Prevalence, Characteristics, and Outcomes of COVID-19 Associated Acute Myocarditis

Enrico Ammirati and Laura Lupi et al.

SUPPLEMENTAL MATERIALS

SUPPLEMENTAL METHODS

Study Population

Centers were queried by E.A. and M.M. regarding cases of myocarditis associated with COVID-19. Patients were identified locally through the International Classification of Diseases, Ninth Revision Clinical Modification (ICD9-CM) diagnostic codes (422.0; 422.91; 422.92; 422.93; 422.99; 429.89) or Tenth Revision (ICD10-CM) codes (140.0; 140.8; 140.9; 141.1; 151.4) recorded in hospital discharge forms, or through review of clinical records and identification of patients with positive cardiac MRI and/or histology.

Comparator group of patients with non-COVID-19 myocarditis:
Among the 443 patients in the Lombardy registry, we excluded patients below 10 years of age (N=7), or with systemic disease (i.e. HIV or systemic autoimmune disorders; N=10), or specific non-lymphocytic myocarditis (i.e. giant cell myocarditis and eosinophilic myocarditis; N=15), thus we considered 411 patients with AM.

Data collection and definitions

Symptoms related with COVID-19 (fever, dyspnea and cough) and cardiovascular symptoms (New York Heart Association [NYHA] class, chest pain, palpitations and syncope) were collected. Data obtained from venous blood samples and arterial samples for blood gas analysis were considered. To allow for comparison, troponin values were normalized to the site and assay-specific upper reference limits (URL). The ratio between oxygen partial pressure at arterial gas analysis and fraction of inspired oxygen (PaO_2/FiO_2) was obtained. Electrocardiographic and transthoracic echocardiographic data were collected. We also analyzed medications used during the hospitalization for the treatment of cardiovascular complications and COVID-19.

Statistical analysis

The first uncertainty is associated to the different inclusion criteria to define a COVID-19 AM case in a medical center. To account for it, we defined a lower prevalence estimate (LPE), because it assesses a lower bound of the prevalence, it means that this estimation is based on a clinically restrictive criteria including just the 54 cases of definite/probable COVID-19 associated AM. We also defined an upper prevalence estimate (UPE), because it assesses an upper bound of the prevalence, it means that this estimation is based on a clinically expanded criteria including all the 97 cases of definite/probable/possible COVID-19 associated AM. The definition of LPE or UPE, in respect to a restrictive or expanded inclusion criteria respectively have been used in this study to better quantify the clinical uncertainty by defining an interval inside which the mean prevalence value can oscillate in respect to the different way in which the patients are clinically assessed for inclusion in the 23 centers (**Figure 2A**). Therefore, the LPE and UPE should not be interpreted and do not imply that an unknown correct reference exists between these values, but they aim to express the extent to which statistical uncertainty can affect the estimation of mean prevalence considering different criteria to define the recruited population. However, there is also a second uncertainty that is associated to how the value of mean LPE or UPE can vary because of the exclusion of a medical center from the sample, and accounting for this uncertainty offers a more robust estimation. Hence, approaching this second uncertainty, we included a second method to estimate the boundaries inside which the sample mean prevalence was expected to occur. This was possible by calculating the mean LPE and UPE and their respective CIs by means of leave-one-out procedure (**Figure 2B**). It means that iteratively excluding a medical center from the sample generates 23 different leave-one-out samples (each one composed of 22 centers), and this generates in turn 23 different estimations of mean LPE and mean UPE with the respective 95% CIs. Software package used was MATLAB R2020a.

