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Phenotypic Heterogeneity of Fulminant COVID-19–Related Myocarditis in Adults

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ABSTRACT

BACKGROUND Adults who have been infected with SARS-CoV-2 can develop a multisystem inflammatory syndrome (MIS-A), including fulminant myocarditis. Yet, several patients fail to meet MIS-A criteria, suggesting the existence of distinct phenotypes in fulminant COVID-19–related myocarditis.

OBJECTIVES This study sought to compare the characteristics and clinical outcome between patients with fulminant COVID-19–related myocarditis fulfilling MIS-A criteria (MIS-A$^+$) or not (MIS-A$^-$).

METHODS A monocentric retrospective analysis of consecutive fulminant COVID-19–related myocarditis in a 26-bed intensive care unit (ICU).

RESULTS Between March 2020 and June 2021, 38 patients required ICU admission (male 66%; mean age 32 ± 15 years) for suspected fulminant COVID-19–related myocarditis. In-ICU treatment for organ failure included dobutamine 79%, norepinephrine 60%, mechanical ventilation 50%, venoarterial extracorporeal membrane oxygenation 42%, and renal replacement therapy 29%. In-hospital mortality was 13%. Twenty-five patients (66%) met the MIS-A criteria. MIS-A$^-$ patients compared with MIS-A$^+$ patients were characterized by a shorter delay between COVID-19 symptoms onset and myocarditis, a lower left ventricular ejection fraction, and a higher rate of in-ICU organ failure, and were more likely to require mechanical circulatory support with venoarterial extracorporeal membrane oxygenation (92% vs 16%; $P < 0.0001$). In-hospital mortality was higher in MIS-A$^-$ patients (31% vs 4%). MIS-A$^+$ had higher circulating levels of interleukin (IL)-22, IL-17, and tumor necrosis factor-α (TNF-α), whereas MIS-A$^-$ had higher interferon-α2 (IFN-α2) and IL-8 levels. RNA polymerase III autoantibodies were present in 7 of 13 MIS-A$^-$ patients (54%) but in none of the MIS-A$^+$ patients.

CONCLUSION MIS-A$^+$ and MIS-A$^-$ fulminant COVID-19–related myocarditis patients have 2 distinct phenotypes with different clinical presentations, prognosis, and immunological profiles. Differentiating these 2 phenotypes is relevant for patients' management and further understanding of their pathophysiology. (J Am Coll Cardiol 2022;80:299–312)

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ABBREVIATIONS AND ACRONYMS

CMR = cardiac magnetic resonance imaging

ELISA = enzyme-linked immunosorbent assay

EMB = endomyocardial biopsy

ICU = intensive care unit

IFN = interferon

IgG = immunoglobulin G

IL = interleukin

LVEF = left ventricular ejection fraction

MIS = multisystem inflammatory syndrome

MIS-A = multisystem inflammatory syndrome in adults

MIS-C = multisystem inflammatory syndrome in children

PCA = principal component analysis

RT-PCR = reverse transcription polymerase chain reaction

SARS-CoV-2 = severe acute respiratory syndrome-coronavirus-2

TNF = tumor necrosis factor

VA-ECMO = venoarterial extracorporeal membrane oxygenation

COVID-19-related myocarditis has been reported since the beginning of the severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) outbreak.[1-6] Fulminant myocarditis is a rare, but life-threatening, form of myocarditis leading to significant morbidity and mortality especially in young patients.[7] First described in children[8] and subsequently in adults,[9] the multisystem inflammatory syndrome (MIS-C and MIS-A, respectively) accounts for a large proportion of COVID-19-related myocarditis. The U.S. Centers for Disease Control and Prevention has developed case definition criteria to standardize its diagnosis.[10] Yet, some patients do not meet these criteria, suggesting the existence of distinct phenotypes in COVID-19-related myocarditis. We conducted a study to compare the clinical, biological, and immunological characteristics of patients with fulminant COVID-19-related myocarditis meeting or not meeting MIS-A criteria.

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METHODS

PATIENTS AND CONTROLS. We retrospectively reviewed the database of our 26-bed intensive care unit (ICU) between March 2020 and June 2021, and included all patients admitted for clinically suspected myocarditis with proven SARS-CoV-2 infection. Clinically suspected myocarditis was then adjudicated as definite or probable myocarditis according to the definition by Bonaca et al[11] (Supplemental Appendix) following clinical investigations. Proven SARS-CoV-2 infection was confirmed by positive reverse transcription polymerase chain reaction (RT-PCR) in either nasopharyngeal aspirate, lower airway respiratory samples, or serum and/or positive serology showing the presence of circulating anti-nucleocapsid protein (anti-N) or anti-spike protein (anti-S) receptor binding domain antibodies in patients not vaccinated against COVID-19. All laboratory analyses were performed as the standard of care in the myocarditis workup of our institution. In addition, healthy SARS-CoV-2–negative individuals (n = 10) were included as control subjects for cytokine measurements.

DATA COLLECTION. The following information was collected on standardized forms: epidemiologic parameters; severity of underlying condition according to the McCabe-Jackson criteria; medical history; COVID-19 infection history, manifestations, and complications; MIS-A criteria (Supplemental Appendix); day 0 Sequential Organ Failure Assessment Score and Simplified Acute Physiology Score II; day 0 and in-ICU clinical and biological parameters; day 0 and in-ICU organ-failure support treatment; day 0, in-ICU, and last-follow-up echocardiography parameters; in-ICU cytokine profiling; in-ICU SARS-CoV-2 and myocarditis-specific treatment; in-ICU and follow-up computed tomography scan and cardiac magnetic resonance imaging (CMR); complications; and vital status at ICU and hospital discharge, as well as at last follow-up.

