed overall, in adults vs. children, and among groups. One-year outcome events included death/heart transplantation, ventricular assist device (VAD) or implantable cardioverter defibrillator (ICD) implantation, and hospitalization for cardiac causes.

Results Endomyocardial biopsy, mainly right ventricular, had a similarly low complication rate in children and adults (4.7% vs. 4.9%, $P = NS$), with no procedure-related death. A classical myocarditis pattern on cardiac magnetic resonance was found in 31.3% of children and in 57.9% of adults with biopsy-proven myocarditis ($P < .001$). At 1-year follow-up, 11/410 patients (2.7%) died, 7 (1.7%) received a heart transplant, 3 underwent VAD (0.7%), and 16 (3.9%) underwent ICD implantation. Independent predictors at diagnosis of death or heart transplantation or hospitalization or VAD implantation or ICD implantation at 1-year follow-up were lower left ventricular ejection fraction and the need for immunosuppressants for new myocarditis diagnosis refractory to non–aetiology-driven therapy.

Conclusions Endomyocardial biopsy was safe, and cardiac magnetic resonance using Lake Louise criteria was less sensitive, particularly in children. Virus-negative lymphocytic myocarditis was predominant both in children and adults, and use of immunosuppressive treatments was low. Lower left ventricular ejection fraction and the need for immunosuppressants at diagnosis were independent predictors of unfavourable outcome events at 1 year.

Structured Graphical Abstract

Key Question

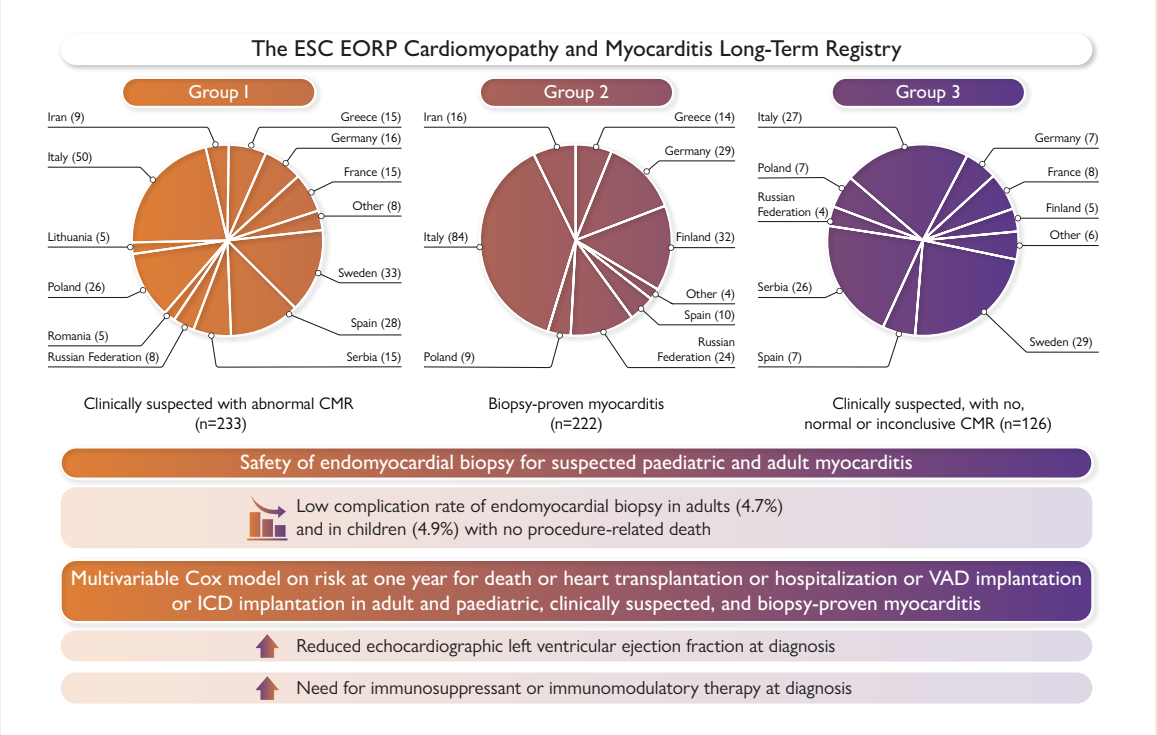
What is the safety and value of endomyocardial biopsy in paediatric and adult patients with suspected myocarditis? What are the predictors of worse outcome in patients with proven myocarditis?

Key Finding

Endomyocardial biopsy was safe in adults and children. Myocarditis on cardiac magnetic resonance was found in 31.3% of children and in 57.9% of adults with biopsy-proven myocarditis. Lower left ventricular ejection fraction and need for immunosuppression at diagnosis were independent predictors of unfavourable outcomes at one-year follow-up.

Take Home Message

In clinically suspected myocarditis endomyocardial biopsy is safe while cardiac magnetic resonance using Lake Louise criteria is less sensitive than endomyocardial biopsy. Lower left ventricular ejection fraction and need for immunosuppression at diagnosis are independent predictors of unfavourable outcomes at follow-up.



The top panel shows the distribution of patients of Group 1 (left piechart), Group 2 (middle piechart), and Group 3 (right piechart) recruited in different ESC countries. At the bottom, the main study results are summarized. CMR, cardiac magnetic resonance; ESC EORP, European Society of Cardiology EURObservational Research Programme; ICD, implantable cardioverter defibrillator; VAD, ventricular assist device.

Keywords Myocarditis • Registry • Endomyocardial biopsy • Immunosuppression

Introduction

Myocarditis may have different clinical presentations, ranging from a pseudoinfarct with normal coronary arteries to acute, subacute, or chronic heart failure, a wide arrhythmia spectrum from mild cases to sudden cardiac death, and life-threatening unexplained cardiogenic shock.[1] The disease is more common in the young and in males, although it may occur at any age.[1] The diagnostic gold standard is endomyocardial biopsy (EMB), including histological, immunological, immunohistochemical, and molecular tools to define its aetiology.[1] However, EMB is performed in a small proportion of patients, generally the most clinically severe cases.[2] In 2013, the European Society of Cardiology (ESC) Working Group on Myocardial and Pericardial Diseases experts proposed diagnostic criteria for biopsy-proven and clinically suspected myocarditis, the latter aimed at refining clinical suspicion in patients not undergoing EMB.[1]

To date, most information about the presentation and natural history of myocarditis has come from retrospective cohort regional registries[3–5] or prospective studies from single tertiary referral centres[6,7] without the use of homogeneous diagnostic criteria. In 2009, the ESC launched the EURObservational Research Programme (EORP) to improve the understanding of medical practice through prospective observational registries. As part of this programme, a cardiomyopathy and myocarditis registry was established.[8,9] Here, we report baseline and 1-year follow-up of the myocarditis registry. Adult and paediatric patients were enrolled using homogeneous criteria, the 2013 ESC diagnostic criteria of clinically suspected, or biopsy-proven myocarditis,[1] with a particular focus on aetiology and outcome.

Methods

General registry design and aims

The ESC EORP Cardiomyopathy and Myocarditis Registry is a prospective, multicentre observational registry of patients with a diagnosis of cardiomyopathy or myocarditis consecutively evaluated at cardiology centres across Europe; detailed methodology has been described.[8,9]

The primary aims of the ESC observational prospective myocarditis registry were (i) to record clinical and diagnostic features and geographical distribution across Europe of both (newly diagnosed) inpatients and (previously diagnosed) outpatients, as well as current management of adult and paediatric myocarditis in patients enrolled using homogeneous criteria, the 2013 ESC diagnostic criteria of clinically suspected, or biopsy-proven myocarditis;[1] (ii) to assess potential differential features in clinically suspected and biopsy-proven myocarditis in adults vs. children; and (iii) to describe the 1-year follow-up and baseline predictors of unfavourable outcome events.

Patient population

Participating centres in each country were selected using pre-specified inclusion and exclusion criteria.[8,9] Each of the 46 participating centres entered consecutive patients over a 12-month period, with new (incident) or previous diagnosis (prevalent), clinically suspected, or biopsy-proven according to 2013 ESC criteria and definitions.[1] Incident vs. prevalent was defined as incident if date of inclusion to date of first evaluation was <1 year and prevalent if date of inclusion to date of first evaluation was ≥1 year. Definitions used for analyses of geographical subgroups were previously detailed.[8,9]

For the purpose of identifying potential differential features between biopsy-proven and clinically suspected myocarditis, the enrolled patients were divided into three groups (G): Group 1 (G1) had clinically suspected myocarditis confirmed at cardiac magnetic resonance (CMR),[1] Group 2 (G2) had biopsy-proven myocarditis with or without CMR confirmation,[1] and Group 3 (G3) had clinically suspected myocarditis, with no, normal, or inconclusive CMR tissue characterization.[1] Late gadolinium enhancement (LGE) was not adjudicated by a core lab, and the classical myocarditic pattern was defined in keeping with the original Lake Louise criteria.[1]

Participating centres managed the approvals of national or regional ethics committees or Institutional Review Boards, according to local regulations (numbers of ethical approval for single centres are provided in Supplement). Written informed consent was obtained from all participants or from the parent for patients <18 years old, before data collection. All diagnostic or therapeutic procedures were left to the discretion of the attending physician. The registry was conducted by an Executive Committee and managed by the EORP department of the ESC which also performed statistical analyses.

Study outcomes

Combined endpoints for outcomes were defined *a priori* as death or heart transplantation or hospitalization or ventricular assist device (VAD) implantation or implantable cardioverter defibrillator (ICD) implantation at 1 year.

Statistical analysis

Baseline clinical and diagnostic features, procedures, medications, and geographical distribution were analysed in the overall cohort, in adults vs. children, and among groups. Statistical analysis was provided independently from the investigators by the EORP statistical team. Univariate analysis was applied to both continuous and categorical variables. Continuous variables were reported as median and interquartile range (IQR). Among-group comparisons were made using a non-parametric test (Kruskal–Wallis test). Categorical variables were reported as percentages. Among-group comparisons were made using a χ^2 test or a Fisher's exact test if any expected cell count was <5. A two-sided *P*-value of <.05 was considered as statistically significant. Plots of Kaplan–Meier curves for the combined endpoints were performed. Cox proportional hazards model was used for survival estimates reporting hazard ratios (HR) and 95% confidence intervals (CI). Univariable analysis of death or heart transplantation or hospitalization or VAD implantation or ICD implantation at 1 year was performed with a Cox proportional hazards model. Variables with $P < .05$ were entered in a multivariable Cox proportional hazards model with a stepwise selection procedure and a significance level of $P = .05$. The list of covariates included in the stepwise selection procedure was previously filtered to avoid including covariates with high correlation (coeff > 0.8). Some measures of model fit were considered: concordance and the goodness-of-fit test proposed by May and Hosmer; Schoenfeld residual test was calculated to verify the assumptions of proportionality. This registry is an observational study, and each variable is analysed according to the data collected, with no handling for missing data. All analyses were performed using SAS statistical software version 9.4 (SAS Institute, Inc., Cary, NC, USA).