SUPPLEMENTAL RESULTS

Clinical presentation

Search for respiratory viruses in nasopharyngeal swab other than SARS-COV2 was performed in 26/54 patients (48.1%) and all results were negative. The most frequent symptoms at presentation were chest pain (55.5%) and dyspnea (53.7%). Among associated or prodromal signs, fever was the

most frequent (79.6%). Laboratory exams on admission showed a significant increase of troponin levels with a median of 21-fold above the URL whilst median peak troponin was 56-folds above the URL. The median peak level of NT-proBNP was 6016 ng/L and in those centers using BNP the median peak level was 1702 ng/L. Search for antinuclear antibodies (ANA) to detect autoimmune disorders was performed in 29/54 patients (53.7%): presence of ANA was found in 2 patients (titer 1:160 and 1:320). In one patient systemic lupus erythematosus was suspected.
On first echocardiogram left ventricular ejection fraction (LVEF) was moderately reduced, with a median value of 40% (Q1-Q3: 29-57), and generally the LV was non-dilated with an LV end-diastolic diameter of 49 mm (Q1-Q3: 45-57).

In-hospital medications

Twenty-one patients (38.9%) received inotropic agents or vasopressors, plus 3 patients received an infusion of levosimendan (one patient received only levosimendan while the other two patients received levosimendan in combination with other inotropic/vasopressor agents). The most frequently used agents were dobutamine (29.6%) and norepinephrine (24.1%). Norepinephrine was administered more frequently in AM patients with pneumonia compared with those without pneumonia (39.1 vs. 12.9%, p=0.026). Immunosuppressive agents were administered in 32 patients (59.2%) and no difference were observed between AM with and without pneumonia. Isolated corticosteroids were used in most cases (22/32, 68.7%), in 8/32 patients (25.0%) a combination of corticosteroids and intravenous immunoglobulin (IVIG) or tocilizumab, and in the remaining 2 cases (6.2%) isolated IVIG were administered. Intravenous corticosteroids were the most frequently used immunosuppressive drugs without differences between patients with and without pneumonia, i.e. 43.4% and 48.3%, respectively (p=0.79). At discharge angiotensin converting enzyme inhibitor (ACEi)/angiotensin II receptor blockers (ARB)/angiotensin II receptor neprilysin inhibitors (ARNI), beta-blockers and mineralocorticoid receptor antagonist (MRA) were prescribed in 51.8%, 55.5%, 30.0% of the patients, respectively.

Hospital course and follow-up

Causes of death in 3 patients who died:

Specifically, one patient had a brain hemorrhage 19 days after admission (age 59 years, female, supported on veno-arterial extracorporeal membrane oxygenation and treated with methylprednisolone plus tocilizumab). The other 2 patients died due to septic shock after 17 days (a 58-year-old male, supported on intra-aortic balloon pump plus veno-arterial extracorporeal membrane oxygenation and treated with hydrocortisone) and after 33 days (a 41-year-old female, supported on dobutamine, with an ongoing cancer).

Other in-hospital events:

According to SCAI classification, 2 patients (9.5%) were in stage B (beginning cardiogenic shock), 12 (57.2%) were in stage C (classic cardiogenic shock), and 7 (33.3%) were in stage D/E (deteriorating/extremis) (**Supplemental Table V**). We reported a trend for significance of a shock SCAI D/E in patients with concurrent pneumonia compared with patients without pneumonia (54.5% vs. 10.0%, respectively, p=0.064).

Septic shock occurred in 11 patients (20.4%) with a significant higher incidence in patients with AM and pneumonia compared to those without pneumonia (39.1% vs. 6.4%, p=0.005). Sixteen patients (29.6%) had tachyarrhythmias, mostly atrial fibrillation and non-sustained ventricular tachycardia; 4 patients, all in the group with COVID-19 AM and pneumonia (17.4% vs. 0%, P=0.028) had advanced AVB, needing for temporary pacemaker. Finally, 9 patients in the AM and pneumonia group (39.1%) and 4 patients (12.9%) in the group without pneumonia needed invasive mechanical ventilation (p=0.05); this support was maintained for a median time of 13 days (Q1-Q3: 3-26).

Vaccination after COVID-19 myocarditis:

Of note, 15 out of the 51 COVID19 associated myocarditis survivors (29.4%) received vaccination against SARS-CoV-2 after a median of 8 months (Q1-Q3: 5-14). Among them, 14 patients received a mRNA vaccine: BNT162b2 (Comirnaty, Pfizer Biontech) in 12 cases and mRNA-1273 (Spikevax Moderna) in 2 cases. One patient received viral vector vaccine Vaxzevria (AstraZeneca). There was no evidence of myocarditis recurrence or other side effects. No further information on follow-up is available for the other patients.