SARS-CoV-2 RT-PCR AND SEROLOGICAL ANALYSES. Detection of SARS-CoV-2 was carried out by RT-PCR in clinical specimens, using the Cobas6800 SARS-CoV-2 Test (Roche Diagnostics) and serological detection of immunoglobulin G (IgG) anti-N and IgG anti-S SARS-CoV-2, was performed by enzyme-linked immunosorbent assay (ELISA) on the Abbott platform (Abbott Diagnostics) in accordance with the manufacturer's specifications.

CYTOKINE MEASUREMENT. Whole blood was collected in anticoagulant-free tubes, and serum was separated by centrifugation and stored at −80°C. Serum concentrations of interleukin (IL)-1β, IL-4, IL-5, IL-6, IL-8, IL-10, IL-12p70, IL-22, interferon (IFN)-γ, and tumor necrosis factor (TNF)-α were measured on a Quanterix SP-X imaging and analysis platform using the Human CorPlex Cytokine Panel Array kit (Quanterix). Single-plex bead-based ultrasensitive immunodetection of IL-17A and IFN-α was performed by digital ELISA using the Simoa (single molecule array) HD-1 analyzer (Quanterix), according to the manufacturer's instructions. Serum IFN-β levels were quantified using a highly sensitive ELISA kit (PBL Assay Science), according to the manufacturer's instructions. Serum cytokine concentrations were interpolated from the correspondent calibration curve taking into account the dilution factor. All cytokine concentrations were expressed in pg/mL. Samples with nondetectable values or those above the detection range were replaced by the limit of

The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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TABLE 1 COVID-19-Related MIS-A Criteria and SARS-CoV-2 Tests Results

	All Patients (N = 38)	MIS-A$^-$ (n = 13)	MIS-A$^+$ (n = 25)	*P* Value
Age, y	27.5 (19.0-37.0)	33.0 (21.5-38.5)	25.0 (18.5-35.5)	0.3
Women	13 (34)	6 (46)	7 (28)	0.3
BMI, kg/m^2	24.8 (22.4-28.6)	25.9 (23.3-28.9)	24.7 (21.7-28.2)	0.7
Time from first COVID-19 symptoms to myocarditis, days	5 (0-26)	3 (0-5)	8 (2-38)	0.04
Time from myocarditis symptoms onset to ICU, days	3 (0-5)	1 (0-3)	4 (1-6)	0.009
ICU admission SOFA score	8 (5-11)	11 (8-13)	6 (4-10)	0.002
ICU admission SAPS-II score	30 (20-40)	33 (25-49)	25 (15-35)	0.04
MIS-A criteria[a]				
Fever	36 (95)	9 (69)	25 (100)	0.01
Primary clinical criteria				
Myocardial involvement	38 (100)	13 (100)	25 (100)	na
Skin involvement	14 (37)	1 (8)	13 (52)	0.01
Secondary clinical criteria				
Neurological involvement	14 (37)	4 (31)	10 (40)	0.5
Shock or hypotension	36 (95)	13 (100)	23 (92)	0.1
Abdominal involvement	22 (58)	7 (54)	15 (60)	0.7
Platelets $<150 \times 10^9$/L	10 (26)	5 (38)	5 (20)	0.09
Laboratory evidence				
Inflammation[b]	29 (76)	2 (15)	25 (100)	<0.0001
Positive SARS-CoV-2 test[c]	38 (100)	13 (100)	25 (100)	na
SARS-CoV-2 tests				
Positive nasopharyngeal RT-PCR	14 (37)	11 (85)	4 (16)	<0.0001
CT value	26 (18-32)	24 (18-28)	32 (21-34)	0.2
Positive serology	26 (68)	2 (15)	24 (96)	<0.0001
IgG anti-S	25 (67)	2 (15)	23/24 (96)	<0.0001
Titer, UA/mL	660 (156-1,440)	2.3 (0.1-59)	854 (528-2,575)	<0.0001
IgG anti-N	26 (68)	2 (15)	24 (96)	<0.0001
Index, value	2.2 (0.1-5.3)	0.4 (0.03-0.8)	4.8 (2.2-5.5)	<0.0001

Values are median (IQR) or n (%). Continuous variables are compared with Wilcoxon's rank test; categorical variables are compared with Fisher exact test. [a]According the Centers for Disease Control and Prevention. [b]Elevated levels of at least 2 of the following biomarkers including: C-reactive protein >10 mg/L, procalcitonin >1 ng/mL, fibrinogen >5 g/L. [c]Positive RT-PCR, serology, or antigen for SARS-CoV-2.

BMI = body mass index; CT = cycle threshold; ICU = intensive care unit; IgG = immunoglobulin G; MIS-A = multisystem inflammatory syndrome in adults; N = nucleocapsid protein; RT-PCR = reverse transcription polymerase-chain reaction; S = spike protein; SAPS-II = Simplified Acute Physiology Score-II; SARS-CoV-2 = severe acute respiratory syndrome-coronavirus-2; SOFA = Sequential Organ Failure Assessment.

detection value and the upper limit of quantification, respectively.

