

# Hellenic Registry on Myocarditis SyndromES on behalf of Hellenic Heart Failure Association: The HERMES-HF Registry

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## Abstract

**Aims** Despite the existence of many studies, there are still limited data about the characteristics of myocarditis in Greece. This led to the creation of the Greek Myocarditis Registry aiming to document the different symptoms and treatment of myocarditis, assess possible prognostic factors, and find similarities and differences to what is already published in literature. This paper is a preliminary descriptive analysis of this Registry.

**Methods and results** We analysed data for the hospitalization period of all patients included in the Registry from December 2015 until November 2017. Statistics are reported as frequency (%) or median and inter-quartile range (IQR) as appropriate. In total, 146 patients were included; 83.3% of the patients reported an infection during the last 3 months. The most common symptom, regardless of the underlying infection, was chest pain (82.2%) followed by dyspnoea (18.5%), while the most common finding in clinical examination was tachycardia (26.7%). Presentation was more frequent in the winter months. ECG findings were not specific, with the repolarization abnormalities being the most frequent (60.3%). Atrial fibrillation was observed in two patients, both of whom presented with a reduced ventricular systolic function. Left ventricular ejection fraction changed significantly during the hospitalization [55% (IQR: 50–60%) on admission vs. 60% (IQR: 55–60%) on discharge,  $P = 0.0026$ ]. Cardiac magnetic resonance was performed in 88 patients (61%), revealing mainly subepicardial and midcardial involvement of the lateral wall. Late gadolinium enhancement was present in all patients, while oedema was found in 39 of them. Only 11 patients underwent endomyocardial biopsy. Discharge medication consisted mainly of beta-blockers (71.9%) and angiotensin-converting enzyme inhibitors (41.8%), while 39.7% of the patients were prescribed both.

**Conclusions** This preliminary analysis describes the typical presentation of myocarditis patients in Greece. It is a first step in developing a better prognostic model for the course of the disease, which will be completed after the incorporation of the patients' follow-up data.

**Keywords** Registry; Myocarditis; Cardiac magnetic resonance

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## Introduction

Myocarditis is an inflammatory disease of the myocardium with a wide clinical spectrum, including cases presenting with myocardial infarction-like syndrome and others with a picture resembling symptomatic heart failure, and a varied outcome, ranging from complete cure to dilated cardiomyopathy or even death. This heterogeneity has been the target of many studies aiming to describe the variance in symptoms and signs as well as the therapeutic options used in its treatment. The results of these studies led to a position statement by the European Society of Cardiology (ESC) Working Group on Myocardial and Pericardial Diseases regarding the aetiology, diagnosis, management, and therapy of myocarditis.<sup>1</sup> To explore whether there are any differences in myocarditis characteristics in Greece, we developed the Greek Myocarditis Registry in 2015. After ~2 years of enrolment, we present a preliminary analysis describing the characteristics of initial presentation of myocarditis.

## Methods

### Patient inclusion criteria

Patients were included in the registry through multiple co-operating centres, provided that a diagnosis of myocarditis was already made through the fulfilment of the diagnostic criteria for clinically suspected myocarditis, as proposed in the aforementioned position statement. The investigation conforms with the principles outlined in the Declaration of Helsinki. The study protocol was approved by the ethics committee of each participating hospital, and all patients gave written informed consent to participate in the study.

### Data obtained

The following information was collected: (i) demographics, (ii) previous medical history, (iii) recent infections, (iv) symptoms, (v) findings through clinical examination, (vi) laboratory findings with known biomarkers, (vii) serological results, (viii) ECG findings, (ix) echocardiographic findings, (x) findings

through cardiac magnetic resonance (CMR), (xi) coronary angiography findings, (xii) Holter ECG monitoring findings, (xiii) biopsy findings along with polymerase chain reaction (PCR) results, and (xiv) treatment options chosen for each patient. Apart from the hospitalization period, the registry included similar queries for follow-up visits along with possible previous or subsequent exacerbations of the disease for future assessment of prognostic factors. In the current paper, the analysis is limited to information regarding the patient hospitalization period.

### Biomarkers

Owing to the multicentre nature of the study, the normal range of each biomarker was different depending on the equipment of the participating hospitals. As such, the results are presented as multiples of upper limit of normal ( $\times$  ULN), taking into account the respective reference range.