Changes in LVEF during hospitalization and follow-up

LVEF by echocardiography improved significantly during hospitalization from a median value of 40% to 55% (N=47; p<0.0001) and this improvement was observed both in patients with AM with pneumonia (p=0.0002) and in those without pneumonia (p=0.004; **Figure 5A-C**). The proportion of patients with LVEF <50% at last echocardiographic examination was similar in patients with AM with pneumonia (5/20, 25.0%) and without pneumonia (9/27, 33.3%, p=0.748). Thirty-three patients (61.1%) underwent a follow-up echocardiogram after discharge. Comparing echocardiographic findings on admission and at last available follow-up (median follow-up 78 days, Q1-Q3: 42-118), there was a significant improvement in LVEF (from a median of 41% to 60%, p<0.001), without significant changes in LV end-diastolic diameter (from a median of 49 mm to 50 mm, p=0.43). Other echocardiographic findings are summarized in the **Supplemental Table VII**.

SUPPLEMENTAL TABLE I. Recruited cases of suspected cases of cute myocarditis from each centers and main reasons for exclusion

Hospital	City; Total number of COVID-19 Hospitalizations	Suspected cases of AM	Definite/ probable cases of AM	Definite/ probable and possible cases of AM	Time period	Main reasons for exclusion								
						Previous Myocardial disease/ Heart transplantation	**Takotsubo**	**Pericarditis**	Cardiac MRI not performed	Cardiac MRI did not confirm the diagnosis	Died without autopsy	No symptoms or troponin elevation	Age >70 years and no Biopsy, Age > 75	CAD not excluded
Niguarda	Milano (Italy) 2035	14	3	9	3/20-3/21	**0**	**2**	**3**	4	1	0	1	0	0
Spedali Civili	Brescia (Italy) 1840	9	5	9	3/20-3/21	**0**	**0**	**0**	0	0	0	0	1	3
Humanitas Mater Domini	Castellanza (Italy) 572	1	1	1	3/20-3/21	**0**	**0**	**0**	0	0	0	0	0	0
Monzino	Milano (Italy) 170	9	3	5	3/20-1/21	**4**	**0**	**0**	0	2	0	0	0	0
San Matteo	Pavia (Italy) 1596	4	2	2	3/20-2/21	**2**	**0**	**0**	0	0	0	0	0	0

Ospedali Riuniti	Ancona (Italy) 640	2	1	2	3/20-11/20	**0**	**0**	**0**	0	0	0	1	0	0
San Raffaele	Milano (Italy) 3500	6	5	5	3/20-3/21	**1**	**0**	**0**	0	0	0	0	0	0
Infermi	Rimini (Italy) 3016	4	1	4	3/20-3/21	**0**	**0**	**0**	0	2	0	0	0	1
Ospedale Civile Modena	Modena (Italy) 1151	1	1	1	3/20-4/21	**0**	**0**	**0**	0	0	0	0	0	0
Ospedale Papa Giovanni	Bergamo (Italy) 3331	3	0	3	3/20-3/21	**0**	**0**	**0**	2	0	1	0	0	0
Nantes University Hospital	Nantes (France) 1472	9	3	8	3/20-1/21	**1**	**0**	**0**	1	2	0	0	2	0
Hopital Pitié-Salpêtrière	Paris (France) 492#	10	6	10	3/20-3/21	**0**	**0**	**0**	3	0	1	0	0	0
Foch	Paris (France) 1437	8	2	8	3/20-1/21	**0**	**0**	**0**	0	2	0	4	0	0
Hopital Cardiologique Louis Pradel	Lyon (France) 11000	4	4	4	3/20-3/21	**0**	**0**	**0**	0	0	0	0	0	0
Antwerp University Hospital	Antwerp (Belgium) 350	2	2	2	3/20-1/21	**0**	**0**	**0**	0	0	0	0	0	0
Clinico Valladolid	Valladolid (Spain) 2698	3	3	3	3/20-6/20	**0**	**0**	**0**	0	0	0	0	0	0