Results

Overall enrolled patients and enrolment by country

Overall, 46 centres from 18 countries participated; the main features of the enrolling centres are shown in Supplementary data online, *Table S1*. The distribution of enrolled patients per country is shown in *Figure 1*; there were 83 patients (14.3%) from East, 113 (19.4%) North, 280 (48. 2%) South, and 78 (13.4%) West Europe, and 27 subjects (4.6%) were from non-ESC countries. A total of 581 (68.0% male) patients was recruited, of whom 493 were adults, with a median age at enrolment of 38 (IQR 27–52) years, and 88 children, median age 8 (IQR 3–13) years. Of the 581 patients, 233 (40.1%) G1 patients had clinically suspected myocarditis with CMR

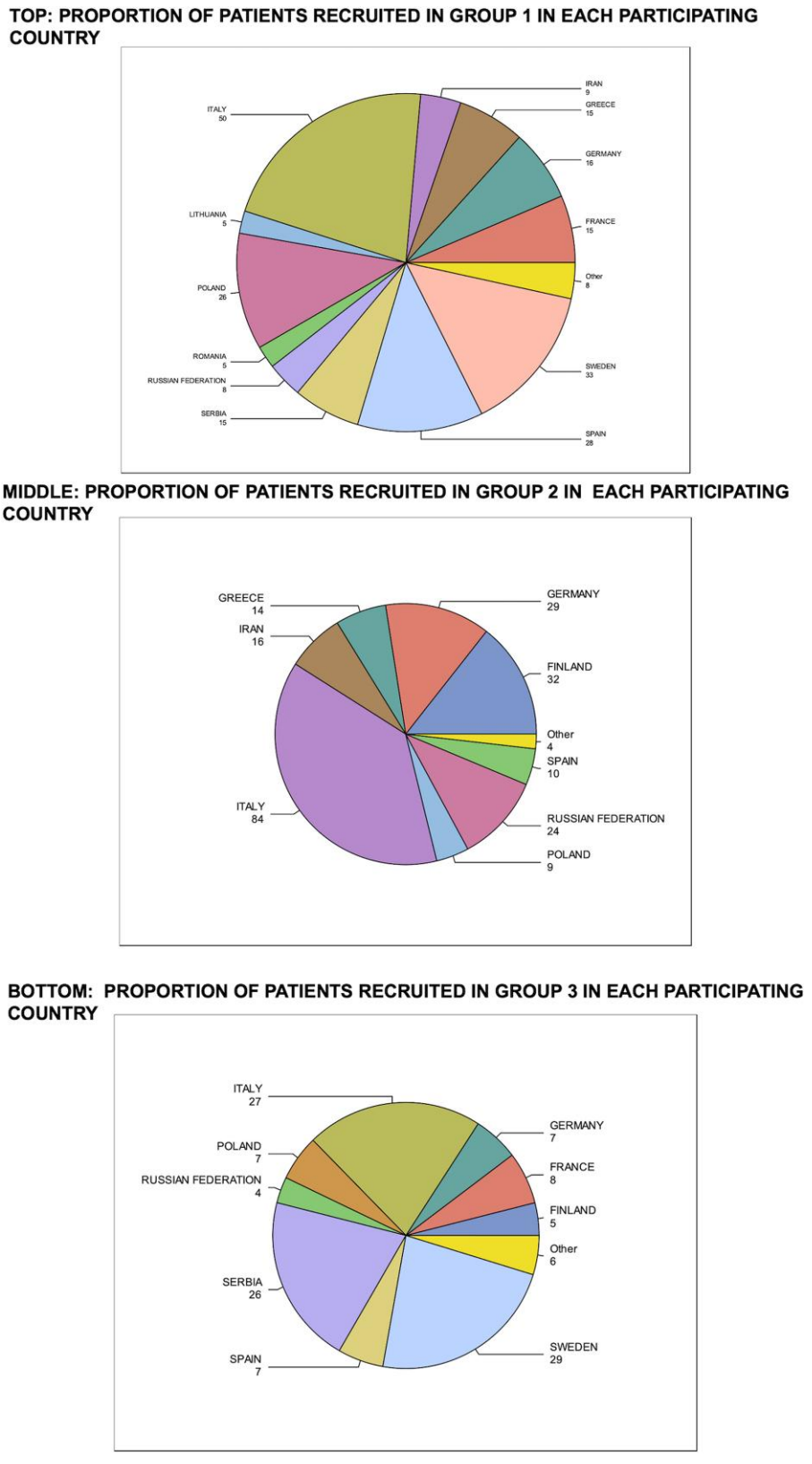


Figure 1 The top panel shows the proportion of Group 1 clinically suspected with abnormal cardiac magnetic resonance (CMR) ($n = 233$), the middle panel Group 2 of biopsy-proven myocarditis patients ($n = 222$), and the bottom panel Group 3 of clinically suspected, with no, normal, or inconclusive CMR ($n = 126$) in each participating country

confirmation, 222 (38.2%) G2 patients had biopsy-proven myocarditis (with or without CMR confirmation), and 126 (21.7%) G3 patients had clinically suspected myocarditis (with no or normal or inconclusive CMR) (*Table 1*).

Of the 579 patients in whom the information was reported, 466 (80.5%) were incident (new) and 113 (19.5%) prevalent cases; of the 581 patients, 428 (73.7%) were inpatients and 153 (26.3%) were outpatients (see Supplementary data online, *Table S2*).

Demographic and baseline characteristics: procedures by age (paediatric vs. adults)

Main demographic and other baseline characteristics in the overall cohort in adults vs. children and according to myocarditis group are shown in *Table 1*; additional features are in Supplementary data online, *Table S2*. Most baseline features were similar in children and in adults, including a similar predominance of male gender in adults (344/493, 69.8%) and children (51/88, 58.0%, $P = .09$). In adults, the predominance of males was lower in G2 biopsy-proven (56.8%) than in G1 (81.3%) and in G3 clinically suspected myocarditis (71.0%, $P < .001$). Among the comorbidities/risk factors, adults had a higher frequency of arterial hypertension ($P < .001$) and renal impairment than children ($P < .02$).

Angina-like chest pain (with normal coronary arteries), palpitation, and history of bundle branch block were less common in children than in adults (37.0% vs. 61.0%, $P < .001$; 17.3% vs. 33.4%, $P = .015$; 1.1% vs. 12.2%, $P = .008$, respectively). Children had higher proportions of New York Heart Association (NYHA) class III and IV compared with adults ($P < .001$) at diagnosis.

Procedures performed prior or at the time of enrolment are shown in *Table 2*. Electrocardiogram (ECG) and echocardiography were performed in almost all patients (97%–98%), CMR in a high proportion (70.7%), and less frequently in children (56.8%) than in adults (73.2%, $P = .008$). Endomyocardial biopsy, mainly from the right ventricle (RV) (75.8%), had a low complication rate, similar in adults (4.9%) and children (4.7%), with no procedure-related deaths. The most frequent complications were pericardial effusions in five patients and cardiac tamponade in three.

The implant of a cardioverter defibrillator (ICD) tended to be less common in children than in adults (3.4% vs. 11.4%, $P = .07$); 24 h ECG Holter monitoring and ventricular assist device implantation were more commonly performed in children (53.4% vs. 33.7%, $P = .002$; 12.5% vs. 1.0%, $P < .001$, respectively).

Demographic and baseline characteristics: procedures by myocarditis group (biopsy-proven vs. clinically suspected)

Grade 2 biopsy-proven adult patients were older and had more frequently hypertension, renal impairment, palpitation, and positive arrhythmia history compared with the G1 and G3 adult clinically suspected patients (*Table 1*). Both in adult and paediatric biopsy-proven patients, angina-like chest pain (with normal coronary arteries) was a less common presentation; conversely, heart failure signs and symptoms were more common than in clinically suspected patients (*Table 1*).

Twenty-four hour ECG Holter monitoring, ICD, pacemaker implantation, and cardiac ablations were performed more frequently in biopsy-proven adults compared with the adult G1 and G3 clinically suspected patients (*Table 2*). Cardiac magnetic resonance was less frequently performed both in biopsy-proven adults and children compared with the clinically suspected groups (*Table 2*).

Both in biopsy-proven adults and children, echocardiographic left ventricular function indexes, in particular left ventricular ejection fraction (LVEF) and per cent fractional shortening, were lower than in clinically suspected patients (see Supplementary data online, *Table S3*). In biopsy-proven adults, right ventricular global systolic dysfunction was more common ($P < .001$); degree of diastolic dysfunction and of mitral regurgitation on Doppler echocardiography was higher than in clinically suspected patients ($P < .001$; $P = .003$, respectively) (see Supplementary data online, *Table S3*).

On CMR, LVEF was lower in biopsy-proven vs. clinically suspected adult patients ($P < .001$) and tended to be lower also in paediatric biopsy-proven vs. clinically suspected subjects (*Table 3*). Oedema and/or a classical LGE myocarditis pattern was less frequently found among biopsy-proven patients compared with clinically suspected groups, both in adults (57.9%, $P < .001$) and in children (31.3%, $P < .001$) (*Table 3*).

Non–aetiology-driven medical treatment in all patients by age and by myocarditis group (biopsy-proven and clinically suspected)

In the overall cohort, beta-blockers were used in 66.4% of patients, angiotensin-converting enzyme (ACE) inhibitors in 52.3%, oral diuretics in 35.3%, mineralocorticoid receptor antagonists in 28.6%, oral anticoagulants in 14.3%, anti-arrhythmic drugs in 12.6%, and amiodarone in 8.6%; oral diuretics and ACE inhibitors were used more frequently in paediatric than in adult patients (see Supplementary data online, *Table S4*).

Among adults, beta-blockers, ACE inhibitors, oral diuretics, mineralocorticoid receptor antagonists, and anti-arrhythmic drugs including amiodarone, digoxin, and statins were more frequently used in G2 biopsy-proven compared with clinically suspected patients (see Supplementary data online, *Table S4*).

2013 European Society of Cardiology criteria in the whole cohort by age and by myocarditis group

The distribution of 2013 ESC criteria is shown in *Table 4*. Overall, angina with unobstructed coronary arteries was common (58.1%), as any heart failure (new-onset or subacute or unexplained cardiogenic shock, 50.2%) followed by any arrhythmia (aborted sudden cardiac death, syncope, or cardiac arrhythmia, 31.7%). Among children, new-onset and any heart failure were more common than in adults ($P < .001$; $P < .001$, respectively). In biopsy-proven adults, angina was less common; more common were all heart failure and arrhythmia presentations as compared with clinically suspected adults. In biopsy-proven children, new-onset or any heart failure was more common than in clinically suspected children (*Table 4*).

Overall, all diagnostic criteria groups identified a high proportion of abnormal findings, i.e. 74.1% for high troponin levels to 65.2% for abnormal tissue characterization by CMR. Abnormal tissue characterization (oedema and/or LGE) by CMR was less common in children than in adults (50.6% vs. 67.7%, $P = .009$) and was found in only 57.9% of adult and 31.3% of paediatric biopsy-proven patients. Conversely, in the whole cohort, ancillary features were found in a minority of patients,

Table 1 Baseline characteristics in relation to myocarditis subtype by age group

	All patients (*N* = 581)	Paediatric (up to 18 years)					Adult (>18 years)					*P*-value paediatric vs. adult
		Total Paediatric (*N* = 88)	Group 1 (*N* = 30)	Group 2 (*N* = 32)	Group 3 (*N* = 26)	*P*-value Group 1 vs. Group 2 vs. Group 3	Total adult (*N* = 493)	Group 1 (*N* = 203)	Group 2 (*N* = 190)	Group 3 (*N* = 100)	*P*-value Group 1 vs. Group 2 vs. Group 3	
Age at enrolment (years)	*N* = 581	*N* = 88	*N* = 30	*N* = 32	*N* = 26	<.001	*N* = 493	*N* = 203	*N* = 190	*N* = 100	<.001	<.001
Median (Q1; Q3)	34.0 (21.0; 48.0)	8.0 (3.0; 13.0)	12.5 (7.0; 15.0)	6.5 (2.0; 10.5)	5.5 (2.0; 12.0)		38.0 (27.0; 52.0)	32.0 (22.0; 42.0)	45.0 (37.0; 58.0)	35.0 (24.0; 51.5)		
Age at diagnosis (years)	*N* = 580	*N* = 88	*N* = 30	*N* = 32	*N* = 26	<.001	*N* = 492	*N* = 203	*N* = 190	*N* = 99	<.001	<.001
Median (Q1; Q3)	33.5 (20.0; 47.0)	7.0 (1.0; 12.5)	12.5 (7.0; 14.0)	2.5 (1.0; 9.0)	3.0 (0.0; 10.0)		37.0 (26.0; 51.0)	32.0 (22.0; 42.0)	44.0 (34.0; 55.0)	32.0 (22.0; 50.0)		
Male	395/581 (68.0%)	51/88 (58.0%)	22/30 (73.3%)	16/32 (50.0%)	13/26 (50.0%)	.220	344/493 (69.8%)	165/203 (81.3%)	108/190 (56.8%)	71/100 (71.0%)	<.001	.091
Hypertension	87/581 (15.0%)	0/88 (0.0%)				NA	87/493 (17.6%)	17/203 (8.4%)	58/190 (30.7%)	12/100 (12.0%)	<.001	<.001
Renal impairment	41/581 (7.1%)	0/88 (0.0%)				NA	41/493 (8.3%)	7/203 (3.4%)	30/190 (15.8%)	4/100 (4.0%)	<.001	.020
Angina chest pain	311/542 (57.4%)	30/81 (37.0%)	20/26 (76.9%)	5/32 (15.6%)	5/23 (21.7%)	<.001	281/461 (61.0%)	156/194 (80.4%)	61/173 (35.3%)	64/94 (68.1%)	<.001	<.001
History of resuscitated ventricular fibrillation/cardiac arrest	22/581 (3.8%)	6/88 (6.8%)	1/30 (3.3%)	3/32 (9.4%)	2/26 (7.7%)	.826[a]	16/493 (3.2%)	3/203 (1.5%)	12/190 (6.3%)	1/100 (1.0%)	.025	.270
History of AV block	33/581 (5.7%)	2/88 (2.3%)	0/30 (0.0%)	1/32 (3.1%)	1/26 (3.8%)	.729[a]	31/493 (6.3%)	6/203 (3.0%)	25/190 (13.2%)	0/100 (0.0%)	<.001	.325
History of sustained ventricular tachycardia	54/581 (9.3%)	8/88 (9.1%)	1/30 (3.3%)	5/32 (15.6%)	2/26 (7.7%)	.435[a]	46/493 (9.3%)	7/203 (3.4%)	35/190 (18.4%)	4/100 (4.0%)	<.001	.997
NYHA class												
Class I	189/473 (40.0%)	22/60 (36.7%)	15/24 (62.5%)	5/22 (22.7%)	2/14 (14.3%)	NC	167/413 (40.4%)	92/168 (54.8%)	45/162 (27.8%)	30/83 (36.1%)	<.001	<.001
Class II	171/473 (36.2%)	11/60 (18.3%)	4/24 (16.7%)	1/22 (4.5%)	6/14 (42.9%)		160/413 (38.7%)	62/168 (36.9%)	53/162 (32.7%)	45/83 (54.2%)		
Class III	87/473 (18.4%)	13/60 (21.7%)	1/24 (4.2%)	9/22 (40.9%)	3/14 (21.4%)		74/413 (17.9%)	12/168 (7.1%)	56/162 (34.6%)	6/83 (7.2%)		
Class IV	26/473 (5.5%)	14/60 (23.3%)	4/24 (16.7%)	7/22 (31.8%)	3/14 (21.4%)		12/413 (2.9%)	2/168 (1.2%)	8/162 (4.9%)	2/83 (2.4%)		
Palpitations	168/542 (31.0%)	14/81 (17.3%)	6/26 (23.1%)	6/32 (18.8%)	2/23 (8.7%)	.612[a]	154/461 (33.4%)	42/194 (21.1%)	89/173 (51.4%)	24/94 (25.5%)	<.001	.015