### Statistical analysis

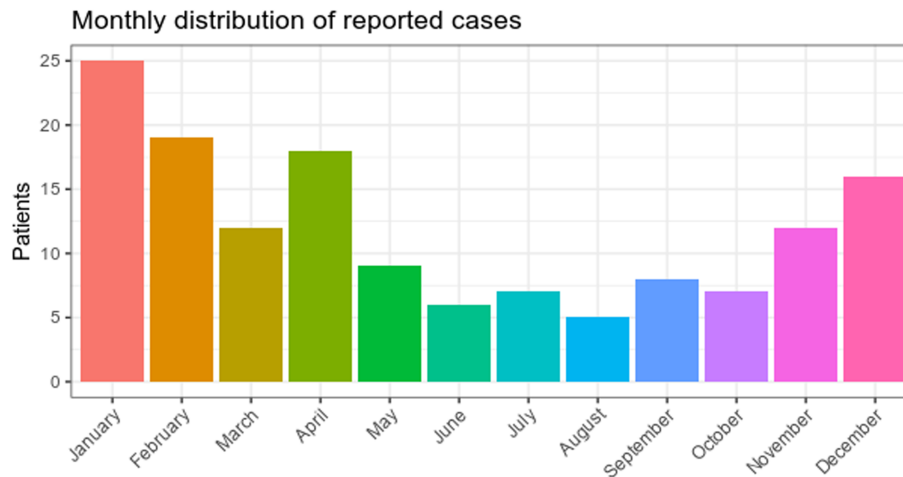
Summary descriptive statistics are presented as frequency (%) or median and inter-quartile range (IQR), as appropriate. Comparisons between findings on different time points during hospitalization were performed using the paired Wilcoxon test. All statistical tests were two-sided with a 5% level of significance using the R programming language for statistical computing (R version 3.6.0)<sup>2</sup> and RStudio (RStudio version 1.2.1355).<sup>3</sup>

## Results

### Demographics

Since the initiation of the Registry on December 2015, 146 patients have been registered up until November 2017 from 19 hospitals from both urban and rural settings around Greek mainland and its islands. The monthly distribution of these cases is presented in *Figure 1*. The majority were male patients, 118 (80.8%) vs. 28 (19.2%) female patients. The median age was 30 years (IQR: 20–39.2 years) (*Table 1*).

**Figure 1** Monthly distribution of reported cases. Monthly distribution of patient admissions due to myocarditis during the reported years in the participating centres.



## Medical history

Each patient was queried about major cardiovascular disease risk factors. Specifically, 43 patients (29.5%) were active smokers, 20 (13.7%) had a family history of cardiovascular disease, 15 (10.3%) had dyslipidaemia, 8 (5.5%) were obese, 7 (4.8%) were hypertensive, and 1 (0.7%) was diabetic. Seven patients had a previous history of myocarditis over a year before current presentation. In addition, 14 patients (9.6%) were receiving chronic medication for non-cardiovascular diseases, while 19 (13%) received medication in the last 3 months prior to the presentation of myocarditis. No patient had a history of autoimmune diseases.

## Recent infections

Each patient was queried about infections in the last 3 months prior to presentation. Specifically, 73 patients (50%) had an upper respiratory tract infection, 15 (10.3%) had a lower respiratory tract infection, 23 (15.8%) had a gastrointestinal infection, and 35 (24%) had other infections of lower incidence each or reported no infection.

**Table 1** Patient age distribution

Age	Years [median (IQR)]	
< 18	%	13.9
18–39	%	66.4
40–59	%	14.6
≥60	%	5.1

IQR, inter-quartile range.

## Clinical presentation

Symptoms were categorized based on the presented infections described in ‘Recent infections’, as follows: (i) respiratory symptoms, (ii) gastrointestinal symptoms, and (iii) common symptoms regardless of the possible underlying infection. As such, of the 88 patients with a respiratory infection, 80 (90.9%) had fever, 44 (50%) had sore throat, and 37 (44.3%) had coughing. Of the 23 patients with a gastrointestinal infection, 23 (100%) had diarrhoea, 18 (78.3%) had fever, 13 (56.5%) had abdominal pain, 7 (30.4%) had vomiting, and 2 (8.7%) had nausea.