Hospital Universitario De La Princesa	Madrid (Spain) 3474	1	1	1	3/20-3/21	**0**	**0**	**0**	0	0	0	0	0	0
Bellvitge University Hospital	Hospitalet De Llobregat (Spain) 2995	1	1	1	3/20-3/21	**0**	**0**	**0**	0	0	0	0	0	0
King's College Hospital	London (UK) 5219	4	2	3	3/20-3/21	**1**	**0**	**0**	0	1	0	0	0	0
Helsinki University Hospital	Helsinki (Finland) 1667	3	2	3	3/20-3/21	**0**	**0**	**0**	0	0	1	0	0	0
University of California San Diego	San Diego (USA) 1490	1	0	0	2/20-2/21	**1**	**0**	**0**	0	0	0	0	0	0
University of Texas Southwestern Medical Center	Dallas (USA) 1622	2	2	2	2/20-3/21	**0**	**0**	**0**	0	0	0	0	0	0
Parkland Health & Hospital System	Dallas (USA) 5196	11	4	11	2/20-3/21	**0**	**0**	**0**	4	2	1	0	0	0
TOTAL	**23 centers 56963**	**112**	**54**	**97**		**10**	**2**	**3**	14	12	4	6	3	4

* Definitive/probable plus possible cases of AM included all suspected cases with the exclusion of patients with a previous diagnosis of ischemic heart disease or cardiomyopathy without histologic evidence of active myocarditis (N=12), patients with final diagnosis of Takotsubo cardiomyopathy (N=2), or pericarditis (N=3) on cardiac MRI. This group included the definitive/probable cases plus possible cases.

#Data from the Hopital Pitié-Salpêtrière refers only to COVID19 patients admitted to the intensive care unit, and not to the overall patients hospitalized in this hospital.

AM indicates acute myocarditis; CAD, coronary artery disease; MRI, magnetic resonance imaging.

SUPPLEMENTAL TABLE II. Characterization of each patient with COVID-19 acute myocarditis with (w/) or without (w/o) pneumonia complicated by cardiogenic shock.

ID	Age, Sex, Origin	W/ or W/o Pneumonia	Clinical presentation/ peak troponin*	First LVEF Lowest LVEF	EMB/ Angio/ CMRI	Time to shock (days)	t-MCS types days on support	Inotropes Types Days on inotropes	Days on MV	Immunosuppression	Outcome	LVEF (last)	Notes
1	20 yo M Italy	w/o	Abdominal pain, diarrhea, nausea/ x 14	40% 40%	Y (lymph)/ 0/ 0	2 d	No	NE: 0.25† E: 0.07 NA	0 d	No	Alive	48%	Concurrent sepsis
2	53 yo F Italy	w/o	Fatigue/ x 149	40% 40%	No/ No CAD/ STIR+ LGE+ on CMRI	1 d	No	Dobu: 4 3 d	0 d	Methylprednisolone 1 mg/kg X 3 d	Alive	62%	-
3	18 yo M France	w/o	Chest pain, dyspnea/ x 63	45% 45%	Y (lymph)/ No CAD/ STIR+ LGE+ on CMRI	3 d	VA-ECMO Impella 6 d	NE: NA 4 d	4 d	Methylprednisolone 1 g X 3 d, then 1 mg/kg	Alive	55%	-
4	16 yo M France	w/o	Dyspnea, diarrhea, nausea/ x180	20% 20%	No/ No CAD /LGE+ T1map+ T2map+ On CMRI	0	No	NE: 0.5 Dobu: 8 4d	5 d	Methylprednisolone 2 mg/kg x 3 days, then 1 mg/kg + IVIG 30 g x 4 days	Alive	60%	-
5	19 yo M France	w/o	Dyspnea, diarrhea/ x17	15% 15%	No/ No CAD/ T1map+ T2map+ On CMRI	0	No	NE: 0.18 Dobu: 5 4 d	0 d	No	Alive	47%	-
6	58 yo M Italy	w/	Dyspnea/ x67	25% 25%	Y (macrophages)/ No CAD/ 0	0	VA-ECMO IABP 6 d	NE: 0.2 Vasopressin : 1.6 U/h Dobu: 3 18 d	18 d	Hydrocortisone 200 mg	Dead (septic shock)	55%	Associated ARDS
7	30 yo M Italy	w/o	Dyspnea, diarrhea/	35% 25%	0/ No CAD/ LGE+	0	No	Dobu: 3 6 d	0 d	No	Alive	66%	Concurrent sepsis