Anti–IFN-α AND RNA POLYMERASE III AUTOANTIBODIES. Autoantibodies against IFN-α were quantified using the anti-IFN-α Antibody Human ELISA Kit (Thermo Fisher, Invitrogen), according to the manufacturer's instructions. Calibrators were run in duplicate and fit with a 4-parameter logistic regression. The concentration of anti-IFN-α antibodies in samples was interpolated from the calibration curve by multiplying the obtained values with the dilution factor. The positivity threshold was 15 ng/mL. For RNA polymerase III autoantibodies screening, an indirect immunofluorescence assay was run on HEp-2000 cells (Immuno Concepts). When positive (≥1/80) and when the immunofluorescence labeling pattern was evocative of RNA polymerase III autoantibodies (fine-speckled nuclear-labeling pattern with small dots), a confirmatory immunodot assay (Euroline Systemic Sclerosis Test, Bio Advance) was carried out.

STATISTICAL ANALYSES. Continuous variables are expressed as median (IQR: 25-75) and compared with Wilcoxon's signed rank tests. Categorical variables are expressed as n (%) and compared with chi-square tests or Fisher exact tests. Cumulative probabilities of survival were calculated using the Kaplan-Meier method and compared with log-rank tests. A 2-tailed *P* value < 0.05 was considered statistically significant. Analyses were computed with StatView software v5.0 (SAS Institute) and IBM SPSS Statistics v22.0 software (IBM Corp). Unsupervised principal component analysis (PCA) was performed using R software v3.6.2 with the FactoExtra and FactoMineR functions, on z-scaled log10-transformed cytokine

TABLE 2 Fulminant COVID-19-Related Myocarditis Findings

	n[a]	All Patients (N = 38)	MIS-A$^-$ (n = 13)	MIS-A$^+$ (n = 25)	*P* Value
Clinical symptoms					
Chest pain		18 (47)	9 (69)	9 (36)	0.09
Faintness		4 (10)	4 (31)	0 (0)	0.01
Syncope		2 (5)	1 (8)	1 (4)	1.0
Sudden death		1 (3)	1 (8)	0 (0)	0.3
Laboratory findings					
Troponin, ng/mL		526 (224-1,227)	441 (177-1,089)	712 (217-2,025)	0.2
Highest value in ICU		1,300 (486-4,750)	2,836 (450-9,634)	1,000 (471-3,036)	0.2
NT-proBNP, ng/L	1	9,931 (2,367-23,934)	2,755 (1,044-8,271)	12,525 (7,000-32,500)	0.007
Creatine phosphokinase, UI/L		312 (131-1,150)	586 (388-1,802)	190 (115-435)	0.003
Electrocardiogram findings					
Normal electrocardiogram		14 (37)	5 (38)	9 (36)	1.0
Sinus rhythm		36 (95)	12 (92)	24 (96)	1.0
Atrial fibrillation		2 (5)	1 (8)	1 (4)	1.0
ST-segment elevation		10 (26)	6 (46)	4 (16)	0.06
ST-segment depression		6 (16)	2 (15)	4 (16)	1.0
Negative T wave		10 (26)	1 (8)	9 (36)	0.1
Complete heart block		1 (3)	0 (0)	1 (4)	1.0
Bundle branch block		5 (13)	1 (8)	4 (16)	0.6
Ventricular rhythm disorders		3 (8)	3 (23)	0 (0)	0.03
Echocardiography findings					
LVEF, %					
First evaluation		30 (20-45)	30 (15-45)	30 (25-42)	0.5
On ICU admission		20 (14-37)	10 (5-30)	30 (15-45)	0.01
Lowest value in ICU		20 (10-30)	10 (5-25)	20 (15-30)	0.02
ICU discharge		42 (30-54)	35 (17-57)	45 (35-52)	0.1
Last follow-up	10	60 (50-64)	59 (44-60)	60 (50-65)	0.5
LVOT VTI, cm					
First evaluation		12 (8-16)	8 (7-17)	12 (9-15)	0.2
On ICU admission		11 (6-15)	5 (2-9)	13 (10-17)	<0.0001
ICU discharge		17 (12-18)	12 (7-18)	17 (15-19)	0.08
Ventricular hypertrophy		16 (42)	8 (62)	8 (32)	0.1
Ventricular dilation		5 (13)	2 (15)	3 (12)	1.0
LVEDD, mm		50 (47-56)	48 (46-55)	50 (47-56)	0.7
Right ventricular involvement		15 (39)	7 (54)	8 (32)	0.3
TAPSE, mm	20	14 (12-17)	12 (8-16)	14 (12-17)	0.2
S wave, cm/s	21	9 (7-11)	6 (1-11)	10 (8-11)	0.1
Mitral valve regurgitation		9 (24)	3 (23)	6 (24)	1.0
Aortic valve regurgitation		3 (8)	0 (0)	1 (4)	1.0
Tricuspid valve regurgitation		3 (8)	0 (0)	3 (12)	0.5
Pericardial effusion		15 (39)	8 (62)	7 (28)	0.08
Pericardiocentesis		4 (10)	4 (31)	0 (0)	0.01

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concentrations. Samples with missing data were excluded from the PCA analysis for 1 MIS-A$^+$ patient and 2 MIS-A$^-$ patients.

ETHICAL CONSIDERATIONS. This study was conducted in accordance with the declaration of Helsinki using the database registered at the Commission Nationale de l'Informatique et des Libertés (CNIL, registration no. 1950673). In agreement with the ethical standards of our hospital's Institutional Review Board, the Committee for the Protection of Human Subjects, and French law, written informed consent was not needed for demographic, physiological, and hospital-outcome data analysis, because this observational study does not modify existing diagnostic or therapeutic strategies; however, patients and/or their relatives were informed of their anonymous inclusion in the study.