Regarding the most common symptoms among all patients, 120 patients (82.2%) had angina-like chest pain, 27 (18.5%) had dyspnoea, 24 (16.4%) had myalgias, 21 (14.4%) had palpitations, 18 (12.3%) had arthralgias, and 4 (2.7%) had a rash.

The most common findings through clinical examination of the cardiovascular system were tachycardia (26.7%), systolic murmur (9.6%), and arrhythmias (5.5%).

## First-line investigations

### Electrocardiogram

The most common ECG changes in patients presented with myocarditis were repolarization abnormalities (60.3%) and sinus tachycardia (21.9%). Repolarization abnormalities were further divided into ST-T segment elevation—of which 35.2% was concave and 23.9% convex—and negative T (51.1%). These abnormalities often persisted until discharge (39.7%), most frequently consisting of negative T (84.5%) rather than the ST-T segment elevation (19%). Atrial fibrillation was observed in two (1.4%) patients during

hospitalization, both of whom presented with left ventricular ejection fraction (LVEF) < 35%. Conduction disorders were rare and not associated with reduced LVEF. Specifically, right bundle branch block was observed in seven (4.8%) patients, left bundle branch block in three (2.1%) patients, and atrioventricular block also in three (2.1%) patients, all of whom were first degree. Four (2.7%) patients developed ventricular tachycardia during hospitalization, all of whom were non-sustained and not associated with reduced LVEF.

### Echocardiography

Echocardiographic studies provide important diagnostic and prognostic factors in cases of myocarditis including the LVEF, the dimensions of the left ventricle, and the possible presence of global or focal hypokinesia. In this population, the median of LVEF on admission was 55% (IQR: 50–60%), the left ventricular end-systolic diameter was 34.2 mm (IQR: 30–38 mm), and the left ventricular end-diastolic diameter was 50 mm (IQR: 46–52.5 mm). The distribution of LVEF on admission can be seen in *Figure 2*. Fifty-seven patients underwent a second echocardiographic evaluation at discharge. A modest but significant increase of LVEF was observed vs. baseline (median LVEF = 60%, IQR: 55–60%,  $P < 0.01$ ). During hospitalization, 64.9% of patients retained a normal LVEF, 5.3% experienced a deterioration, 22.8% experienced an increase, and 7% retained an impaired LVEF (*Figure 3*).

In addition, hypokinesia was reported on all walls at different frequencies. Specifically, the interventricular septum (16.4%) and the inferior (16.4%) and posterior (15.8%) walls were most frequently affected, followed by the lateral wall (11.6%), the apex (11.6%), and the anterior wall (10.3%).

Pericardial effusion was observed in 25 patients (17.1%), while mitral regurgitation was the most common valve

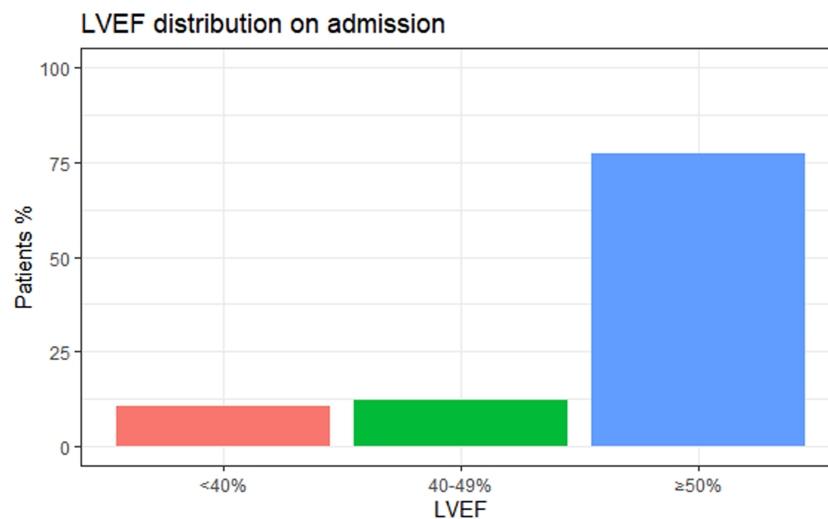
disorder having been observed in 33 patients (22.6%), being mild in the vast majority of cases (90.9%). Pulmonary hypertension and right ventricular dysfunction were rarely reported.