Continued

Table 1 *Continued*

	All patients (N = 581)	Paediatric (up to 18 years)					Adult (>18 years)					
		Total Paediatric (N = 88)	Group 1 (N = 30)	Group 2 (N = 32)	Group 3 (N = 26)	*P*-value Group 1 vs. Group 2 vs. Group 3	Total adult (N = 493)	Group 1 (N = 203)	Group 2 (N = 190)	Group 3 (N = 100)	*P*-value Group 1 vs. Group 2 vs. Group 3	*P*-value paediatric vs. adult
Ankle oedema	77/542 (14.2%)	10/81 (12.3%)	0/26 (0.0%)	8/32 (25.0%)	2/23 (8.7%)	.027[a]	67/461 (14.5%)	7/194 (3.6%)	55/173 (31.8%)	5/94 (5.3%)	<.001	.873
Orthopnoea	95/542 (17.5%)	13/81 (16.0%)	0/26 (0.0%)	8/32 (25.0%)	5/23 (21.7%)	.026[a]	82/461 (17.8%)	17/194 (8.8%)	48/173 (27.7%)	17/94 (18.1%)	<.001	.931
Paroxysmal nocturnal dyspnoea	47/542 (8.7%)	5/81 (6.2%)	0/26 (0.0%)	4/32 (12.5%)	1/23 (4.3%)	.275[a]	42/461 (9.1%)	8/194 (4.1%)	28/173 (16.2%)	6/94 (6.4%)	<.001	.687
History of bundle branch block	61/581 (10.5%)	1/88 (1.1%)	1/30 (3.3%)	0/32 (0.0%)	0/26 (0.0%)	.569[a]	60/493 (12.2%)	9/203 (4.4%)	49/190 (25.8%)	2/100 (2.0%)	<.001	.008
History of atrial fibrillation	52/581 (9.0%)	0/88 (0.0%)				NA	52/493 (10.5%)	8/203 (3.9%)	40/190 (21.1%)	4/100 (4.0%)	<.001	.006

[a]Fisher's exact test.
NYHA, New York Heart Association; NC, not computed; NA, not applicable.

the most common being fever at presentation or within the preceding 30 days (40.2% of all patients).

Endomyocardial biopsy findings and aetiology-directed therapy

Endomyocardial biopsy findings in the whole biopsy-proven cohort and by age are shown in Supplementary data online, *Table S5*, and histology type and detected viruses in children and adults in *Figure 2*. Overall, the histology distribution according to the Dallas criteria showed active myocarditis in 52.5%, borderline in 36.2%, and healed myocarditis in 11.3%; the most common histology type was lymphocytic (82.6%), followed by giant cell (7.6%), sarcoid (6.3%), and eosinophilic (3.5%) myocarditis; immunohistology was positive in 82.6% of cases. In the whole population, at least one positive viral polymerase chain reaction on EMB was found in 34.1% of patients [most commonly parvovirus B19 (PVB19), 21.7%, followed by human herpes virus 6 (HHV6), 9.5%] and more commonly in children than in adults (75.9% vs. 25.7%, $P < .001$). Parvovirus B19 and HHV6 were more frequently detected in paediatric vs. adults (51.7% vs. 15.3%, $P < .001$; 34.6% vs. 4.5%, $P < .001$, respectively). Serum anti-heart autoantibodies were more frequently detected in adults than in children (44/64, 68.8%, vs. 1/14, 7.1%, $P < .001$). The use of aetiology-directed therapy is shown in Supplementary data online, *Table S6*. Overall, antiviral therapy was given to a minority of patients (5.7%), regardless of biopsy-proven diagnosis, and more frequently in children than adults (23.3% vs. 2.6%, $P < .001$); steroids were used in 24.7% and immunosuppression (IS) in 22.6%, again regardless of biopsy-proven diagnosis. In children, steroids were given in 25.3% and IS in 25.6% and to similar proportions of G1, G2, and G3. In G2 biopsy-proven adults, steroids were given in 52.1% and IS in 39.5% and more frequently than in G1 or G3 patients ($P < .001$; $P < .001$, respectively).

European Society of Cardiology criteria, histology types, and aetiological therapy by geographical area

There were significant differences in all 2013 ESC-defined presentations, except for cardiac arrhythmia, among the five geographical regions (see Supplementary data online, *Table S7*). Chest pain was more frequent in the North (69.9%) and South (60.7%) ($P = .005$) compared with East, West, and non-ESC regions; new-onset heart failure was more common in the West (53.2%, $P < .001$); subacute/chronic heart failure was predominant in the East (33.7%, $P < .001$) and aborted sudden cardiac death and syncope in the non-ESC area (11.1%, $P = .036$; 22.2%, $P = .03$, respectively); unexplained cardiogenic shock was most common in the West (14.3%, $P = .023$).

There were differences in all 2013 ESC-defined diagnostic criteria, except for tissue characterization by CMR, by geographical area. The ECG/Holter/stress test category was fulfilled more frequently in the East (86.7%, $P < .001$), abnormally high troponin levels (from local laboratory values) in the North (96.5%, $P < .001$), and new functional and structural abnormalities on cardiac imaging in the non-ESC area (92.6%, $P = .015$). There were also differences in the distribution of two of the 2013 ESC-defined ancillary features. In particular, fever at presentation or within the preceding 30 days was more commonly reported in the South (48.6%) and in the East (48.2%) ($P < .001$); personal or family history of allergic asthma, other types of allergies, extracardiac auto-immune diseases, and toxic agents were also more frequently present in the South (15.0%) and in the East (12.0%)

Table 2 Procedures prior or at the time to enrolment in relation to myocarditis subtype by age group

	All patients (*N* = 581)	Paediatric (up to 18 years)					Adult (>18 years)					
		Total Paediatric (*N* = 88)	Group 1 (*N* = 30)	Group 2 (*N* = 32)	Group 3 (*N* = 26)	*P*-value Group 1 vs. Group 2 vs. Group 3	Total Adult (*N* = 493)	Group 1 (*N* = 203)	Group 2 (*N* = 190)	Group 3 (*N* = 100)	*P*-value Group 1 vs. Group 2 vs. Group 3	*P*-value paediatric vs. adult
Electrocardiogram (ECG)	568/581 (97.8%)	83/88 (94.3%)	30/30 (100.0%)	30/32 (93.8%)	23/26 (88.5%)	.289[a]	485/493 (98.4%)	201/203 (99.0%)	187/190 (98.4%)	97/100 (97.0%)	.627[a]	.060
Echocardiogram	565/581 (97.2%)	86/88 (97.7%)	30/30 (100.0%)	32/32 (100.0%)	24/26 (92.3%)	.252[a]	479/493 (97.2%)	195/203 (96.1%)	186/190 (97.9%)	98/100 (98.0%)	.678	.956
Cardiac magnetic resonance	411/581 (70.7%)	50/88 (56.8%)	30/30 (100.0%)	12/32 (37.5%)	8/26 (30.8%)	<.001	361/493 (73.2%)	203/203 (100.0%)	107/190 (56.3%)	51/100 (51.0%)	<.001	.008
Holter ECG	213/581 (36.7%)	47/88 (53.4%)	22/30 (73.3%)	20/32 (62.5%)	5/26 (19.2%)	<.001	166/493 (33.7%)	63/203 (31.0%)	81/190 (42.6%)	22/100 (22.0%)	.004	.002
Endomyocardial biopsy (EMB) samples from:												
Right	163/215 (75.8%)	24/30 (80.0%)	0/0 (0.0%)	24/30[b] (80.0%)	0/0 (0.0%)	1.000[a]	139/185 (75.1%)	0/0 (0.0%)	139/185[b] (75.1%)	0/0 (0.0%)	1.000	.987
Left	43/215 (20.0%)	5/30 (16.7%)	0/0 (0.0%)	5/30[b] (16.7%)	0/0 (0.0%)		38/185 (20.5%)	0/0 (0.0%)	38/185[b] (20.5%)	0/0 (0.0%)		
Both ventricles	9/215 (4.2%)	1/30 (3.3%)	0/0 (0.0%)	1/30[b] (3.3%)	0/0 (0.0%)		8/185 (4.3%)	0/0 (0.0%)	8/185[b] (4.3%)	0/0 (0.0%)		
EMB complications:	10/215 (4.7%)	1/30 (3.3%)	0/0 (0.0%)	1/30[b] (3.3%)	0/0 (0.0%)	1.000[a]	9/185 (4.9%)	0/0 (0.0%)	9/185[b] (4.9%)	0/0 (0.0%)	1.000	.934
ICD implanted	59/581 (10.2%)	3/88 (3.4%)	1/30 (3.3%)	2/32 (6.3%)	0/26 (0.0%)	.769[a]	56/493 (11.4%)	4/203 (2.0%)	48/190 (25.3%)	4/100 (4.0%)	<.001	.075
Reason for cardioverter defibrillator												
Primary prophylaxis	30/59 (50.8%)	0/3 (0.0%)				NA	30/56 (53.6%)	1/4 (25.0%)	26/48 (54.2%)	3/4 (75.0%)	.589[a]	.259[a]
Secondary prophylaxis	29/59 (49.2%)	3/3 (100.0%)	1/1 (100.0%)	2/2 (100.0%)	0/0 (0.0%)		26/56 (46.4%)	3/4 (75.0%)	22/48 (45.8%)	1/4 (25.0%)		
Pacemaker implanted (any cause)	28/581 (4.8%)	2/88 (2.3%)	0/30 (0.0%)	2/32 (6.3%)	0/26 (0.0%)	.378[a]	26/493 (5.3%)	1/203 (0.5%)	20/190 (10.5%)	5/100 (5.0%)	<.001	.480
Reason for pacemaker: bradyarrhythmia	13/28 (46.4%)	2/2 (100.0%)		2/2 (100.0%)		NA	11/26 (42.3%)	1/1 (100.0%)	9/20 (45.0%)	1/5 (20.0%)	.542[a]	.375[a]

Continued

Table 2 *Continued*

	All patients (*N* = 581)	Paediatric (up to 18 years)					Adult (>18 years)					
		Total Paediatric (*N* = 88)	Group 1 (*N* = 30)	Group 2 (*N* = 32)	Group 3 (*N* = 26)	*P*-value Group 1 vs. Group 2 vs. Group 3	Total Adult (*N* = 493)	Group 1 (*N* = 203)	Group 2 (*N* = 190)	Group 3 (*N* = 100)	*P*-value Group 1 vs. Group 2 vs. Group 3	*P*-value paediatric vs. adult
Reason for pacemaker: cardiac resynchronization therapy	13/28 (46.4%)	1/2 (50.0%)		1/2 (50.0%)		1.000[a]	12/26 (46.2%)	0/1 (0.0%)	8/20 (40.0%)	4/5 (80.0%)	.328[a]	1.000[a]
Ventricular assist device	16/581 (2.8%)	11/88 (12.5%)	2/30 (6.7%)	8/32 (25.0%)	1/26 (3.8%)	.089[a]	5/493 (1.0%)	1/203 (0.5%)	4/190 (2.1%)	0/100 (0.0%)	.375[a]	<.001
Heart transplant	2/581 (0.3%)	0/88 (0.0%)				NA	2/493 (0.4%)	0/203 (0.0%)	2/190 (1.1%)	0/100 (0.0%)	.434[a]	1.000[a]
Cardiac ablation	12/581 (2.1%)	2/88 (2.3%)	1/30 (3.3%)	1/32 (3.1%)	0/26 (0.0%)	1.000[a]	10/493 (2.0%)	0/203 (0.0%)	8/190 (4.2%)	2/100 (2.0%)	.015[a]	.989

[a]Fisher's exact test.
[b]Among Group 2 patients, seven did not undergo EMB but had histological diagnosis performed either at explanted heart or at ventricular assist device positioning.
ICD, implantable cardioverter defibrillator.