			X247		Pericardial eff. on CMRI								
8	45 yo M Italy	w/	Dyspnea, chest pain, diarrhea, nausea x3	34% 34%	Y (lymph)/ No CAD/ T1map+ On CMRI	0	VA-ECMO IABP 6 d	NE: HD E: HD 5 d	0 d	No	Alive	45%	-
9	64 yo M Italy	w/o	Syncope, OHCA/ x35	15% 15%	Y (lymph)/ Concurrent CAD/ STIR+ LGE+ T1map+ T2map+ on CMRI	0	No	NE: HD E: HD 1 d	3 d	No	Alive	37%	-
10	20 yo M Belgium	w/	Dyspnea, chest pain, diarrhea, nausea x10	35% 35%	0/ No CAD/ LGE+ T1map+ On CMRI	4 d	No	Dobu: 2.5 3 d	0 d	Methylprednisolone 160 mg x 2d	Alive	62%	Concurrent sepsis
11	41 yo M Spain	w/	Diarrhea/ x1321	10% 10%	0/ No CAD/ LGE+ STIR+ On CMRI	13 d	IABP 14 d	NE: 2.5 Dobu: 7 NA	2 d	Methylprednisolone 1 g x 3d	Alive	30%	Concurrent sepsis Associated ARDS
12	59 yo F Spain	w/	Dyspnea/ x1250	32% 25%	Y (lymph) / No CAD / 0	8 d	VA-ECMO 5 d	NE: 2.1 Dobu: 10 14 d	13 d	Methylprednisolone 500 mg x 3 d + Tocilizumab 6 mg/kg (1 dose)	Dead (brain hemorrhage)	25%	Associated ARDS, Active lymphoma
13	44 yo M Spain	w/	Dyspnea, chest pain, diarrhea/ x53	15% 5%	Y (neg) / No CAD / STIR+ LGE+ T1map+ Pericardial eff. on CMRI	0 d	VA-ECMO IABP 7d	Dobu: 7 12 d	8 d	Methylprednisolone 1 g	Alive	60%	Associated ARDS, t-PM for advanced AV block
14	26 yo F Spain	w/	Dyspnea, chest pain, syncope, nausea/ x323	15% 8%	Y (lymph)/ No CAD/ STIR+ T1map+ T2map+ on CMRI	0 d	VA-ECMO CentriMag 31 d	Dobu: 26 NE: 0.5 NA	81 d	Methylprednisolone 500 mg x 3 d + Tocilizumab 6 mg/kg (1 dose)	Alive	63%	Associated ARDS, Concurrent sepsis, t-PM for advanced AV block
15	41 yo F France	w/	Dyspnea/ x245	30% 20%	Y (lymph)/ No CAD/ 0	13 d	No	NE: 3.5 Dobu: 5	22 d	No	Dead (septic shock)	45%	Associated ARDS, Concurrent sepsis, Active