### Cardiac magnetic resonance

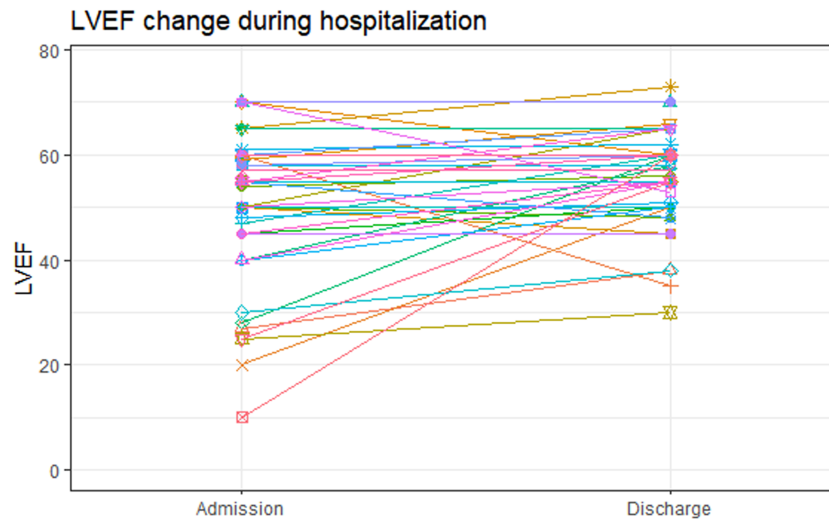
CMR is the most accurate diagnostic procedure for myocarditis, second only to the endomyocardial biopsy. In total, CMR was performed in 88 patients (61%) at a median period of 5 days (IQR: 0–13.3 days) following admission. The median LVEF was 59.2% (IQR: 53.3–62.6%), while right ventricular EF (RVEF) was 58.6% (52.1–65.8%). The median values of left ventricular end-diastolic volume were 159 mL (IQR: 133–186 mL) and of left ventricular end-systolic volume 61 mL (IQR: 51–79.8 mL), while the median respective right ventricular volumes were 147 mL (IQR: 126.8–186 mL) and 65 mL (IQR: 47–80 mL). The median stroke volume was 91.7 mL (IQR: 79–106.2 mL), the median cardiac output was 6.3 L/min, (IQR: 5.3–7.6 L/min) and the median left ventricular mass was 118 g (IQR: 100.7–147.5 g).

Hypokinesia was observed in 12 patients (13.6%). Late gadolinium enhancement (LGE) was observed in all patients, mostly localized in the subepicardial (67.1%) and midcardial (25%) layers, followed by transmural (5.7%) involvement and the subendocardial (2.3%) layer of the myocardium. Early gadolinium enhancement was found in 22 patients also affecting the subepicardial (19.3%) and midcardial (10.2%) layers, while it was generally absent in the rest of the myocardium. Oedema was found in 39 patients affecting the subepicardial (35.2%) and midcardial (5.7%) layers, with 8% of the patients having transmural involvement. The localization of the most prominent findings according to the American Heart Association segmentation can be seen in

**Figure 2** LVEF distribution on admission. Categorization of patients into three categories depending on the LVEF on admission: < 40%, 40–49%, and  $\geq 50\%$ . LVEF, left ventricular ejection fraction.