Table 3 Cardiac magnetic resonance baseline characteristics in relation to myocarditis subtype by age group

	All patients (*N* = 581)	Paediatric (up to 18 years)					Adult (>18 years)					
		Total Paediatric (*N* = 88)	Group 1 (*N* = 30)	Group 2 (*N* = 32)	Group 3 (*N* = 26)	*P*-value Group 1 vs. Group 2 vs. Group 3	Total adult (*N* = 493)	Group 1 (*N* = 203)	Group 2 (*N* = 190)	Group 3 (*N* = 100)	*P*-value Group 1 vs. Group 2 vs. Group 3	*P*-value paediatric vs. adult
CMR	411/581 (70.7%)	50/88 (56.8%)	30/30 (100.0%)	12/32 (37.5%)	8/26 (30.8%)	<.001	361/493 (73.2%)	203/203 (100.0%)	107/190 (56.3%)	51/100 (51.0%)	<.001	.008
Oedema and/or LGE of classical[b] myocarditic pattern on gadolinium-enhanced CMR	377/578 (65.2%)	43/85[a] (50.6%)	26/28 (92.9%)	10/32 (31.3%)	7/25 (28.0%)	<.001	334/493 (67.7%)	193/203 (95.1%)	110/190 (57.9%)	31/100 (31.0%)	<.001	.009
LVEDV (mL)	*N* = 355	*N* = 43	*N*=27	*N* = 10	*N* = 6	.371	*N* = 312	*N* = 175	*N* = 92	*N* = 45	<.001	<.001
Median (Q1; Q3)	151.0 (118.0; 187.0)	96.0 (76.0; 146.0)	126.0 (84.0; 146.0)	87.5 (73.0; 113.0)	84.5 (68.0; 115.0)		157.2 (127.5; 189.0)	154.0 (128.0; 186.0)	178.0 (134.5; 227.2)	145.0 (111.0; 158.0)		
LVEF (%)	*N* = 381	*N* = 45	*N* = 27	*N* = 11	*N* = 7	.084	*N* = 336	*N* = 191	*N* = 97	*N* = 48	<.001	.295
Median (Q1; Q3)	55.0 (43.7; 61.0)	58.0 (44.0; 63.0)	59.0 (50.0; 64.0)	50.0 (28.0; 58.0)	62.0 (30.0; 67.0)		54.0 (43.4; 61.0)	58.0 (51.0; 62.0)	40.0 (27.0; 50.0)	58.5 (52.0; 64.0)		

[a]Data on oedema and/or LGE missing in three paediatric patients.
[b]Classical myocarditic LGE pattern as defined by the original Lake Louise criteria, as follows: (i) at least one focal lesion with non-ischaemic regional distribution in inversion recovery-prepared gadolinium-enhanced T1-weighted images (LGE), (ii) images obtained at least 5 min after gadolinium injection (foci typically exclude the subendocardial layer, are often multifocal, and involve the subepicardium), and (iii) if the LGE pattern clearly indicates myocardial infarction and is colocalized with a transmural regional oedema, acute myocardial infarction is more likely and is reported.
CMR, cardiac magnetic resonance; LGE, late gadolinium enhancement; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction.

Table 4 2013 European Society of Cardiology clinical and diagnostic criteria in relation to myocarditis subtype by age group

	All patients (*N* = 581)	Paediatric (up to 18 years)					Adult (>18 years)					
		Total paediatric (*N* = 88)	Group 1 (*N* = 30)	Group 2 (*N* = 32)	Group 3 (*N* = 26)	*P*-value Group 1 vs. Group 2 vs. Group 3	Total adult (*N* = 493)	Group 1 (*N* = 203)	Group 2 (*N* = 190)	Group 3 (*N* = 100)	*P*-value Group 1 vs. Group 2 vs. Group 3	*P*-value paediatric vs. adult
Type of clinical presentation [*n* (%)]												
Acute chest pain	337/580 (58.1%)	35/87 (40.2%)	20/29 (69.0%)	9/32 (28.1%)	6/26 (23.1%)	.002	302/493 (61.3%)	167/203 (82.3%)	63/190 (33.2%)	72/100 (72.0%)	<.001	.001
Heart failure (new-onset or subacute or unexplained cardiogenic shock)	291/580 (50.2%)	60/87 (69.0%)	15/29 (51.7%)	29/32 (90.6%)	16/26 (61.5%)	.008	231/493 (46.9%)	58/203 (28.6%)	133/190 (70.0%)	40/100 (40.0%)	<.001	<.001
New-onset (days up to 3 months) heart failure signs and symptoms	226/580 (39.0%)	51/87 (58.6%)	11/29 (37.9%)	29/32 (90.6%)	11/26 (42.3%)	<.001	175/493 (35.5%)	46/203 (22.7%)	90/190 (47.4%)	39/100 (39.0%)	<.001	<.001
Cardiac arrhythmia	171/580 (29.5%)	25/87 (28.7%)	11/29 (37.9%)	10/32 (31.3%)	4/26 (15.4%)	.313	146/493 (29.6%)	28/203 (13.8%)	104/190 (54.7%)	14/100 (14.0%)	<.001	.986
Aborted sudden cardiac death or syncope or cardiac arrhythmia	184/580 (31.7%)	29/87 (33.3%)	12/29 (41.4%)	10/32 (31.3%)	7/26 (26.9%)	.7080[a]	155/493 (31.4%)	32/203 (15.8%)	108/190 (56.8%)	15/100 (15.0%)	<.001	.941
Syncope	50/580 (8.6%)	6/87 (6.9%)	2/29 (6.9%)	1/32 (3.1%)	3/26 (11.5%)	.625[a]	44/493 (8.9%)	10/203 (4.9%)	29/190 (15.3%)	5/100 (5.0%)	.002	.824
Unexplained cardiogenic shock	36/580 (6.2%)	20/87 (23.0%)	2/29 (6.9%)	10/32 (31.3%)	8/26 (30.8%)	.095	16/493 (3.2%)	3/203 (1.5%)	11/190 (5.8%)	2/100 (2.0%)	.092	<.001
Diagnostic criteria												
ECG/Holter/stress test features of myocarditis: (newly abnormal 12-lead ECG and/or Holter and/or stress testing)	410/579 (70.8%)	61/86 (70.9%)	22/29 (75.9%)	24/32 (75.0%)	15/25 (60.0%)	.563	349/493 (70.8%)	138/203 (68.0%)	129/190 (67.9%)	82/100 (82.0%)	.054	1.000
Elevated TnT/TnI (from local lab values)	429/579 (74.1%)	66/86 (76.7%)	26/29 (89.7%)	24/32 (75.0%)	16/25 (64.0%)	.169	363/493 (73.6%)	175/203 (86.2%)	105/190 (55.3%)	83/100 (83.0%)	<.001	.831
New functional and structural abnormalities on cardiac imaging (echo/angio/CMR)	419/579 (72.4%)	69/86 (80.2%)	23/29 (79.3%)	28/32 (87.5%)	18/25 (72.0%)	.542	350/493 (71.0%)	130/203 (64.0%)	163/190 (85.8%)	57/100 (57.0%)	<.001	.210

Continued

Table 4 *Continued*

	All patients (*N* = 581)	Paediatric (up to 18 years)					Adult (>18 years)					
		Total paediatric (*N* = 88)	Group 1 (*N* = 30)	Group 2 (*N* = 32)	Group 3 (*N* = 26)	*P*-value Group 1 vs. Group 2 vs. Group 3	Total adult (*N* = 493)	Group 1 (*N* = 203)	Group 2 (*N* = 190)	Group 3 (*N* = 100)	*P*-value Group 1 vs. Group 2 vs. Group 3	*P*-value paediatric vs. adult
Oedema and/or LGE of classical[c] myocarditic pattern on gadolinium-enhanced CMR	377/578 (65.2%)	43/85[b] (50.6%)	26/28 (92.9%)	10/32 (31.3%)	7/25 (28.0%)	<.001	334/493 (67.7%)	193/203 (95.1%)	110/190 (57.9%)	31/100 (31.0%)	<.001	.009
Ancillary criteria												
Fever at presentation or within the preceding 30 days	233/580 (40.2%)	59/87 (67.8%)	17/29 (58.6%)	24/32 (75.0%)	18/26 (69.2%)	NA	174/493 (35.3%)	89/203 (43.8%)	38/190 (20.0%)	47/100 (47.0%)	NA	NA
Peri-partum	4/580 (0.7%)	0/87 (0.0%)				NA	4/493 (0.8%)	0/203 (0.0%)	2/190 (1.1%)	2/100 (2.0%)	NA	NA
Personal or family history of allergic asthma, other types of allergy, extra-cardiac auto-immune diseases, and toxic agents	64/580 (11.0%)	9/87 (10.3%)	5/29 (17.2%)	2/32 (6.3%)	2/26 (7.7%)	NA	55/493 (11.2%)	14/203 (6.9%)	35/190 (18.4%)	6/100 (6.0%)	NA	NA
Family history of dilated cardiomyopathy	12/580 (2.1%)	1/87 (1.1%)	0/29 (0.0%)	1/32 (3.1%)	0/26 (0.0%)	NA	11/493 (2.2%)	1/203 (0.5%)	10/190 (5.3%)	0/100 (0.0%)	NA	NA
Family history of myocarditis	7/580 (1.2%)	2/87 (2.3%)	0/29 (0.0%)	2/32 (6.3%)	0/26 (0.0%)	NA	5/493 (1.0%)	2/203 (1.0%)	3/190 (1.6%)	0/100 (0.0%)	NA	NA

[a]Fisher's exact test.
[b]Data on oedema and/or LGE missing in three paediatric patients.
[c]Classical myocarditic LGE pattern as defined by the original Lake Louise criteria, as follows: (i) at least one focal lesion with non-ischaemic regional distribution in inversion recovery-prepared gadolinium-enhanced T1-weighted images (LGE), (ii) images obtained at least 5 min after gadolinium injection (foci typically exclude the subendocardial layer, are often multifocal, and involve the subepicardium), and (3) if the LGE pattern clearly indicates myocardial infarction and is colocalized with a transmural regional oedema, acute myocardial infarction is more likely and is reported.
ECG, electrocardiogram; CMR, cardiac magnetic resonance; LGE, late gadolinium enhancement; NA, not applicable.

($P = .044$). Regarding differences in the distribution of histology types, in the North, giant cell (26.1%) and sarcoid (39.1%) myocarditis was more common than in the other areas ($P < .001$; $P < .001$, respectively); lymphocytic myocarditis predominated in the East (95.5%), West (100.0%), and South (95.0%) ($P < .001$) (not shown). Steroids (38.6%), other immunosuppressants, or immunomodulatory drugs (39.8%) were more frequently prescribed in the East ($P = .019$; $P = .003$, respectively).