								11 d					Cancer
16	31 yo F France	w/	Dyspnea, chest pain, diarrhea, nausea/ x434	30% 10%	0/ No CAD/ LGE+ on CMRI	0 d	VA-ECMO 6 d	NE: 0.17 Dobu: 7 5 d	7 d	Dexamethasone 6 mg/kg x 6 d	Alive	60%	Concurrent sepsis
17	34 yo F France	w/o	Dyspnea, chest pain/ x861	36% 35%	Y (lymph)/ 0/ STIR+ LGE+ on CMRI	1 d	IABP 3 d	Dobu: 5 3 d	0 d	Dexamethasone 6 mg/kg x 6 d	Alive	55%	-
18	48 yo F UK	w/	Chest pain/ x126	60% 60%	0/ 0/ LGE+ T2map+ Pericardial eff. on CMRI	2 d	No	NE: NA Milrinone: NA 2 d	0 d	No	Alive	60%	Previous myocarditis, Concurrent sepsis
19	51 yo F USA	w/o	Diarrhea, chest pain, nausea/ x319	24% 24%	0/ No CAD/ LGE+ T1map+ T2map+ on CMRI	0 d	No	Dobu: 2 5 d	0 d	Methylprednisone 1 g x 2d, then 500 mg x 3d	Alive	24%	-
20	35 yo M USA	w/o	Chest pain, nausea x40	18% 18%	Y (lymph)/ 0/ 0	0 d	IABP Impella 9 d	E: 0.12 Milrinone 0.4 Dobu: 7.5 16 d	16 d	Methylprednisone 1 mg/kg x 5d + IVIG 1 g/kg x 2d	Alive	43%	-
21	33 yo M France	w/	Chest pain, diarrhea x993	20% 20%	0/ No CAD/ LGE+ T2map+ on CMRI	0 d	No	NE: 0.77 Dobu 10 2 d	0 d	Prednisone 1 mg/kg x 10 d + IVIG 2 g/kg x 3 d	Alive	60%	-

* Indicates the increase of the troponin above the upper reference limit (URL); for example, x14 indicates an increase of troponin 14-folds above the URL.

† Dose of inotropic agents or vasopressors expressed ad µg/kg/min. NA indicates that dosage or the duration of administration of these drugs is not available. HD indicates high dose.

Abbreviations: Angio, coronary angiography or coronary angio computed tomography; AV, atrioventricular; ARDS, acute respiratory distress syndrome; CAD, coronary artery disease; CMRI, cardiac magnetic resonance imaging; Dobu, dobutamine; E, epinephrine; eff., effusion; EMB, endomyocardial biopsy; HD; IABP, intra-aortic balloon pump; ID, identity; IVIG, intravenous immunoglobulins; LGE, late gadolinium enhancement; LV, left ventricular/ventricle; LVEF, left ventricular ejection fraction; lymph, lymphocytic myocarditis; Map, Mapping; MV, mechanical ventilation; NA, not available; NE, norepinephrine; neg, negative (no active myocarditis); OHCA, out-of-hospital cardiac arrest; STIR, short tau inversion recovery; t-MCS, temporary mechanical circulatory support; t-PM, temporary pace-maker; VA-ECMO, veno-arteriosus extracorporeal membrane oxygenator; significance; Y, yes; yo, year-old.

SUPPLEMENTAL TABLE III. Endomyocardial biopsies findings in patients admitted with COVID-19 associated acute myocarditis with pneumonia or without pneumonia.

	COVID-19 Acute myocarditis with available EBM			
	ALL	**WITH pneumonia**	**WITHOUT pneumonia**	**P-value**
Overall n	17	10	7	
$CD3^+$ T-lymphocytes ≥ 7 cells/mm^2, n (%)	14 (82.3)	7 (70.0)	7 (100.0)	0.228
Diffuse inflammatory cells without infiltrates, n (%)	11 (64.7)	5 (50.0)	6 (85.7)	0.304
Moderate inflammatory cells without infiltrates, n (%)	6 (35.3)	5 (50.0)	1 (14.3)	0.304
No fibrosis, n (%)	12 (70.6)	7 (70.0)	5 (71.4)	1.000
Mild fibrosis, n (%)	4 (23.5)	2 (20.0)	2 (28.6)	1.000
Moderate fibrosis, n (%)	1 (5.9)	1 (10.0)	0 (0)	1.000
Viral PCR search performed, n (%)	15 (88.2)	9 (90.0)	6 (85.7)	1.000
Viral PCR search positive, n (%)	4 (26.7)*	3 (33.3)*	1 (16.7)*	0.604

Abbreviations: EBM, endomyocardial biopsy; PCR, polymerase chain reaction

* the proportions of patients were calculated on the number of patients with available data.