RESULTS

GENERAL PATIENT CHARACTERISTICS. Between March 2020 and June 2021, 38 patients requiring ICU admission for clinically suspected fulminant COVID-

TABLE 2 Continued

	n[a]	All Patients (N = 38)	MIS-A⁻ (n = 13)	MIS-A⁺ (n = 25)	P Value
CMR findings					
Number performed in ICU/hospital		26 (68)	5 (38)	21 (84)	
Time from symptoms to CMR, days		7 (4-18)	16 (9-33)	5 (4-10)	
Myocardial edema		19/26 (73)	3/5 (60)	16/21 (76)	0.6
Late gadolinium enhancement		14/26 (54)	4/5 (80)	10/21 (48)	0.3
Myocarditis classification[b]					
Definite myocarditis		29 (76)	9 (69)	20 (80)	
Probable myocarditis		9 (24)	4 (31)	5 (20)	
Pathology		2 (5)	2 (15)	1 (4)	
Imaging					
Cardiac magnetic resonance		22 (58)	4 (31)	18 (72)	
Echocardiography WMA		32 (84)	13 (100)	24 (96)	
Coronary angiography performed and normal		10 (26)	6 (46)	4 (16)	
Electrocardiogram		23 (60)	8 (61)	15 (60)	
Syndrome		38 (100)	13 (100)	25 (100)	
Biomarkers		38 (100)	13 (100)	25 (100)	

Values are median (IQR), n (%), or n/N (%), unless otherwise indicated. Continuous variables are compared with Wilcoxon's rank test; categorical variables are compared with Fisher exact test. [a]Number of missing values. [b]According to the myocarditis classification proposed by Bonaca et al.[11]

CMR = cardiac magnetic resonance; LVEDD = left ventricular end-diastolic diameter; LVEF = left ventricular ejection fraction; LVOT VTI = left ventricle outflow tract velocity-time integral; NT-proBNP = N-terminal pro-B-type natriuretic peptide; TAPSE = tricuspid annular plane systolic excursion; WMA = wall motion abnormality; other abbreviations as in Table 1.

19-related myocarditis were included in this study. They were mostly men (66%) of young age (median age 27.5 years [IQR: 19-37 years]) with few comorbidities. Their baseline characteristics are reported in Table 1 and Supplemental Table 1. All had positive SARS-CoV-2 RT-PCR (37%) or serology (68%) with a median delay of 5 days between COVID-19 symptom onset and the first manifestation of myocarditis. None had previously received any COVID-19 vaccine. Most frequent symptoms were fever (95%), abdominal pain or nausea (60%), chest pain (47%), and dyspnea (42%).

At admission, patients had severely impaired left ventricular function (left ventricular ejection fraction [LVEF] 20% [IQR: 14%-37%], LVOT-VTI 11 cm [IQR: 6-15 cm]), an increased high-sensitivity T-troponin (median 1,300 ng/mL [IQR: 486-4,750 ng/mL]), and 79% presented with cardiogenic shock. When performed (n = 10), coronary angiography was normal. COVID-19 pneumonia was noted on computed tomography scan examination in 29% of cases. In the 26 patients who had CMR evaluation, myocardial edema, and late gadolinium enhancement were reported in 73% and 54%, respectively.

Three patients without recovery of cardiac function underwent myocardial biopsy. None were CMR-guided, as all were taken under mechanical circulatory support. Two surgical biopsies were taken in patients during venoarterial extracorporeal membrane oxygenation (VA-ECMO) centralization. The first one was an apical surgical biopsy in a patient cannulated under cardiopulmonary resuscitation, which was inconclusive. The second surgical biopsy highlighted myocarditis with an inflammatory infiltrate associated with myocyte dystrophy and edema. SARS-CoV-2 RT-PCR was negative, and electron microscopy analysis failed to identify viral particles in cardiomyocytes despite active myocarditis lesions on the evaluated sample. The last biopsy was endomyocardial and disclosed a mild lymphohistiocytic myocarditis with no edema, but with severe necrosis. SARS-CoV-2 RT-PCR was negative. Twenty-nine patients (76%) met the Bonaca classification criteria for definite myocarditis, whereas the others had probable myocarditis (Table 2).

IN-ICU EVOLUTION AND OUTCOMES. Median length of stay in ICU was 6 days. Seventy-nine percent of the patients received dobutamine, 60% norepinephrine, 50% mechanical ventilation, and 29% renal replacement therapy (Table 3). Four patients had a large pericardial effusion requiring drainage. Sixteen patients (42%) required mechanical circulatory support with VA-ECMO 1 day (IQR: 0-1 day) following ICU admission, for a median duration of 7 days. Twenty-eight (74%) were treated with corticosteroids, and 27 (74%), with intravenous immunoglobulins. In-hospital mortality was 13%. None of the survivors required cardiac transplantation or long-term ventricular assist device implantation. Among the 5 deceased patients, all had multiorgan failure before

TABLE 3 Organ Failure Support, Myocarditis Treatment, Complications, and Outcome in ICU