Follow-up and 1-year outcome and univariable and multivariable predictors at diagnosis of unfavourable outcome

Among the 581 patients at baseline, only 554 patients are in the final database (as 27 myocarditis patients were enrolled in sites non-compliant with European Community regulatory agreements and therefore removed in transfer after lock of initial database). Among these 554 patients, 410 performed their 1-year follow-up (74.0%). There were no differences in baseline characteristics between those with and without follow-up data (not shown). The main clinical and diagnostic features at 1-year follow-up in the whole cohort and by group are shown in Supplementary data online, *Table S8*; overall, 11 patients (2.7%) died, 7 (1.7%) received a heart transplant, 3 underwent VAD (0.7%), and 16 (3.9%) underwent ICD implantation. At follow-up, G2 biopsy-proven patients had worse clinical and diagnostic features (advanced NYHA class, more heart failure signs and symptoms, more arrhythmia, and lower biventricular function) and higher frequency of ICD implantation and of heart transplant compared with the remaining clinically suspected patients. Baseline univariate predictors of unfavourable outcome at 1-year follow-up (*Table 5*) included young age, history of stroke and of hypertension, the presence of subacute/chronic heart failure signs and symptoms, echocardiographic biventricular dysfunction indexes, detection of HHV6 on EMB, and the need of medical therapy and VAD. Risk of death or heart transplant at 1 year in all patients was higher in G2 biopsy-proven patients vs. G1, with HR (95% CI) 4.22 (1.21; 14.69), $P = .024$ (*Figure 3A*); risk of death or heart transplantation or hospitalization or VAD implantation or ICD implantation at 1 year in all patients was also higher in G2 biopsy-proven patients vs. G1, with HR (95% CI) 1.72 (1.11; 2.65), $P = .014$ (*Figure 3B*). The results of the Cox multivariable model on risk at 1 year for death or heart transplantation or hospitalization or VAD implantation or ICD implantation are shown in *Table 6*. A high value of echocardiographic LVEF at diagnosis was an independent predictor of lower risk to have the event (HR 0.98; 95% CI 0.97–0.99, $P = .004$). New start of immunosuppressant or immunomodulatory drug intake at new myocarditis diagnosis indicated a higher risk to have the event (HR 1.92; 95% CI 1.26–2.92, $P = .002$).

Discussion

This work reports the first observational cross-sectional prospective data and several novel observations regarding clinical presentations, diagnosis and management, and outcome predictors in children and adults with clinically suspected and biopsy-proven myocarditis across a broad range of centres, using homogeneous criteria and definitions, i.e. the 2013 ESC consensus criteria and definitions.[1] In this registry, the population is less heterogeneous than all previously published single-centre and multicentre myocarditis registries.[3–5] The ESC definition is the most strict definition of clinically suspected myocarditis, since in addition to clinical and diagnostic parameters, it requires exclusion of other causes that may explain the syndrome (Takotsubo, myocardial infarct with normal coronary arteries, and dilated or arrhythmogenic cardiomyopathy).[1] In addition, only 126 of the 581 reported patients had clinically suspected myocarditis without a CMR proven or a biopsy-proven diagnosis.

Paediatric vs. adult myocarditis

This registry confirms that both biopsy-proven and clinically suspected myocarditis is a disease predominantly affecting the relatively young.[1–7] Virus-negative lymphocytic myocarditis was predominant both in children and adults; immunosuppressants were underutilized. Epidemiological features and 1-year outcome were similar in children and adults; myocarditis was more common in males, in keeping with previous observations.[10] However, predominance of males was lower among biopsy-proven children and adults that had lower indexes of biventricular function, higher frequency of heart failure, and advanced NYHA class, all features previously associated with worse prognosis,[1–7] and that were confirmed here as univariate predictors of dismal evolution. An independent negative prognostic role of male gender is not yet established; a recent single-centre study showed that female gender was an independent negative predictor in the pre-IS era[6]; thus, more studies are warranted. In this registry, heart failure was more common in children. This may indicate that children can be less aware of symptoms than adults, so that diagnosis is delayed until heart failure signs are overt. In an experimental murine model of enterovirus-induced myocarditis, the very young and the very old animals developed severe myocarditis and had worse outcome.[11,12] Although the relevance of these observations to humans is unknown, and enterovirus is not frequently detected in contemporary biopsy-proven cohorts,[1,2] as confirmed here, the present registry data suggest that paediatric cardiologists should always suspect an underlying myocarditis in children with unexplained heart failure or dilated cardiomyopathy.[13–15] Last but not least, paediatric and adult myocarditis cases, diagnosed by homogeneous criteria, had more similarities than differences. This may be useful from clinical operational point of view, in that the patients may be diagnosed using similar approaches. However, the diseases in children and adults may still have different pathophysiological trajectories; thus, it should not be assumed *a priori* that they share the same treatment or outcomes.

Biopsy-proven vs. clinically suspected myocarditis

In the registry, biopsy-proven patients, at baseline, had a higher frequency of heart failure and arrhythmia, more advanced NYHA class, lower indexes of biventricular function, more frequent use of all classes of cardioactive medications, and underwent ICD implantation more frequently. At 1-year follow-up, biopsy-proven patients had worse clinical and diagnostic features, a higher risk of death or heart transplant, as well as higher risk of death or heart transplantation or hospitalization or VAD or ICD implantation. These findings strongly suggest a selection bias in performance of EMB in the sickest patients regardless of age, in keeping with most guidelines and expert consensus.[16–19]

Diagnostic contribution of endomyocardial biopsy and cardiac magnetic resonance

This registry provides important unbiased multicentre information across Europe on the diagnostic contribution of EMB and CMR to

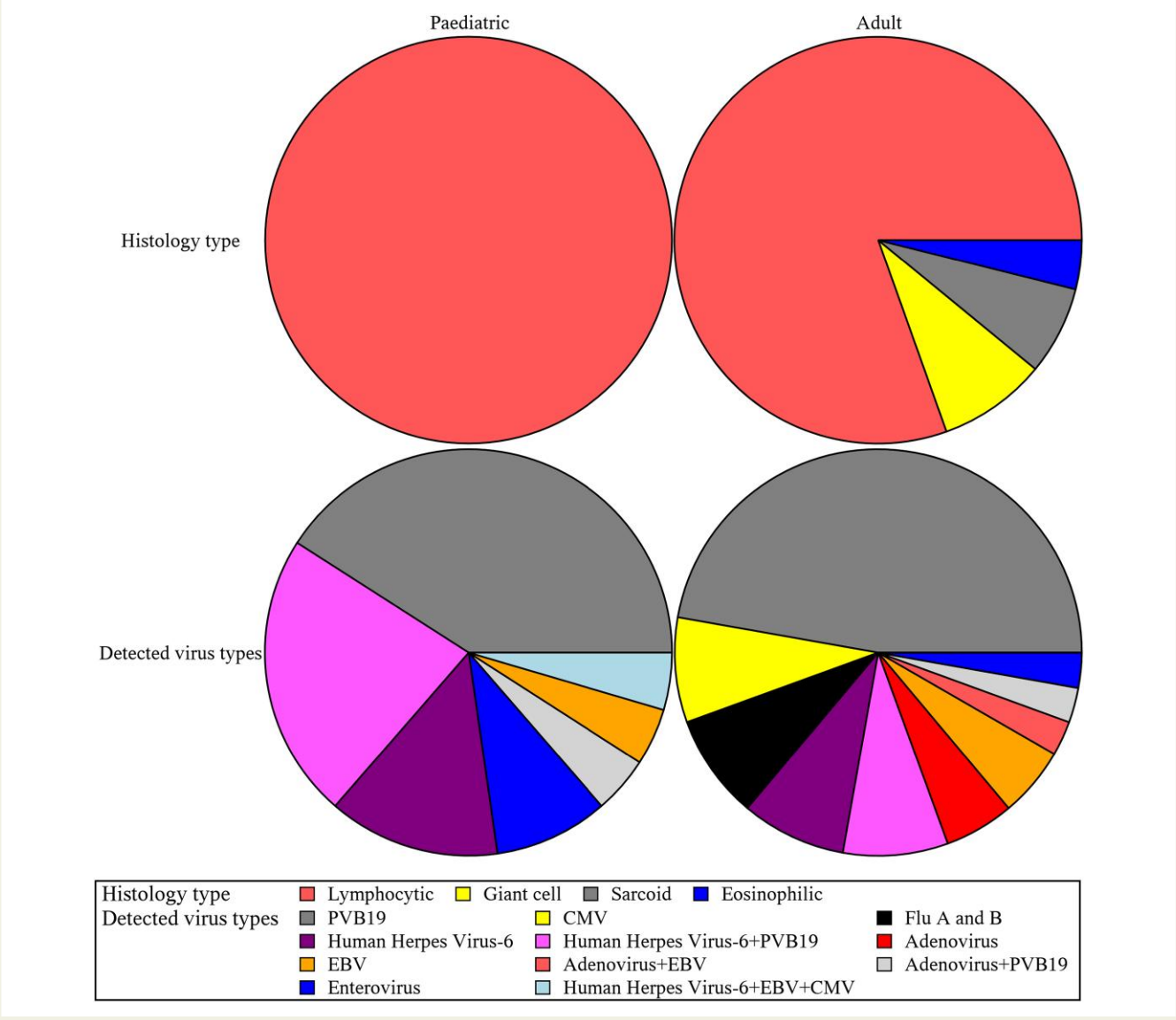


Figure 2 The top panel shows histology types in paediatric (left) and in adult myocarditis (right). The bottom panel shows the distribution of detected viruses on endomyocardial biopsy (EMB) in paediatric (left) and in adult myocarditis (right)

myocarditis diagnosis. First of all, although EMB was mainly performed in the sickest patients, it was safe, with a low frequency of complications and no procedure-related death, even in children, in keeping with a recent statement on EMB endorsed by the European, Japanese, and US heart failure societies.[18] The slightly higher complication rate in this registry compared with the EMB statement[18] (~5% vs. 1%) may relate to the inclusion of centres with a lower number of procedures. These figures are in keeping with the proposals of the ESC and of other non-ESC societies to refer particularly the sickest clinically suspected patients to referral centres with expertise in EMB, mechanical assist device, and IS.[1,2,16–19] As shown here, the frequency of severe presentations is not negligible and may be underestimated, since EMB is performed in only a minority of severely ill patients; thus, it would be relevant to raise awareness among the cardiological communities and the health authorities to develop in each country pre-defined hub and spoke myocarditis networks. Our finding that only 70.7% of patients had CMR may reflect underutilization and/or lack of availability/expertise. In this registry, CMR was also less frequently performed in biopsy-proven cases; since such patients have the most severe presentations, this may relate to safety considerations, i.e. haemodynamic instability and/or life-threatening arrhythmias, in keeping with current recommendations.[1,2,18] Last but not least, the results of this registry show that, in children and adults who had both CMR and EMB, CMR, using the original Lake Louise criteria, was less sensitive in heart failure and in arrhythmia presentations,[1,20] particularly in children, leading to an underdiagnosis of biopsy-proven disease. Although adult and paediatric cohorts were rather unbalanced to allow reliable assessment of CMR sensitivity (493 vs. 88 patients), this is a registry and gives an unbiased picture of the enrolled patients. The registry data, obtained across a wide range of European centres and blindly from the opinion of the investigators, confirm a previous single-centre study in adults[20] and support the ESC,[1,17,18] American Heart Association,[19] and World Health Organization[21] as well as the Cardiovascular Pathology scientific statements[22] that EMB is still the diagnostic gold standard of myocarditis.