SUPPLEMENTAL TABLE IV. Baseline cardiac magnetic resonance imaging findings in patients with COVID-19 myocarditis.

	Cardiac Magnetic Resonance Imaging in COVID-19 myocarditis			
	ALL	**WITH pneumonia**	**WITHOUT pneumonia**	**P-value**
Overall n	50	20	30	
Non-ischemic myocardial LGE, n (%)	44 (88.0)	18 (90.0)	26 (86.7)	1.000
Myocardial edema on T2W images, n (%)	26 (53.1)*	10 (52.6)*	16 (53.3)	1.000
Increased myocardial native T1, n (%)	29 (90.6)*	13 (92.8)*	16 (88.9)*	1.000
Increased myocardial native T2, n (%)	31 (96.9)*	13 (100)*	18 (94.7)*	1.000
LVEF, %, median (Q1-Q3)	55 (44-62)	54 (48-64)	57 (43-62)	0.684
LVEDVi, mL, median (Q1-Q3)	74 (65-93)	70 (64-89)	78 (67-95)	0.276
RVEF, %, median (Q1-Q3)	56 (43-60)	57 (49-60)	54 (42-59)	0.312
RVEDVi, mL, median (Q1-Q3)	79 (63-94)	73 (64-91)	79 (62-95)	0.529
Cardiac mass index, g/m2, median (Q1-Q3)	66 (50-91)	54 (45-95)	71 (57-90)	0.132
Regional wall motion abnormalities, n %)	26 (52.0)	8 (40.0)	18 (60.0)	0.248
Pericardial effusion, n (%)	18 (36.0)	5 (25.0)	13 (43.3)	0.237
Time interval between hospital admission and cardiac MRI, days, median (Q1-Q3)	8 (3-15)	12 (6-27)	5 (3-10)	**0.010**

Abbreviations: MRI, magnetic resonance imaging; LGE, late gadolinium enhancement; T2W, T2 weighted, LVEF, left ventricular ejection fraction; LVEDVi, left ventricular end-diastolic volume index; RVEF, right ventricular ejection fraction; RVEDVi, right ventricular end-diastolic volume index.

* The proportions of patients were calculated on the number of patients with available data.

SUPPLEMENTAL TABLE V. Severity of shock presentation according to SCAI classification in patients with acute myocarditis associated with pneumonia and patients without pneumonia.

Severity of shock	All	COVID-19 associated AM With Pneumonia	COVID-19 associated AM Without Pneumonia	
Overall	21	11	10	
Shock SCAI A	0 (0)	0 (0)	0 (0)	
Shock SCAI B	2 (9.5)	1 (9.1)	1 (10.0)	1
Shock SCAI C	12 (57.2)	4 (36.3)	8 (80.0)	0.080
Shock SCAI D/E	7 (33.3)	6 (54.5)	1 (10.0)	0.064

SUPPLEMENTAL TABLE VI. Main characteristics and in-hospital events between COVID-19 associated acute myocarditis (AM) and non-COVID-19 AM derived from the Lombardy registry.