	All Patients (N = 38)	MIS-A$^-$ (n = 13)	MIS-A$^+$ (n = 25)	*P* Value
Time in ICU, days	6 (4-16)	12 (7-30)	5 (2-6)	<0.0001
Cardiac arrest before ICU	1 (3)	1 (8)	0 (0)	0.3
Organ failure support in ICU				
Dobutamine	30 (79)	12 (92)	18 (72)	0.2
Norepinephrine	23 (60)	12 (92)	11 (44)	0.005
Mechanical ventilation	19 (50)	11 (85)	8 (32)	0.005
Time on mechanical ventilation, days	15 (6-28)	15 (8-35)	11 (4-25)	0.3
Renal replacement therapy	11 (29)	8 (61)	3 (12)	0.003
VA-ECMO	16 (42)	12 (92)	4 (16)	<0.0001
VA-ECMO under CPR	4 (11)	4 (31)	0 (0)	0.02
Time on VA-ECMO, days	7 (5-12)	8 (6-12)	5 (4-12)	0.1
Time from admission to VA-ECMO, days	1 (0-1)	0 (0-1)	1 (0-5)	0.4
VV-ECMO	4 (10)	2 (15)	2 (8)	0.6
Time on VV-ECMO, days	18 (14-29)	24 (16-24)	17 (14-17)	0.4
Myocarditis treatment in ICU				
Corticosteroids	28 (74)	7 (54)	21 (84)	0.06
Intravenous immunoglobulins	27 (71)	8 (61)	19 (76)	0.5
Tocilizumab	0 (0)	0 (0)	0 (0)	Na
Outcome				
In-ICU mortality	5 (13)	4 (31)	1 (4)	0.04
In-hospital mortality	5 (13)	4 (31)	1 (4)	0.04
3-month probability of survival, %[a]	86 ± 6	68 ± 13	96 ± 4	0.01

Values are median (IQR), n (%), or mean ± SD. Continuous variables are compared with Wilcoxon's rank test; categorical variables are compared with Fisher exact test. [a]Probability of survival were calculated using Kaplan-Meier method and compared with log-tank tests.

CPR = cardiopulmonary resuscitation; VA-ECMO = venoarterial extracorporeal membrane oxygenation; VV-ECMO = venovenous extracorporeal membrane oxygenation; other abbreviations as in Table 1.

VA-ECMO implantation, including 3 cannulations during cardiopulmonary resuscitation. None could be weaned from VA-ECMO because of severe cardiac dysfunction. Median LVEF at ICU and hospital discharge was 42% (IQR: 30%-54%) and 60% (IQR: 50%-64%), respectively. Twenty-one survivors (64%) received beta-blockers at discharge, and 25 (76%) were treated with angiotensin-converting enzyme inhibitors, until distant evaluation with a cardiologist. At the last follow-up (median: 235 days [IQR: 155-359 days]), 32 patients were alive, and all but 1 had a normal LVEF. One patient was lost to follow-up.

COMPARISON BETWEEN MIS-A$^+$ AND MIS-A$^-$ PATIENTS. Twenty-five patients (66%) met the MIS-A criteria (Table 1). By definition, MIS-A$^+$ patients had more frequent fever, skin rash, enanthema, pharyngitis, and conjunctivitis, as compared with MIS-A$^-$ patients (Table 1). In addition, they had, as expected by the MIS-A definition, higher levels of systemic inflammation markers, including circulating leukocytes, procalcitonin, C-reactive protein, and fibrinogen (Table 4).

The median delay between COVID-19 symptoms onset and occurrence of myocarditis was shorter in MIS-A$^-$ patients: 3 vs 8 days. Noteworthy, the delay between first COVID-19 symptoms and myocarditis was 32 days (IQR: 25-44 days) among the 12 MIS-A$^+$ patients with prior proven symptomatic SARS-CoV-2 infection. The rate of positive serology was lower in MIS-A$^-$ patients (15% vs 96%), and their titer was also much lower than in MIS-A$^+$ patients ($P < 0.0001$). Conversely, positive nasopharyngeal RT-PCR at the time of myocarditis was infrequent in MIS-A$^+$ patients (16%), as compared with MIS-A$^-$ patients (85%).

MIS-A$^-$ patients had swifter ICU admission after myocarditis onset (1 vs 4 days) with a more severe presentation (day 0 Sequential Organ Failure Assessment score of 11 vs 6 in MIS-A$^+$ patients). They had a lower LVEF (10% vs 30%) and LVOT-VTI (5 cm vs 13 cm) (Table 2) and were more likely to receive norepinephrine, mechanical ventilation, and renal replacement therapy. Large pericardial effusions were also more frequently observed in MIS-A$^-$ patients. The median lactate level was 5.5 vs 2.1 mmol/L in MIS-A$^-$ and MIS-A$^+$ patients, respectively. Finally, MIS-A$^-$ patients were more likely to require VA-ECMO than MIS-A$^+$ patients (92% vs 16%), and had a higher in-ICU mortality (31% vs 4%; $P = 0.04$) (Table 3). The 3-month cumulative probabilities of survival ± standard error for MIS-A$^-$ and MIS-A$^+$ patients were, respectively, 68% ± 13% and 96% ± 4%; log-rank test $P = 0.01$.

Cytokine profiling highlighted the presence of 2 distinct cytokine production profiles (Figure 1, Table 4): MIS-A$^+$ had higher IL-22 (9.93 vs 1.5 pg/mL; $P < 0.0001$), IL-17 (3.2 vs 0.15 pg/mL; $P < 0.0001$), and TNF-α (21.1 vs 8.0 pg/mL; $P = 0.05$) levels, as compared with MIS-A$^-$ patients, whereas the latter had higher IFN-α2 (2.4 vs 0.013 pg/mL; $P = 0.001$) and IL-8 (158.7 vs 65.7 pg/mL; $P = 0.02$), respectively. Moreover, RNA polymerase III autoantibodies were found in 7 MIS-A$^-$ patients (54%), 5 of them being female (Table 4).