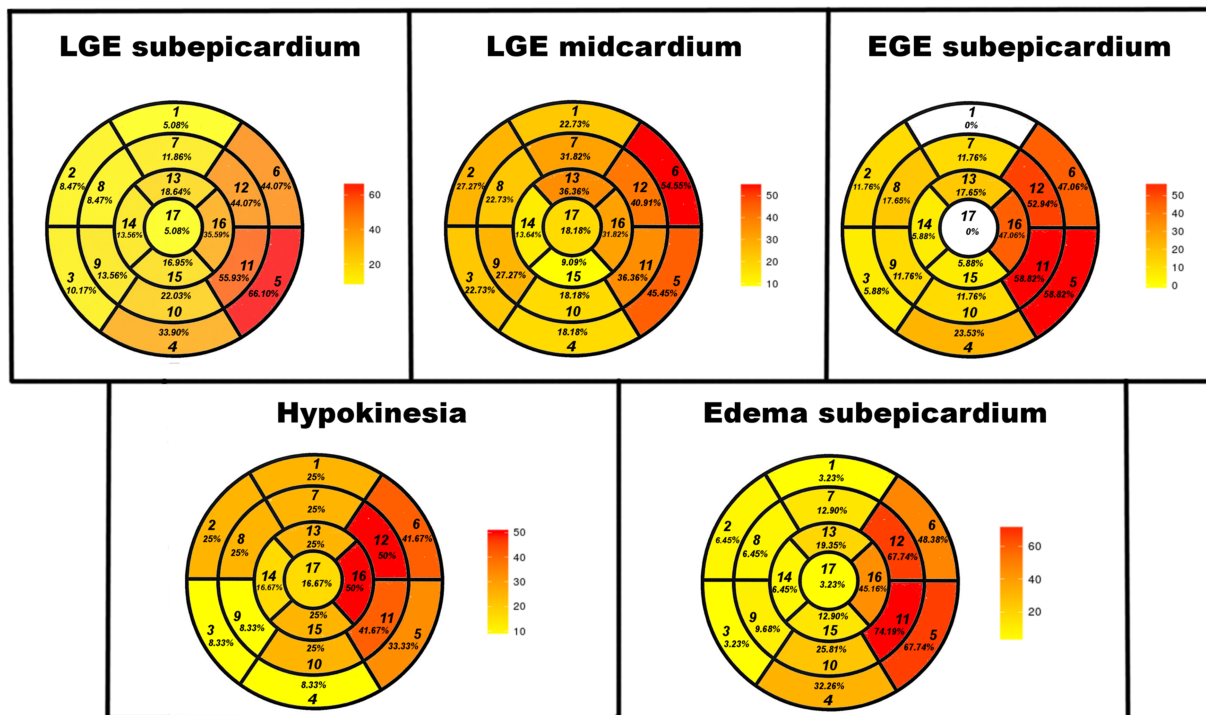


**Figure 3** Individual patient LVEF change during hospitalization. LVEF change during hospitalization on an individual patient basis. LVEF, left ventricular ejection fraction.



**Figure 4** Localization of CMR findings according to the AHA segmentation. Localization of LGE, EGE, hypokinesia, and oedema according to the AHA segmentation on the layers most frequently affected. AHA, American Heart Association; CMR, cardiac magnetic resonance; EGE, early gadolinium enhancement; LGE, late gadolinium enhancement.

### CMR characteristics



**Figure 4.** Mild pericardial effusion was revealed in 22 patients (25%). Pleural effusion and underlying lung disorder were rarely reported.

#### Biomarkers

**Inflammatory markers** C-reactive protein levels were  $2 \times$  ULN (IQR:  $0.5\text{--}5.2 \times$  ULN) on admission (with 58.25% of



the patients having an elevated value) and  $0.6 \times \text{ULN}$  (IQR:  $0.2\text{--}1.9 \times \text{ULN}$ ) on discharge and peaked at  $2.5 \times \text{ULN}$  (IQR:  $0.5\text{--}7.6 \times \text{ULN}$ ). Erythrocyte sedimentation rate (ESR) was  $25 \text{ mm/h}$  (IQR:  $8.25\text{--}42 \text{ mm/h}$ ) on admission and  $20 \text{ mm/h}$  (IQR:  $13\text{--}36.5 \text{ mm/h}$ ) on discharge.

**Cardiac troponins and N-terminal pro-brain natriuretic peptide levels** Troponin levels were registered as either regular troponin (Tn) or high-sensitivity troponin (hs-Tn). Tn levels on admission were  $45.8 \times \text{ULN}$  (IQR:  $6.9\text{--}86 \times \text{ULN}$ ), while hs-Tn levels were  $16.9 \times \text{ULN}$  (IQR:  $5.1\text{--}38.2 \times \text{ULN}$ ). These levels changed significantly during the course of the disease reaching their peak at  $72.6 \times \text{ULN}$  (IQR:  $19.1\text{--}107.8 \times \text{ULN}$ ,  $P < 0.001$ ) and  $18.2 \times \text{ULN}$  (IQR:  $9.7\text{--}47.5 \times \text{ULN}$ ,  $P = 0.001$ ) and being generally normalized on discharge at  $1.2 \times \text{ULN}$  (IQR:  $0.3\text{--}5.8 \times \text{ULN}$ ,  $P < 0.001$ ) and  $0.8 \times \text{ULN}$  ( $0.2\text{--}2.9$ ,  $P < 0.001$ ), respectively. A relatively same course was followed by NT-proBNP levels, being on admission at  $7.3 \times \text{ULN}$  (IQR:  $2.9\text{--}40.6 \times \text{ULN}$ ) and on discharge at  $1.7 \times \text{ULN}$  (IQR:  $1\text{--}2.2 \times \text{ULN}$ ,  $P < 0.01$ ). The rest of the collected cardiac enzymes, among other biochemical findings, are described in *Table 2* and shown in *Figure 5*.