	COVID-19 associated AM	**Non-COVID-19 AM (Lombardy registry)**	**P-value**
Overall n	54	411	
Demographics			
Age, years, median (Q1-Q3)	38 (25-53)	34 (24-42)	**0.02**
Female, n (%)	21 (38.9)	74 (18.0)	**0.001**
Ethnicity - Non-Hispanic white, n (%) - Hispanic white, n (%) - Black, n (%)	 39 (76.5)* 4 (7.8)* 8 (15.7)*	 389 (94.6)* 7 (1.7)* 15 (3.6)*	 **<0.0001** **0.03** **0.002**
Main presenting symptoms			
Dyspnea, n (%)	29 (53.7)	61 (14.8)	**<0.0001**
Chest pain, n (%)	30 (55.5)	368 (89.5)	**<0.0001**
Clinical presentation			
Cardiogenic shock/fulminant presentation, n (%)	21 (38.9)	34 (8.3)	**<0.0001**
Diagnostic evaluations			
Cardiac MRI, n (%)	50 (92.6)	397 (96.6)	0.14
Endomyocardial biopsy, n (%)	17 (31.5)	38 (9.2)	**<0.0001**
- Diffuse inflammatory infiltrates (Positive/borderline Dallas criteria), n (%)	6/17 (35.3)	27/38 (71.1)	**0.018**
- $CD3^+$ T-lymphocytes ≥ 7 cells/mm^2, n (%)	14/17 (82.3)	35/38 (92.1)	0.36
- Diffuse inflammatory cells without infiltrates, n (%)	11/17 (64.7)	31/38 (81.6)	0.19

Coronary CT/coronary angiography, n (%)	34 (63.0)	189 (46.0)	**0.02**
Echocardiography on admission			
LVEF, %, median (Q1-Q3)	40 (29-57)	55 (50-60)	**<0.0001**
In-hospital events			
Overall mortality	3 (5.5)	5 (1.2)	0.054
Need for t-MCS, n (%)	10 (18.5)	21* (5.1)	**0.001**
Patients who died or required t-MCS	11 (20.4)	23* (5.6)	**0.0007**

Abbreviations: CT, computed tomography; LVEF, left ventricular ejection fraction; MRI, magnetic resonance imaging; t-MCS, temporary mechanical circulatory support.

*Among the t-MCS we included also 1 patient who received a long-term left ventricular assist device.

SUPPLEMENTAL TABLE VII. Echocardiographic findings on hospital admission and at follow-up in 33 patients with COVID-19 myocarditis. The median time interval between the two echocardiographic examinations was 78 days (Q1-Q3: 42-118).

	Echocardiographic findings in COVID-19 myocarditis		
	HOSPITAL ADMISSION	**FOLLOW-UP**	**P-value**
Overall n	33	33	
LVEF, %, median (Q1-Q3)	41 (27-57)	60 (55-63)	**<0.001**
LVEDD, mm, median (Q1-Q3)	49 (45-58)	50 (46-52)	0.425
LVEDVi, mL, median (Q1-Q3)	49 (42-56)	51 (42-59)	0.401
Diastolic dysfunction on transmitral inflow pattern, n (%)	17 (56.7)*	11 (36.7)*	0.195
RV TAPSE < 17mm, n (%)	10 (32.2)*	0 (0)	**<0.001**
PASP, mmHg, median (Q1-Q3)	26 (25-39)	25 (25-29)	**0.018**
More than moderate MR, n (%)	1 (3.1)*	0 (0)	1.000
Dilated inferior vena cava, n (%)	9 (28.1)*	0 (0)	**0.002**
Pericardial effusion, n (%)	12 (36.4)	3 (9.7)*	**0.017**

Abbreviations: LVEF, left ventricular ejection fraction; LVEDD, left ventricular end diastolic diameter; LVEDVi, left ventricular end diastolic volume idex; RV-TAPSE, right ventricle tricuspid annular plane systolic excursion, PASP, pulmonary arterial systolic pressure; MR, mitral regurgitation.

* the proportions of patients were calculated on the number of patients with available data.

SUPPLEMENTAL VIDEO 1 LEGEND. Cardiac magnetic resonance imaging (MRI) of a patient with COVID-19 associated acute myocarditis (AM) during hospitalization: Four-chamber cine image showing pericardial effusion and preserved global systolic function (left ventricular ejection fraction was 63%).

SUPPLEMENTAL VIDEO 2 LEGEND. Cardiac magnetic resonance imaging (MRI) of a patient with COVID-19 associated acute myocarditis (AM) at 6-month follow up: Four-chamber cine image showing persistent pericardial effusion and preserved global systolic function (left ventricular ejection fraction was 69%).