Finally, to elucidate the relative importance of the various bioclinical parameters listed in the preceding text with the clinical profile of MIS-A$^+$ or MIS-A$^-$ patients, we performed nonsupervised PCA using study parameters contributing, in a statistically significant manner, to interpatient variation (Tables 1, 2, and 3). The results from PCA underlined important overall differences between MIS-A$^+$ and MIS-A$^-$ patients (Figure 2). The data also further highlight parameters most contributing to either clinical status, that is, fibrinogen ($P < 0.0001$), CRP ($P < 0.0001$), IL-17 ($P < 0.0001$), IL-22 ($P < 0.0001$), IFN-α2 ($P = 0.001$) levels, SARS-CoV-2 serology ($P < 0.0001$), and SARS-CoV-2 RT-PCR ($P < 0.0001$), LVEF ($P = 0.01$) values on admission, and the presence of RNA polymerase III autoantibodies ($P = 0.001$).

TABLE 4 Laboratory Findings and Cytokine Profiling in the ICU

Day 0 Laboratory Findings	n[a]	All Patients (N = 38)	MIS-A$^-$ (n = 13)	MIS-A$^+$ (n = 25)	*P* Value
Hemogram and hemostasis					
Leukocytes, 10^9/L		12.6 (9.2-19.7)	8.7 (5.7-11.4)	18.5 (11.7-21.0)	<0.001
Lymphocytes, 10^9/L		0.8 (0.5-1.5)	1.2 (0.6-2.3)	0.8 (0.5-1.2)	0.08
Polymorphonuclear cells, 10^9/L		10.7 (5.8-18.0)	5.8 (3.4-8.1)	15.6 (10.3-19.0)	<0.001
Hemoglobin, g/dL		12,1 (11.1-13.5)	12.5 (10.4-16.0)	12 (11.6-13.3)	0.8
Platelets 10^9/L		192 (152-247)	192 (92-258)	206 (160-243)	0.7
Prothrombin time, %		72 (64-81)	65 (56-90)	72 (69-77)	0.4
D-dimers, μg/L	3	3,860 (1,290-6,700)	2,500 (396-20,000)	4,217 (1,602-6,035)	0.6
Inflammatory parameters					
C-reactive protein, mg/L	5	257 (110-329)	5 (4-72)	277 (226-376)	<0.0001
Procalcitonin, ng/mL		7.4 (0.5-46)	0.2 (0.1-1.1)	12.8 (3.7-65)	<0.0001
Fibrinogen, g/L		6.8 (4.2-8.5)	3.2 (2.2-4.3)	7.9 (6.8-9.2)	<0.0001
Biochemical findings					
Serum creatinine, μmol/L		105 (69-156)	85 (60-105)	134 (71-265)	0.038
LDH, IU/L	2	419 (315-634)	619 (320-973)	385 (307-526)	0.2
AST, IU/L		83 (46-139)	70 (42-168)	94 (46-129)	0.9
ALT, IU/L		50 (32-101)	39 (26-110)	60 (37-101)	0.4
Serum total bilirubin, μmol/L		11 (8-19)	6 (4-14)	12 (10-21)	0.006
pH	1	7.43 (7.30-7.46)	7.31 (7.15-7.42)	7.44 (7.41-7.47)	0.004
pO_2, mm Hg	1	90 (70-120)	106 (80-235)	81 (69-99)	0.06
pCO_2, mm Hg	1	30 (24-36)	29 (20-46)	30 (27-36)	0.7
Serum bicarbonates, mmol/L	2	19 (15-23)	16 (10.4-19.4)	21 (17-24)	0.005
Arterial lactate, mmol/L	2	2.5 (1.7-3.9)	5.5 (1.8-8.2)	2.1 (1.5-2.7)	0.009
Highest value in ICU, mmol/L	2	3.1 (2.4-7.1)	7.5 (5.2-15.5)	2.7 (1.7-3.4)	<0.0001
Serum protein, g/L		61 (52-68)	51 (40-57)	65 (58-70)	<0.0001
Serum albumin, g/L		25 (22-28)	27 (23-33)	25 (20-27)	0.1
Triglycerides, mmol/L	15	2 (1.7-3)	2.0 (1.1-3.0)	2.3 (1.8-3.2)	0.4
Immunological findings					
RNA polymerase 3 autoantibodies		7 (18)	7 (54)	0 (0)	0.001
Serum cytokine levels in ICU					
IL-12p70, pg/mL	3	0.03 (0.01-0.4)	0.03 (0.01-0.1)	0.03 (0.01-0.4)	0.3
IL-1β, pg/mL	3	0.2 (0.02-0.4)	0.3 (0.01-0.9)	0.2 (0.02-0.3)	0.5
IL-4, pg/mL	3	0.4 (0.2-1.1)	0.3 (0.3-0.5)	0.6 (0.2-2.1)	0.3
IL-5, pg/mL	3	0.1 (0.01-0.5)	0.04 (0.01-0.6)	0.3 (0.06-0.6)	0.1
IFN-γ, pg/mL	3	0.4 (0.2-2.2)	0.4 (0.09-2.0)	1.2 (0.2-2.6)	0.2
IL-6, pg/mL	3	55.2 (25.1-207.6)	39.6 (16.6-225.4)	57.8 (26.9-198.9)	0.7
IL-8, pg/mL	3	82.7 (58.2-166.4)	158.7 (74.9-784.2)	65.7 (55.7-118.3)	0.02
IL-22, pg/mL	3	6.4 (2.3-15.7)	1.5 (0.7-2.9)	9.93 (5.28-28.99)	<0.0001
TNF-α, pg/mL	3	14.2 (8.9-38.1)	8.0 (4.9-34.0)	21.1 (9.9-41.9)	0.05
IL-10, pg/mL	3	50.3 (15.9-76.6)	67.8 (20.1-143.1)	44.2 (12.8-68.4)	0.3
IL-17A, pg/mL	3	1.6 (0.2-5.2)	0.15 (0.08-0.3)	3.2 (0.8-6.2)	<0.0001
IFN-α2, pg/mL	3	0.02 (0.005-1.3)	2.4 (0.2-15.0)	0.013 (0.002-0.04)	0.001
IFN-β, pg/mL	4	0.6 (0.6-0.6)	0.6 (0.6-1.8)	0.6 (0.6-0.6)	0.2
Anti-IFNα autoantibodies	4	5 (15)	1 (10)	4 (17)	1