Table 5 Univariable predictors at diagnosis of risk at 1 year (death or heart transplantation or hospitalization or ventricular assist device implantation or implantable cardioverter defibrillator implantation)

Variable	Modality	Realization of one of the events	No events realized	Hazard ratio (95% CI)	Sample size	*P*-value	*P*-value global
Age at diagnosis (years)	Cont.	Mean = 26.97	Mean = 40.27	0.982 (0.967; 0.996)	87/405	.015	.015
Anti-arrhythmic drugs	No	78/343 (22.7%)	265/343 (77.3%)	Ref.	405/405		.002
	Yes	27/62 (43.5%)	35/62 (56.5%)	2.047 (1.307; 3.204)		.002	
Diuretics	No	47/242 (19.4%)	195/242 (80.6%)	Ref.	371/405		<.001
	Yes	52/129 (40.3%)	77/129 (59.7%)	2.126 (1.385; 3.264)		<.001	
Human herpesvirus 6	Negative	34/115 (29.6%)	81/115 (70.4%)	Ref.	123/405		.026
	Positive	5/8 (62.5%)	3/8 (37.5%)	2.948 (1.138; 7.634)		.026	
Ankle oedema	No	73/313 (23.3%)	240/313 (76.7%)	Ref.	375/405		.002
	Yes	30/62 (48.4%)	32/62 (51.6%)	2.042 (1.286; 3.243)		.002	
History of stroke	No	96/390 (24.6%)	294/390 (75.4%)	Ref.	403/405		.022
	Stroke	6/9 (66.7%)	3/9 (33.3%)	3.126 (1.364; 7.166)		.007	
	TIA	2/4 (50.0%)	2/4 (50.0%)	1.640 (0.397; 6.766)		.494	
Hypertension	No	75/327 (22.9%)	252/327 (77.1%)	Ref.	405/405		.033
	Yes	30/78 (38.5%)	48/78 (61.5%)	1.617 (1.040; 2.512)		.033	
Type of patient	Inpatient	80/287 (27.9%)	207/287 (72.1%)	Ref.	405/405		.038
	Outpatient	25/118 (21.2%)	93/118 (78.8%)	0.614 (0.388; 0.973)		.038	
Renal impairment	No	88/369 (23.8%)	281/369 (76.2%)	Ref.	405/405		.017
	Yes	17/36 (47.2%)	19/36 (52.8%)	1.911 (1.124; 3.248)		.017	
Presence of symptoms	No	2/30 (6.7%)	28/30 (93.3%)	Ref.	405/405		.023
	Yes	103/375 (27.5%)	272/375 (72.5%)	5.063 (1.247; 20.562)		.023	
E-wave deceleration time	Cont.	Mean = 150.16	Mean = 192.73	0.990 (0.985; 0.996)	163/405	<.001	<.001
LGE of classical myocarditis pattern	No	16/67 (23.9%)	51/67 (76.1%)	Ref.	281/405		.797 (NS)
	Yes	49/214 (22.9%)	165/214 (77.1%)	1.122 (0.467; 2.691)		.797 (NS)	
LV ejection fraction	Cont.	Mean = 44.26	Mean = 50.58	0.982 (0.969; 0.995)	378/405	.007	.007

Continued

Table 5 *Continued*

Variable	Modality	Realization of one of the events	No events realized	Hazard ratio (95% CI)	Sample size	*P*-value	*P*-value global
RV global systolic dysfunction	No	83/352 (23.6%)	269/352 (76.4%)	Ref.	394/405		.025
	Yes	19/42 (45.2%)	23/42 (54.8%)	1.806 (1.076; 3.034)		.025	
Anti-arrhythmic drugs: amiodarone	No	78/343 (22.7%)	265/343 (77.3%)	Ref.	385/405		.006
	Yes	19/42 (45.2%)	23/42 (54.8%)	2.064 (1.237; 3.445)		.006	
Calcium antagonists	No	94/383 (24.5%)	289/383 (75.5%)	Ref.	405/405		.013
	Yes	11/22 (50.0%)	11/22 (50.0%)	2.236 (1.182; 4.228)		.013	
Mineralocorticoid receptor antagonists	No	59/278 (21.2%)	219/278 (78.8%)	Ref.	405/405		.014
	Yes	46/127 (36.2%)	81/127 (63.8%)	1.662 (1.109; 2.491)		.014	
Endomyocardial biopsy	No	2/4 (50.0%)	2/4 (50.0%)	Ref.	172/405		.050
	Yes	55/168 (32.7%)	113/168 (67.3%)	0.240 (0.058; 1.001)		0.050	
Other immunosuppressants or immunomodulatory drugs	No	59/287 (20.6%)	228/287 (79.4%)	Ref.	404/405		.003
	Yes	45/117 (38.5%)	72/117 (61.5%)	1.870 (1.243; 2.814)		.003	
Subacute/chronic (>3 months) heart failure signs and symptoms	No	79/344 (23.0%)	265/344 (77.0%)	Ref.	405/405		.020
	Yes	26/61 (42.6%)	35/61 (57.4%)	1.741 (1.090; 2.780)		.020	
Ventricular assist device	No	95/393 (24.2%)	298/393 (75.8%)	Ref.	405/405		<.001
	Yes	10/12 (83.3%)	2/12 (16.7%)	4.569 (2.337; 8.931)		<.001	

LV, left ventricle; RV, right ventricle.

Performance of the 2013 European Society of Cardiology criteria and definitions

In this registry, the pseudoinfarct was as common as any heart failure presentation; arrhythmia was also well represented. Conversely, the ancillary 2013 ESC features[1] identified only a minority of patients, the most common being fever at presentation or within the previous month, which was present in 40% of all cases, in keeping with the experts' proposal of these features being 'ancillary' for the diagnosis.[1] These data also reinforce the concept that there is not a pathognomonic clinical presentation of myocarditis[1–7] and support the 2013 ESC proposal that a combination of clinical and diagnostic features is needed to fulfil the definition of 'clinically suspected myocarditis', the diagnosis of certainty being provided by EMB.[1] This registry is the first attempt to apply the 2013 ESC criteria to children. It is of interest that they were also applicable in this cohort.

Biopsy-proven myocarditis: histopathology, aetiological diagnosis, and aetiology-directed therapies

The registry results confirm previous single-centre studies reporting that lymphocytic myocarditis is the commonest histopathological form[1–7] and the contemporary shift in the cardiotropic virus genomes detected in EMB tissue, PVB19, and HHV6 being most frequently involved.[1,2,23,24] For the first time, this registry documents that these viruses were more common in children than in adults. In adults, it is controversial whether PVB19 and HHV6 have a direct pathogenic role or represent innocent bystanders.[1, 2] Some investigators have proposed that high PVB19 load and active virus replication differentiate pathogenic infection.[1,2,25,26] The pathogenicity of these viruses might be more frequent in children, in whom PVB19 causes the fifth disease.[25]

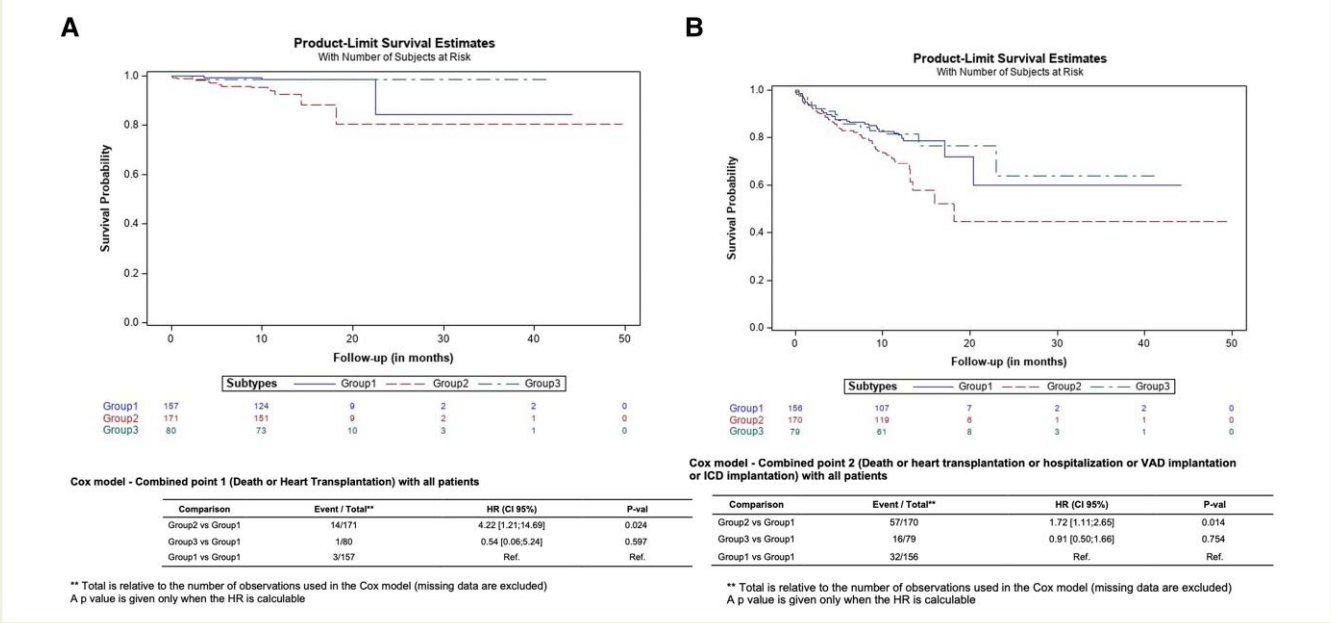


Figure 3 The left panel shows the risk of death or heart transplantation at 1 year with all myocarditis patients by group (univariable Cox model). The right panel shows the risk of death or heart transplantation or hospitalization or VAD implantation or ICD implantation at 1 year with all myocarditis patients by group (univariable Cox model)

Interestingly, the registry also shows a predominance of virus-negative myocarditis and a high frequency of detection of serum anti-heart autoantibodies, in keeping with a previous single-centre study suggesting that currently the most frequent biopsy-proven form is immune-mediated/auto-immune.[6] Clearly, since only one-third of the patients consecutively recruited in this registry underwent EMB, the true distribution of aetiologies in myocarditis is undefined. Infectious agents might have been more frequent in the remaining two-thirds of clinically suspected patients; in addition, some of the virus-negative biopsy-proven patients might have had an early virus infection that was cleared prior to EMB, triggering post-infectious immune-mediated myocarditis in genetically susceptible subjects.[1,2]

The registry shows that antiviral therapy was given to a patient minority, mainly children, regardless of biopsy-proven diagnosis. Steroids or immunosuppressants were prescribed in both children and adults, in children regardless of biopsy-proven diagnosis and in adults mainly in biopsy-proven patients, as recommended.[1,2,17,18] The lack of adherence within the paediatric setting may relate to the fact that the 2013 ESC statement was mainly diffused among adult cardiologists. Overall immunosuppressive agents for virus-negative myocarditis were underutilized; the registry was not specifically designed to identify potential reasons for this finding, and new surveys are warranted to clarify this important issue.

Geographical differences across Europe

One of the goals of the myocarditis registry was to report on standards of diagnosis and management across Europe, to show adherence to guidelines and to provide information on provision of care. There were geographical differences; some of them may reflect heterogeneity in clinical set-ups and hospital facilities and access to various diagnostic tests among ESC countries. However, some differences may capture genuine associations. In particular, the frequency of giant cell myocarditis (GCM) and cardiac sarcoidosis was higher in biopsy-proven patients in the North. The highest frequency of sarcoidosis and of GCM was reported in Northern Europe.[2,27,28] Since the differential histopathological diagnosis among the two entities is subtle, it is possible that some cases reported as GCM were indeed cardiac sarcoidosis. Anyhow, given the dismal prognosis of both myocarditis forms and the response to immunosuppressive therapy,[2,27,28] this finding should alert cardiologists from North European countries to perform EMB more frequently, particularly in clinically suspected patients with severe heart failure or arrhythmia.

One-year outcome and univariable and multivariable predictors at diagnosis of unfavourable outcome

In this study, univariable predictors at diagnosis of unfavourable outcome were younger age, subacute/chronic heart failure signs and symptoms, renal dysfunction, biventricular dysfunction, the need of medical therapy, and biopsy-proven status, in keeping with previous retrospective cohort regional registries[3–5] and prospective studies from single tertiary referral centres.[6,7]

In the present registry, independent predictors of death or heart transplantation or hospitalization or VAD or ICD implantation were lower LVEF and the need for immunosuppressant drugs at diagnosis (*Structured Graphical Abstract*). The independent role of the former has been previously identified.[3–7] A novel finding from this registry is the independent higher risk associated with the need of immunosuppressants at diagnosis. The cross-sectional registry study design does not allow to infer conclusions on safety and efficacy of immunosuppressant and other aetiology-directed therapies as it captures a

Table 6 Multivariable Cox model on risk at 1 year for death or heart transplantation or hospitalization or ventricular assist device implantation or implantable cardioverter defibrillator implantation

Sample size	Covariate	*P*-value global	Modality	HR (95% CI)	*P*-value HR
377/405	Group of myocarditis	.265	Group 1 vs. Group 2	0.80 (0.50–1.27)	.339
			Group 3 vs. Group 2	0.58 (0.30–1.15)	.120
	LV ejection fraction	.004	Cont.	0.98 (.97–0.99)	.004
	Other immunosuppressants or immunomodulatory drugs	.002	Yes vs. no	1.92 (1.26–2.92)	.002

HR, hazard ratio; CI, confidence interval; DF, degrees of freedom; LV, left ventricle.

heterogeneous range of treatment modalities and indications. The 2013 ESC consensus paper[1] and the 2021 ESC heart failure guidelines[17] recommend IS only in biopsy-proven virus-negative myocarditis refractory to standard heart failure therapy, but this registry is a real-world picture of myocarditis management and of compliance with the ESC recommendations in European countries. Although, in keeping with these recommendations, most patients treated with immunosuppressive agents were adults with biopsy-proven virus-negative myocarditis; in some cases, mainly steroids were given in the absence of biopsy-proven myocarditis, particularly in children.[1,2,17,18] The need for IS was a qualitative index included in the registry, but treatment was left to the local investigators' decisions; therefore, the registry design does not allow to define the specific indications to IS. Thus, the independent higher risk associated with the need for immunosuppressant drugs at diagnosis reported here may reflect the independent worse prognosis of the immune-mediated biopsy-proven myocarditis forms,[6,28] *a priori* bias by the providers towards sicker patients, and/or harm due to the inappropriate use of these drugs in patients without a biopsy-proven aetiological diagnosis. Prospective studies are warranted to clarify this important issue.