### Serological findings

The most commonly identified pathogens were cytomegalovirus (CMV) (12 positive out of 61 samples—19.7%) and Epstein–Barr virus (EBV) (12 positive out of 56 samples—21.4%). Other pathogens were rarely isolated. In select cases,

**Table 2** Biochemical markers included in the Registry

	Unit	Median (IQR)	P
Tn admission	$\times \text{ULN}$	45.8 (6.9–86)	$< 0.001$
Tn peak	$\times \text{ULN}$	72.6 (19.1–107.8)	
Tn discharge	$\times \text{ULN}$	1.2 (0.3–5.8)	
hs-Tn admission	$\times \text{ULN}$	16.9 (5.1–38.2)	$< 0.001$
hs-Tn peak	$\times \text{ULN}$	18.2 (9.7–47.5)	
hs-Tn discharge	$\times \text{ULN}$	0.8 (0.2–2.9)	
CPK admission	$\times \text{ULN}$	2.1 (1.1–3.6)	$< 0.001$
CPK peak	$\times \text{ULN}$	2.3 (1.3–4.8)	
CK-MB admission	$\times \text{ULN}$	11.3 (4.8–16.8)	$< 0.001$
CK-MB peak	$\times \text{ULN}$	12.8 (5.8–22.9)	
AST admission	$\times \text{ULN}$	1.5 (0.9–2.5)	$< 0.001$
AST peak	$\times \text{ULN}$	1.8 (1.2–3)	
ALT admission	$\times \text{ULN}$	1.2 (0.8–1.9)	$< 0.001$
ALT peak	$\times \text{ULN}$	1.4 (0.9–2.5)	
LDH admission	$\times \text{ULN}$	1.3 (1–1.7)	$< 0.001$
LDH peak	$\times \text{ULN}$	1.6 (1.2–2.1)	
C-reactive protein admission	$\times \text{ULN}$	2 (0.5–5.2)	$< 0.001$
C-reactive protein peak	$\times \text{ULN}$	2.5 (0.5–7.6)	
C-reactive protein discharge	$\times \text{ULN}$	0.6 (0.2–1.9)	
ESR admission	mm/h	25 (8.25–42)	$< 0.05$
ESR discharge	mm/h	20 (13–36.5)	
NT-proBNP admission	$\times \text{ULN}$	7.3 (2.9–40.6)	$< 0.01$
NT-proBNP discharge	$\times \text{ULN}$	1.7 (1–2.2)	

ALT, alanine aminotransferase; AST, aspartate aminotransferase; CK-MB, creatine kinase-muscle/brain; CPK, creatine phosphokinase; ESR, erythrocyte sedimentation rate; hs-Tn, high-sensitivity troponin; LDH, lactate dehydrogenase; NT-proBNP, N-terminal pro-brain natriuretic peptide; Tn, troponin; ULN, upper limit of normal.

on the basis of presenting symptoms, patients underwent further investigation for autoimmune diseases, which proved negative in all patients.

## Second-level investigations

### Coronary angiography

Coronary angiography was performed on 36 patients (24.7%), while coronary computed tomography angiography was performed on four patients. Given the observational nature of this study, no recommendations were given to the centres for performing coronary angiographies. Those performed were done so upon the respective medical teams' discretion according to each patient's risk factors and ventricular systolic function. No significant stenoses were detected in any of the patients.