Values are median (IQR) or n (%), unless otherwise indicated. Continuous variables are compared with Wilcoxon's rank test; categorical variables are compared with Fisher exact test. [a]Number of missing values.

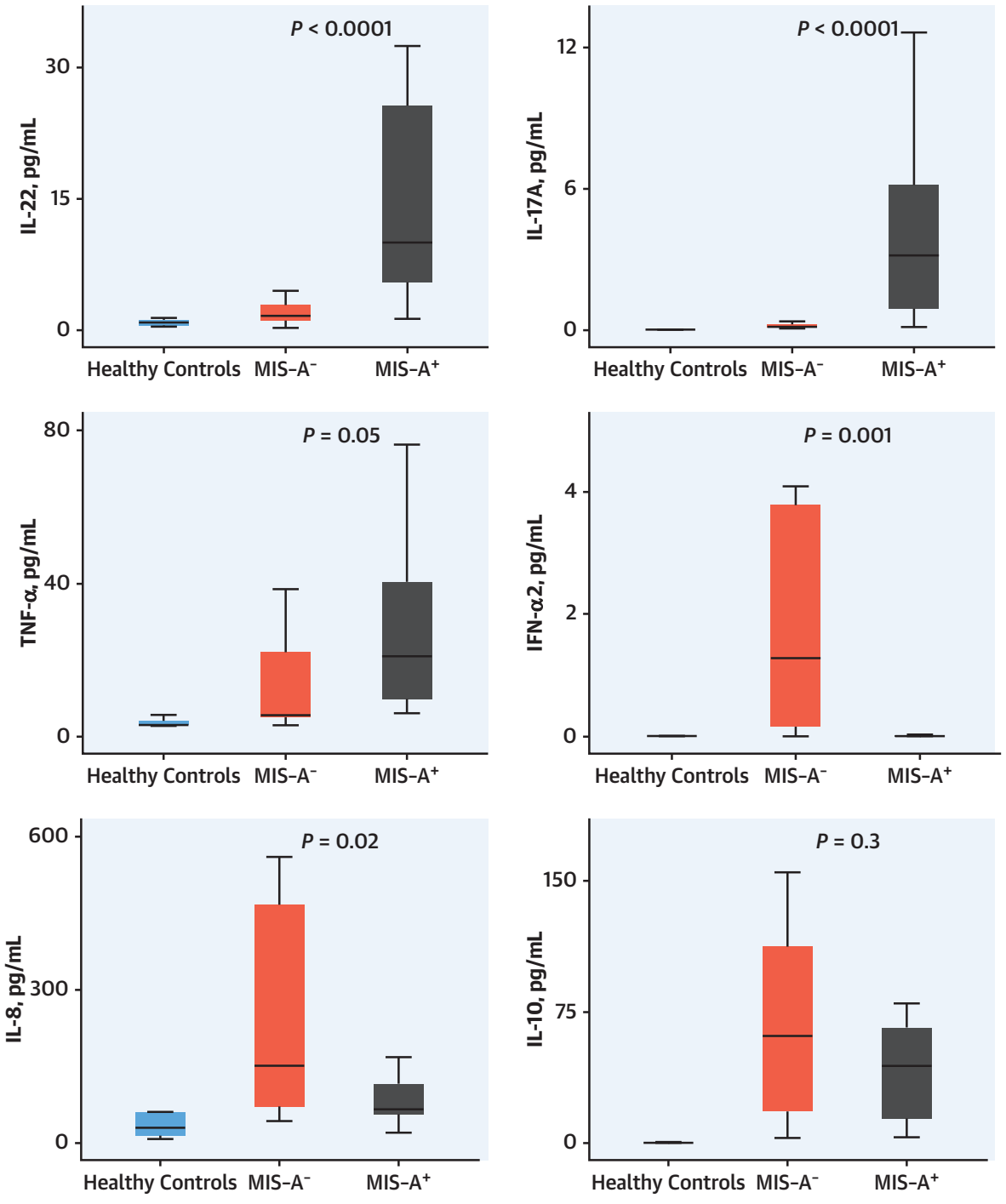
ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; IFN = interferon; IL = interleukin; LDH = lactate dehydrogenase; TNF = tumor necrosis factor; other abbreviations as in Table 1.

DISCUSSION

In this retrospective monocenter cohort of fulminant COVID-19-related myocarditis, we applied the MIS-A criteria case definition, and we identified 2 subsets of patients with very different clinical/biological presentations, outcomes, and immunological profiles. This phenotypic heterogeneity being likely explained by important differences in pathophysiological mechanisms.