Limitations

The registry shows that EMB is safe even in children. However, most centres performing EMB in the registry were tertiary centres with expertise in interventional techniques; therefore, these results should not be translated to all centres, especially those with a low number of procedures.

Although this registry collected detailed information, a limitation is that information on virus load and replication state of PVB19 in biopsy-proven myocarditis was not requested; thus, it is not possible to draw conclusions in relation to pathogenicity issue. To this end, additional prospective data are warranted. The registry closed before the COVID-19 outbreak, therefore, no information on a possible association of COVID-19 and myocarditis can be inferred. Another limitation is that there is no handling of missing data. This registry is an observational study, and each variable is analysed according to the data collected. The univariable comparisons were carried out in an exploratory manner, in the setting of an observational descriptive study, and certain patient groups have a low number of data.

Conclusions

In patients with clinically suspected myocarditis, EMB was safe in children and adults and is still the diagnostic gold standard; CMR using Lake Louise criteria was less sensitive, particularly in children. Lower LVEF and the need for immunosuppressant drugs at diagnosis were independent predictors of unfavourable outcome at 1 year.

Acknowledgements

The authors thank the EORP Oversight Committee and the Registry Executive Committee of the EORP. Data collection was conducted by the EORP department from the ESC by Rachid Mir Hassaine as Clinical Project Manager; Emanuela Fiorucci, Myriam Glémot, and Patti-Ann McNeill as Project Officers; and Marème Konté and Sebastien Authier as Data Managers. Statistical analyses were performed by C.L. Overall activities were coordinated and supervised by A.P.M. (EORP Scientific Coordinator). All investigators are listed in the Appendix.

Supplementary data

Supplementary data are available at *European Heart Journal* online.

Declarations

Disclosure of Interest

A.L.P.C., L.C., S.S., C.L., A.F., I.K., A.A., and O.B. report no conflicts. J.P.K. reports consulting fees from DiNAqor, Cytokinetics, and Tenaya (outside of the submitted work). M.T. reports consulting fees from Bayer, Janssen-Cilag, Kowa, Perfuse Group, and Servier (unrelated to the submitted work). T.H. reports consulting fees/honoraria from Bristol-Myers Squibb and Research Collaboration with Blueprint Genetics Quest (outside of the submitted work). J.G. reports advisory board roles with no consulting fees from Novartis and MSD. D.B. reports consulting fees from Novartis and Merck (steering committee, advisory board). P.C. reports consulting fees (outside the submitted work) from Alnylam, Amicus, Bristol-Myers Squibb, and Pfizer. P.M.E. reports consulting fees from Pfizer, Sarepta, Sanofi, DiNAqor, Freeline, BMS, and Cardior. G.S. reports personal fees for consultancies, trial committee work, and/or lectures from Vifor, AstraZeneca, Novartis, Impulse Dynamics, Biotronik, Abbott, Boston, Bayer, Pfizer, and Boehringer Ingelheim (outside the submitted work). P.M.S. reports speakers bureaus from Servier, AstraZeneca, Menarini, Boehringer Ingelheim, Novartis, and Roche Diagnostics (outside the submitted work). M.F. reports honoraria/grants from AstraZeneca, Novartis, Vifor Pharma, Bayer, MSD, and Pharmacosmos (outside the submitted work). A.P.M. reports honoraria from AstraZeneca, Novartis, Bayer, and Fresenius for participation in study committees, outside the present work. L.T. reports honoraria from Servier and

for trial committee membership and speaker bureau (outside the submitted work).

Data Availability

Data are available at EORP.

Funding

Since the start of EORP, the following companies have supported the programme: Abbott Vascular Int. (2011–21), Amgen Cardiovascular (2009–18), AstraZeneca (2014–21), Bayer AG (2009–18), Boehringer Ingelheim (2009–19), Boston Scientific (2009–12), Bristol-Myers Squibb and Pfizer Alliance (2011–19), Daiichi Sankyo Europe GmbH (2011–20), The Alliance Daiichi Sankyo Europe GmbH and Eli Lilly and Company (2014–17), Edwards (2016–19), Gedeon Richter Plc. (2014–16), Menarini Int. Op. (2009–12), MSD-Merck & Co. (2011–14), Novartis Pharma AG (2014–20), ResMed (2014–16), Sanofi (2009–11), SERVIER (2009–21), and Vifor (2019–22).

Ethical Approval

This study complies with the Declaration of Helsinki. Participating centres managed the approvals of national or regional ethics committees or Institutional Review Boards, according to local regulations. Written informed consent was obtained from all participants or from the parent for patients <18 years old, before data collection. All diagnostic or therapeutic procedures were left to the discretion of the attending physician.

Pre-registered Clinical Trial Number

None supplied.

Appendix

EORP Oversight Committee

2014–16: R. Ferrari, IT (Chair); A. Alonso, ES; J. Bax, NL; C. Blomström-Lundqvist, SE; S. Gielen, DE; P. Lancellotti, BE; A.P. Maggioni, IT; N. Maniadakis, GR; F. Pinto, PT; F. Ruschitzka, CH; L. Tavazzi, IT; P. Vardas, GR; F. Weidinger, AT; U. Zeymer, DE. **2016–18**: A. Vahanian, FR (Chair); A. Budaj, PL; N. Dagres, DE; N. Danchin, FR; V. Delgado, NL; J. Emberson, GB; O. Friberg, SE; C.P. Gale, GB; G. Heyndrickx, BE; B. Iung, FR; S. James, SE; A.P. Kappetein, NL; A.P. Maggioni, IT; N. Maniadakis, GR; K.V. Nagy, HU; G. Parati, IT; A-S. Petronio, IT; M. Pietila, FI; E. Prescott, DK; F. Ruschitzka, CH; F. Van de Werf, BE; F. Weidinger, AT; U. Zeymer, DE. **2018–20**: C.P. Gale, GB (Chair); B. Beleslin, RS; A. Budaj, PL; O. Chioncel, RO; N. Dagres, DE; N. Danchin, FR; J. Emberson, GB; D. Erlinge, SE; M. Glikson, IL; A. Gray, GB; M. Kayikcioglu, TR; A.P. Maggioni, IT; K.V. Nagy, HU; A. Nedoshivin, RU; A-P. Petronio, IT; J.W. Roos-Hesselink, NL; L. Wallentin, SE; U. Zeymer, DE. **2020–22**: B.A. Popescu, RO (Chair); D. Adlam, GB; A.L.P. Caforio, IT; D. Capodanno, IT; M. Dweck, GB; D. Erlinge, SE; M. Glikson, IL; J. Hausleiter, DE; B. Iung, FR; M. Kayikcioglu, TR; P. Ludman, GB; L. Lund, SE; A.P. Maggioni, IT; S. Matskeplishvili, RU; B. Meder, DE; K.V. Nagy, HU; A. Nedoshivin, RU; D. Neglia, IT; A.A. Pasquet, BE; J.W. Roos-Hesselink, NL; F.J. Rossello, ES; S.M. Shaheen, EG; A. Torbica, IT.

Executive Committee

Alida Caforio (Chair), IT; Juan Ramon Gimeno Blanes, ES; Philippe Charron, FR; Perry Elliott, GB; Juan Pablo Kaski, GB; Aldo P. Maggioni, IT; Luigi Tavazzi, IT; Michal Tendera, PL.

Investigators

Finland: *Helsinki*: J. Pihkala, T. Ojala, A. Hiippala, T. Jarvinen, *Helsinki*: J. Lommi, T. Helio, J. Sinisalo, **France**: *Paris*: D. Bonnet, D. Khraiche, I. Szezepanski, *Paris*: P. Charron, S. Mankikian, C. Maupain, J-P. Collet, E. Gandjbakhch, M. Kerneis, J-F. Pruny, **Germany**: *Crailsheim*: A. Bauer, B. Pfeiffer, *Greifswald*: S.B. Felix, D. Beug, M. Dorr, S. Kaczmarek, K. Lehnert, A-L. Pedersen, M. Bruder, *Heidelberg*: M. Gorenflo, R. Arnold, S. Uhl, V. Ziesenitz, A. Jung, E. Roesch, *Homburg/Saar*: M. Böhm, I. Kindermann, Y. Linicus, C. Werner, B. Neurath, M. Schild-Ungerbuehler, *Saarbrucken*: M. Kindermann, **Great Britain**: *London*: J.P. Kaski, G. Norrish, E. Field, *London*: P. Elliott, M. Lorenzini, O. Watkinson, E. Wicks, **Greece**: *Athens*: A. Anastasakis, K. Ritsatos, V. Vlagkouli, *Athens*: S. Rammos, G. Kourelis, *Athens*: A. Giannakopoulou, E. Karanasios, P. Papachristou, G. Papadopoulos, G. Servos, **Iran**: *Tehran*: M. Maleki, F. Noohi Bezanjani, A. Amin, N. Naderi, M. Parsaee, S. Taghavi, B. Ghadrdoost, S. Jafari, M. Khoshavi, **Italy**: *Milan*: P. Della Bella, S. Sala, G. Peretto, *Naples*: R. Calabro, G. Pacileo, M.G. Russo, G. Limongelli, A. Esposito, F. Gragnano, R. Gravino, T. Marrazzo, D. Masarone, V. Pazzanese, M. Rubino, S. Tramonte, F. Valente, M. Caiazza, P. Calabro, A. Cirillo, *Naples*: B. Trimarco, M-A. Losi, C. Di Nardo, A. Giamundo, F. Pacelli, G. Canciello, *Padua*: S. Iliceto, A. Caforio, C. Calore, L. Leoni, M. Perazzolo Marra, I. Rigato, G. Tarantini, A. Schiavo, M. Testolina, *Rome*: F. Fedele, A. Frustaci, M. Alfarano, C. Chimenti, *Rome*: F. Drago, A. Baban, *Rome*: L. Calò, C. Lanzillo, A. Martino, *Rome*: M. Uguccioni, E. Zachara, G. Halasz, F. Re, *Trieste*: G. Sinagra, C. Carriere, M. Merlo, F. Ramani, **Lithuania**: *Kaunas*: A. Kavoliuniene, A. Krivickiene, E. Tamuleviciute-Prasciene, M. Viezelis, *Vilnius*: J. Celutkiene, L. Balkeviciene, M. Laukyte, E. Paleviciute, **Netherlands**: *Utrecht*: F. Asselbergs, N. De Jonge, J.H. Kirkels, J. Van Der Heijden, L. Van Laake, A. Sammani, **Poland**: *Katowice*: K. Mizia-Stec, M. Tendera, M. Wybraniec, A. Czekaj, A. Sikora-Puz, A. Skoczynska, *Krakow*: P. Rubis, S. Wisniowska-Smialek, *Warsaw*: J. Grzybowski, N. Ojrzynska, *Warsaw*: Z. Bilinska, P. Chmielewski, B. Foss-Nieradko, E. Michalak, M. Stepien-Wojno, B. Mazek, *Warsaw*: G. Brzezinska-Rajszys, L. Ziolkowska, A. Boruc, E. Plodzien, **Portugal**: *Almada*: L. Rocha Lopes, A.R. Almeida, I. Cruz, A.C. Gomes, A.R. Pereira, **Romania**: *Bucharest*: C. Ginghina, R. Jurcut, E. Apetrei, S. Militaru, I. Mircea Coman, A. Mursa, B.A. Popescu, *Targu-Mures*: A. Frigy, L. Fehervari, Z. Fogarasi, I. Kocsis, I.A. Szabo, **Russian Federation**: *Moscow*: I. Nikitin, E. Resnik, M. Komissarova, V. Lazarev, M. Shebzukhova, D. Ustyuzhanin, *Moscow*: O. Blagova, I. Alieva, V. Kulikova, Y. Lutokhina, E. Pavlenko, N. Varionchik, *Moscow*: E. Zaklyazminskaya, S. Dzemeshkevich, E. Kolbasova, N. Kotlukova, V. Rusinova, **Serbia**: *Belgrade*: A.D. Ristic, P.M. Seferovic, A. Pavlovic, G. Radovanovic, D. Simeunovic, I. Zivkovic, I. Milinkovic, **Spain**: *Barcelona*: F. Gran Ipina, F. Roses Noguer, D. Albert Brotons, *Barcelona*: A. Cequier, J. Salazar-Mendiguchia, J. Gonzalez, N. Manito, *Madrid*: P. Garcia-Pavia, A. Briceno, M. Cobo-Marcos, F. Dominguez, *Murcia*: J.R. Gimeno Blanes, F.J. Castro, C. Munoz Esparza, M. Sabater Molina, M. Sorli García, D. Lopez Cuenca, *Palma de Mallorca*: T. Ripoll-Vera, J. Alvarez, J. Nunez, Y. Gomez, *Salamanca*: P.L. Sanchez Fernandez, E. Villacorta, C. Avila, L. Bravo, E. Diaz-Pelaez, M. Gallego-Delgado, L. Garcia-Cuenllas, B. Plata, **Sweden**: *Gothenburg*: M. Fu, **Turkey**: *Ankara*: U. Canpolat.