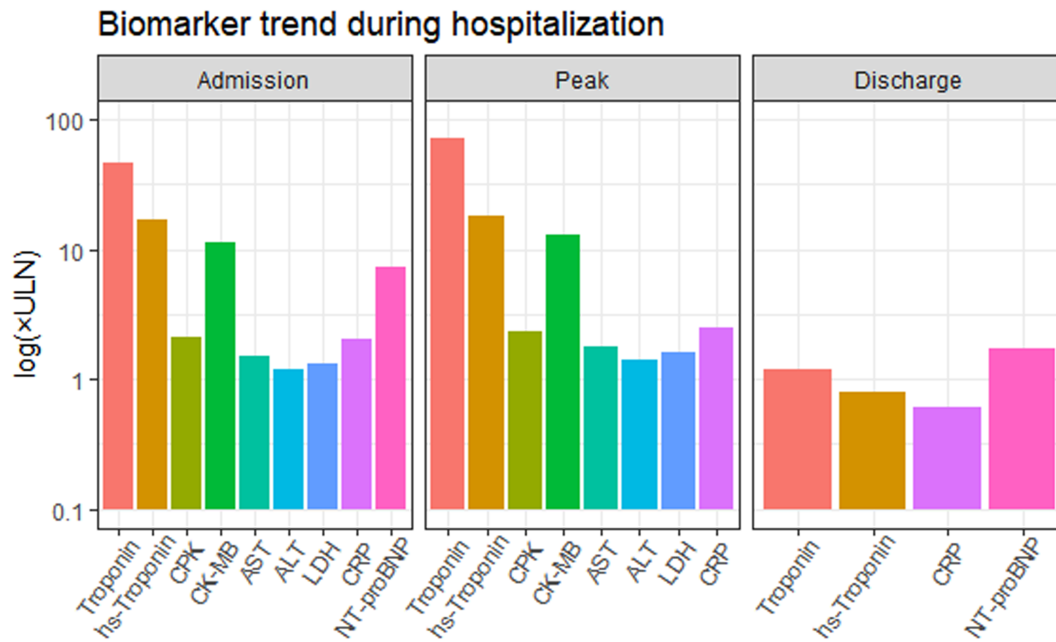
### Endomyocardial biopsy

Endomyocardial biopsy (EMB) was performed on 11 patients (7.5%) along with PCR for common pathogens. The EMBs were performed in three hospitals. The first one is the only heart transplant centre in Greece performing dozens of EMBs annually mostly in heart transplant recipients and new-onset cardiomyopathies with ~12 of them annually being for myocarditis workup. The other two are major university hospitals performing around five EMBs annually each. The criteria used for performing EMB were (i) reduced EF at admission, (ii) recurrent myocarditis, (iii) development of sustained ventricular tachycardia, and (iv) suspicion for underlying systemic disease (amyloidosis, sarcoidosis, eosinophilic myocarditis, etc.). In total, only three patients had a positive sample (two for parvovirus B19 and one for human herpesvirus-6).

## Management of myocarditis

Pharmaceutical options for the treatment of myocarditis include standard heart failure treatment and immunomodulatory/immunosuppressive agents. Regarding conventional heart failure treatment, 105 patients (71.9%) received beta-blockers, 61 (41.8%) received angiotensin-converting enzyme (ACE) inhibitors, 58 (39.7%) received both, 4 (2.7%) received angiotensin receptor blockers, 13 (8.9%) received mineralocorticoid receptor antagonists (MRAs), and 8 (5.5%) received loop diuretics. When separating the population in patients with normal LVEF during hospitalization (Group A,  $n = 94$ ) or in patients who experienced an impaired LVEF  $< 50\%$  during hospitalization (Group B,  $n = 28$ ), we recognized that seven out of 10 patients in both groups received a beta-blocker (74.5% vs. 71.4% respectively), 38.3% in Group A vs. 57.1% in Group B received an ACE-I, and 3.2% in Group A vs. 32.1% in Group B received an MRA. Out of six patients who presented with acute heart failure requiring inotrope administration, three

**Figure 5** Biomarker trend during hospitalization. Levels of biomarkers during hospitalization. Note that a logarithmic scale is used for better visualization of the values. ALT, alanine aminotransferase; AST, aspartate aminotransferase; CK-MB, creatine kinase-muscle/brain; CPK, creatine phosphokinase; hs-troponin, high-sensitivity troponin; LDH, lactate dehydrogenase; NT-proBNP, N-terminal pro-brain natriuretic peptide; ULN, upper limit of normal.



further required mechanical circulatory support, specifically intra-aortic balloon pump or extracorporeal life support system, and one of them unfortunately died. Corticosteroids were prescribed to two patients following a virus negative EMB result. No patients received any kind of antibiotic treatment owing to the assumed viral aetiology of the disease.