Table A1 **CMY Long-Term Registry: myocarditis cohort—ethical approval reference numbers**

Country	Centre number	Ethical approval reference number	Date of approval
Finland	FI19	134/13/03/03/2015	29 April 2015
Finland	FI2a	398/13/03/01/12	11 January 2013
France	FR41b	15 163	11 March 2015
France	FR6c	15 163	11 March 2015
Germany	DE112b	154/15	14 July 2015
Germany	DE257	BB 063/15	22 April 2015
Germany	DE402	154/15	14 July 2015
Germany	DE68	B-F-2018-122	19 February 2019
Germany	DE90c	S-372/2015	6 August 2015
Greece	GR18c	No reference number	6 March 2020
Greece	GR18f	No valid ethics approval: patients removed from FU statistical analyses	
Greece	GR30b	No valid ethics approval: patients removed from FU statistical analyses	
Iran	IR12d	RHC.AC.IR.REC.1396.87	14 October 2017
Italy	IT115c	104	12 December 2016
Italy	IT128b	1223-OPBG-2016	04 October 2016
Italy	IT168c	3255/AO/14	24 July 2014
Italy	IT224b	101_2015	6 May 2015
Italy	IT231	35/2015	26 August 2015
Italy	IT287d	106/2015	4 June 2015
Italy	IT306b	224	21 February 2017
Italy	IT44b	1223-OPBG-2016	4 October 2016
Lithuania	LT1g	BEC-LSMU(R)-16	29 September 2014
Lithuania	LT7c	158200-15-761-276	13 January 2015
Netherlands	NL36a	WAG/om/14/008031	14 March 2014
Nigeria	NG01b	ADM/DCST/HREC/APP/095	15 May 2015
Poland	PL136b	IK-NP-0021-95/1473/14	4 November 2014
Poland	PL136d	IK-NP-0021-95/1473/2014	24 November 2014
Poland	PL183	31/KBE/2017	21 June 2017

Continued

Table A1 *Continued*

Country	Centre number	Ethical approval reference number	Date of approval
Poland	PL5a	Ethical approval unnecessary in this region for this kind of study at the time of patient enrolment	
Poland	PL5b	Ethical approval unnecessary in this region for this kind of study at the time of patient enrolment	
Poland	PL67g	No reference number	15 November 2014
Portugal	PT5c	3851/2015	31 October 2015
Romania	RO7f	9749	19 May 2015
Russian Federation	RU186	1159	17 February 2020
Russian Federation	RU191	10–18	30 October 2018
Russian Federation	RU192	Ethical approval unnecessary in this region for this kind of study at the time of patient enrolment	
Serbia	RS14c	1393/18	18 November 2014
Spain	ES24c	0025	15 June 2015
Spain	ES5d	303	27 October 2014
Spain	ES88c	Ethical approval unnecessary in this region for this kind of study at the time of patient enrolment	
Spain	ES9	No reference number	5 February 2016
Spain	ES92a	14 October	27 October 2014
Sweden	SE2e	026–16	27 September 2017
Turkey	TR40a	Ethical approval unnecessary in this region for this kind of study at the time of patient enrolment	
UK	GB103	15HC03	27 April 2016
UK	GB122	15/LO/1346	28 October 2015

References

1. Caforio ALP, Pankuweit S, Arbustini E, Basso C, Gimeno-Blanes J, Felix SB, *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**:2636–48. https://doi.org/10.1093/eurheartj/eht210
2. Tschöpe C, Ammirati E, Bozkurt B, Caforio ALP, Cooper LT, Felix SB, *et al.* Myocarditis and inflammatory cardiomyopathy: current evidence and future directions. *Nat Rev Cardiol* 2021;**18**:169–93. https://doi.org/10.1038/s41569-020-00435-x
3. Ammirati E, Cipriani M, Moro C, Raineri C, Pini D, Sormani P, *et al.* Clinical presentation and outcome in a contemporary cohort of patients with acute myocarditis: Multicenter Lombardy Registry. *Circulation* 2018;**138**:1088–99. https://doi.org/10.1161/CIRCULATIONAHA.118.035319
4. Ammirati E, Veronese G, Brambatti M, Merlo M, Cipriani M, Potena L, *et al.* Fulminant versus acute nonfulminant myocarditis in patients with left ventricular systolic dysfunction. *J Am Coll Cardiol* 2019;**74**:299–311. https://doi.org/10.1016/j.jacc.2019.04.063
5. Ammirati E, Cipriani M, Lilliu M, Sormani P, Varrenti M, Raineri C, *et al.* Survival and left ventricular function changes in fulminant versus nonfulminant acute myocarditis. *Circulation* 2017;**136**:529–45. https://doi.org/10.1161/CIRCULATIONAHA.117.026386
6. Baritussio A, Schiavo A, Basso C, Giordani A, Cheng C-Y, Pontara E, *et al.* Predictors of relapse, death or heart transplantation in myocarditis before the introduction of immunosuppression: negative prognostic impact of female gender, fulminant onset, lower ejection fraction and serum autoantibodies. *Eur J Heart Fail* 2022;**24**:1033–44. https://doi.org/10.1002/ejhf.2496
7. Anzini M, Merlo M, Sabbadini G, Barbati G, Finocchiaro G, Pinamonti B, *et al.* Long-term evolution and prognostic stratification of biopsy-proven active myocarditis. *Circulation* 2013;**128**:2384–94. https://doi.org/10.1161/CIRCULATIONAHA.113.003092
8. Elliott P, Charron P, Blanes JR, Tavazzi L, Tendera M, Konté M, *et al.* EURObservational Research Programme of the European Society of Cardiology. *Eur Heart J* 2016;**37**:164–73. https://doi.org/10.1093/eurheartj/ehv497
9. Charron P, Elliott PM, Gimeno JR, Caforio ALP, Kaski JP, Tavazzi L, *et al.* The Cardiomyopathy Registry of the EURObservational Research Programme of the European Society of Cardiology: baseline data and contemporary management of adult patients with cardiomyopathies. *Eur Heart J* 2018;**39**:1784–93. https://doi.org/10.1093/eurheartj/ehx819
10. Fairweather D, Cooper LT, Blauwet LA. Sex and gender differences in myocarditis and dilated cardiomyopathy. *Curr Probl Cardiol* 2013;**38**:7–46. https://doi.org/10.1016/j.cpcardiol.2012.07.003
11. Woodruff JF. Viral myocarditis. A review. *Am J Pathol*. 1980;**101**:425–84
12. Liu PP, Mason JW. Advances in the understanding of myocarditis. *Circulation* 2001;**104**:1076–82. https://doi.org/10.1161/hc3401.095198
13. Lipshultz SE, Sleeper LA, Towbin JA, Lowe AM, Orav EJ, Cox GF, *et al.* The incidence of paediatric cardiomyopathy in two regions of the United States. *N Engl J Med* 2003;**348**:1647–55. https://doi.org/10.1056/NEJMoa021715
14. Nugent AW, Daubeney PE, Chondros P, Carlin JB, Cheung M, Wilkinson LC, *et al.* The epidemiology of childhood cardiomyopathy in Australia. *N Engl J Med* 2003;**348**:1639–46. https://doi.org/10.1056/NEJMoa021737
15. Wilkinson JD, Westphal JA, Bansal N, Czachor JD, Razoky H, Lipshultz SE. Lessons learned from the Paediatric Cardiomyopathy Registry (PCMR) Study Group. *Cardiol Young* 2015;**25**:140–53. https://doi.org/10.1017/S1047951115000943
16. Cooper LT, Baughman K, Feldman AM, Frustaci A, Jessup M, Kuhl U, *et al.* The role of endomyocardial biopsy in the management of cardiovascular disease: a scientific statement from American Heart Association, the American College of Cardiology, and the European Society of Cardiology. *J Am Coll Cardiol* 2007;**50**:1914–31. https://doi.org/10.1016/j.jacc.2007.09.008
17. McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, Böhm M, *et al.* 2021 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur Heart J* 2021;**42**:3599–726. https://doi.org/10.1093/eurheartj/ehab368
18. Seferović PM, Tsutsui H, McNamara DM, Ristić AD, Basso C, Bozkurt B, *et al.* Heart Failure Association of the ESC, Heart Failure Society of America and Japanese Heart Failure Society position statement on endomyocardial biopsy. *Eur J Heart Fail* 2021;**23**:854–71. https://doi.org/10.1002/ejhf.2190
19. Bozkurt B, Colvin M, Cook J, Cooper LT, Deswal A, Fonarow GC, *et al.* Current diagnostic and treatment strategies for specific dilated cardiomyopathies: a scientific statement from the American Heart Association. *Circulation* 2016;**134**:e579–646. https://doi.org/10.1161/CIR.0000000000000455
20. Francone M, Chimenti C, Galea N, Scopelliti F, Verardo R, Galea R, *et al.* CMR sensitivity varies with clinical presentation and extent of cell necrosis in biopsy-proven acute myocarditis. *JACC Cardiovasc Imaging* 2014;**7**:254–63. https://doi.org/10.1016/j.jcmg.2013.10.011
21. Richardson P, McKenna W, Bristow M, Maisch B, Mautner B, O'Connell J, *et al.* Report of the 1995 World Health Organization/International Society and Federation of Cardiology Task Force on the Definition and Classification of Cardiomyopathies. *Circulation* 1996;**93**:841–2. https://doi.org/10.1161/01.CIR.93.5.841
22. Leone O, Veinot JP, Angelini A, Baandrup UT, Basso C, Berry G, *et al.* 2011 consensus statement on endomyocardial biopsy from the Association for European Cardiovascular Pathology and the Society for Cardiovascular Pathology. *Cardiovasc Pathol* 2012;**21**:245–74. https://doi.org/10.1016/j.carpath.2011.10.001
23. Pankuweit S, Moll R, Baandrup U, Portig I, Hufnagel G, Maisch B. Prevalence of parvovirus B 19 genome in endomyocardial biopsy specimen. *Hum Pathol* 2003;**34**:80–6. https://doi.org/10.1016/S0046-8177(03)00078-9
24. Kühl U, Pauschinger M, Noutsias M, Seeberg B, Bock T, Lassner D, *et al.* High prevalence of viral genomes and multiple viral infections in the myocardium of adults with "idiopathic" left ventricular dysfunction. *Circulation* 2005;**111**:887–93. https://doi.org/10.1161/01.CIR.0000155616.07901.35
25. Pankuweit S, Klingel K. Viral myocarditis: from experimental models to molecular diagnosis in patients. *Heart Fail Rev* 2013;**18**:683–702. https://doi.org/10.1007/s10741-012-9357-4
26. Bock CT, Klingel K, Kandolf R. Human parvovirus B19-associated myocarditis. *N Engl J Med* 2010;**362**:1248–9. https://doi.org/10.1056/NEJMc0911362
27. Blauweit LA, Cooper LT. Myocarditis. *Prog Cardiovasc Dis* 2010;**52**:274–88. https://doi.org/10.1016/j.pcad.2009.11.006
28. Cooper LT Jr, Hare JM, Tazelaar HD, Edwards WD, Starling RC, Deng MC, *et al.* Giant Cell Myocarditis Treatment Trial Investigators. Usefulness of immunosuppression for giant cell myocarditis. *Am J Cardiol* 2008;**102**:1535–9. https://doi.org/10.1016/j.amjcard.2008.07.041