## Discussion

This analysis focused mainly on the clinical presentation and in-hospital management of myocarditis patients in Greece with the aim to provide useful insights to physicians dealing with the disease as well as to highlight similarities or differences to already published information.

According to our results, a typical myocarditis patient in Greece is a young man without traditional cardiovascular risk factors but with a recent—often respiratory—infection presenting with acute coronary-like syndrome. Presentation usually occurs in the winter months. ECG findings are non-specific, most commonly being repolarization abnormalities. Echocardiography reveals an EF at the lower end of normal range, occasionally with regional wall motion abnormalities. Laboratory findings typically include elevated inflammatory markers (C-reactive protein and ESR) and elevated cardiac enzymes and NT-proBNP levels. Unfortunately, there are

not enough data to identify common pathogens, with CMV and EBV being most frequently isolated with serology.

Our findings are mostly consistent with those reported in literature. Specifically, the initial presentation of chest pain being the most common, followed by dyspnoea, is consistent with most studies.<sup>4–7</sup> However, fever was not always reported,<sup>6</sup> in contrast to our analysis where fever was always present regardless of the type of the infection. ECG findings on admission consisted mainly of non-specific repolarization abnormalities, while echocardiographic findings revealed mainly regional hypokinesia, which is consistent with other studies' findings.<sup>5,6,8</sup> Atrial fibrillation was associated with reduced LVEF, as has been reported in the literature<sup>9</sup>; however, it was observed in only two patients in our registry. In addition, repeated evaluation of cardiac function during hospitalization may be necessary because LVEF may change in one-fourth of patients. Coronary angiography was performed on 27.1% of the patients overall, which is similar to the usually reported rates.<sup>5</sup>

EMB was performed on a selective basis (11 patients out of 146), resulting in few isolated pathogens (only in three patients). This is presumably due to the low number of centres properly equipped for conducting EMBs. As a result, it is often easier to settle for serological results rather than coordinate transportation to a tertiary centre with expertise in EMB in contrast to the recommendations by the ESC position statement. As such, we were not able to confirm our previous findings regarding the prevalence of infectious agents in EMB

samples where herpesvirus and chlamydia were found to be the most common pathogens, which can be attributed to the different study populations (patients with recent-onset dilated cardiomyopathy with a history of recent infection).<sup>10</sup>

A significant proportion of our patients (61%) underwent CMR, a finding that highlights the major role of CMR for the diagnosis of myocarditis in the acute setting.<sup>4,5</sup> Even in the setting of myocarditis with preserved EF, different patterns of LGE presentation were associated with different outcomes as shown by the ITAMY study.<sup>11</sup> Specifically, the presence of LGE in the midwall layer of the anteroseptal wall was associated with worse prognosis.

The long-term management of acute myocarditis with respect to minimizing the possibility towards progression to dilated cardiomyopathy is a controversial issue. Although patients with reduced EF (< 40%) should be treated according with the HF guidelines consisting mainly of beta-blockers, ACE-Is, and MRAs when it comes to drug therapy, very scarce data exist on the administration of beta-blockers in patients with preserved EF or mid-range EF.<sup>12</sup> In our sub-population with mid-range or reduced LVEF, 71.4% received a beta-blocker, 57.1% received an ACE-I, and 32.1% received an MRA at discharge. It is important to note that the decision for MRA administration seems to be based more on the presence of reduced LVEF rather than the extent of LGE.

A limitation in our study is the registration of a low—as yet—number of patients with severely reduced LVEF as can be seen in *Figure 2*. We expect that there will be a fairer representation of this population with the addition of more patients until the completion of the Registry. In addition, this study does not include patient follow-up analysis, which would permit risk estimation for myocarditis recurrence or heart failure development.

In the recent years, there have been published results from similar registries by centres in the USA<sup>13</sup> and Italy.<sup>14</sup> The

results from the USA registry were consistent with our findings when it comes to the descriptive analysis; however, no data were included from the clinical or imaging characteristics of the patient population. The results from the Multicenter Lombardy Registry are also consistent with our study, but the investigators have included follow-up data to their analysis.

The MYKKE registry, a myocarditis registry in children and adolescents, showed a clear relationship of impaired LVEF and younger age with a more severe course of disease.<sup>15</sup> Our study aims to provide prognostic tools for adult patients with the addition of follow-up data in the near future.

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## Conflict of interest

None declared.

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