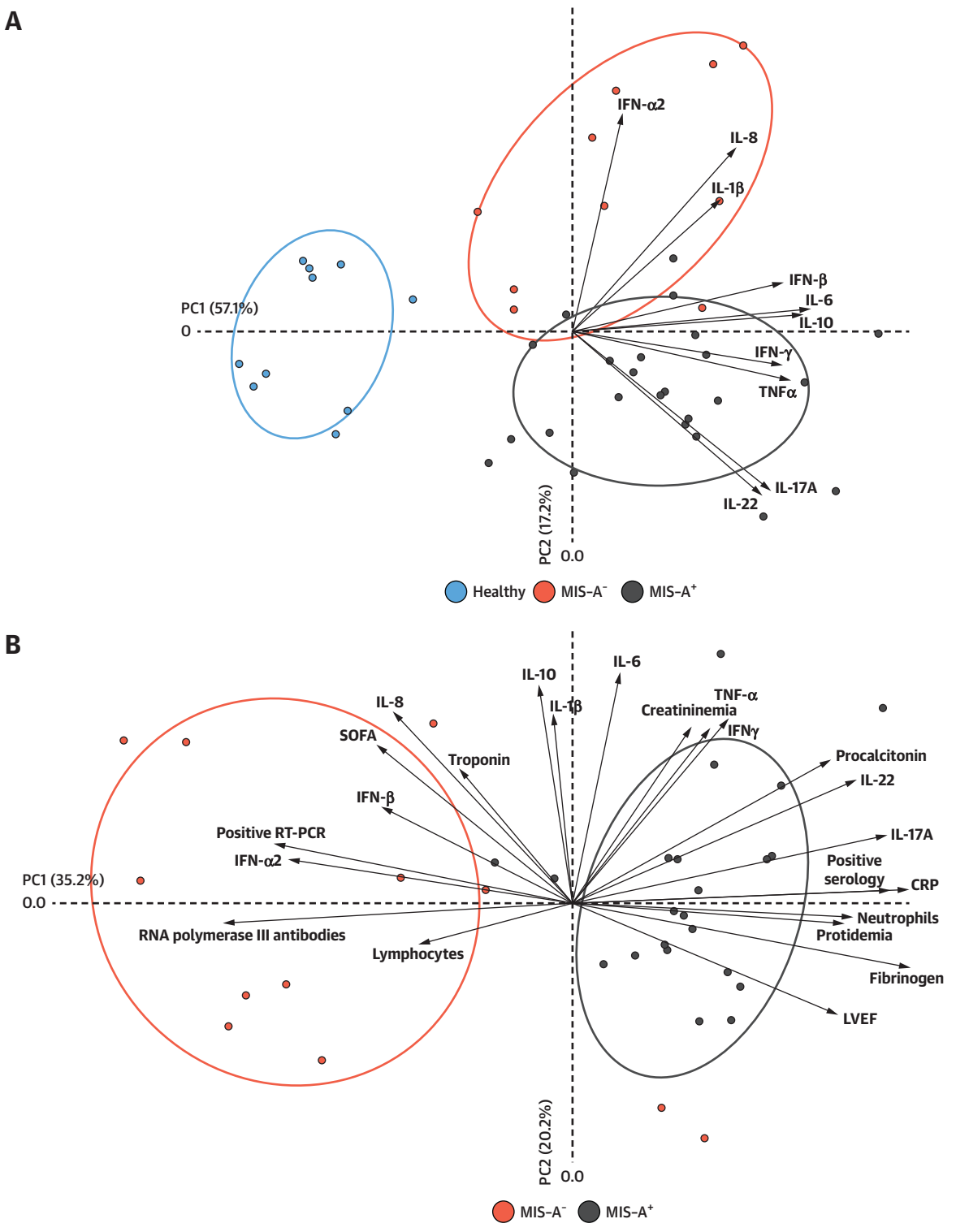
The patients in this cohort were mostly young men with severely impaired cardiac function, frequently

FIGURE 1 **Circulating Cytokines Levels in Fulminant COVID-19–Related Myocarditis**



Comparison of 6 circulating serum cytokines levels (IL-8, -10, -17, -22, IFN-α2, and TNF-α) in patients with MIS-A$^+$/MIS-A$^-$ and healthy controls. MIS-A$^+$ had higher IL-22, IL-17, and TNF-α, whereas MIS-A$^-$ had higher IFN-α2 and IL-8. Methods: serum concentrations of IL-8, IL-10, IL-22 and TNF-α were measured on a Quanterix SP-X imaging and analysis platform using the Human CorPlex Cytokine Panel Array kit (Quanterix). Single-plex bead-based ultrasensitive immunodetection of IL-17A and IFN-α was performed by digital ELISA using the Simoa (single molecule array) HD-1 analyzer (Quanterix), according to the manufacturer's instructions. For box and whisker plots: the **center line** denotes the median value (50th percentile), whereas the **box** contains the 25th to 75th percentiles of dataset. The **whiskers** mark the 5th and 95th percentiles. IFN = interferon; IL = interleukin; MIS-A = multisystem inflammatory syndrome in adults; TNF = tumor necrosis factor.

FIGURE 2 **PCA of Parameters Associated With COVID-19–Related Myocarditis**



Unsupervised PCA was performed using R software v3.6.2 with the FactoExtra and FactoMineR functions, on z-scaled log10-transformed cytokine concentrations. Samples with missing data were excluded from the PCA analysis for 1 MIS-A$^+$ patient and 2 MIS-A$^-$ patients. Ellipses with 66% CI are drawn for each group. **(A)** The principal component analysis of 10 circulating serum cytokines. **(B)** The principal component analysis including clinical findings, laboratory findings and immunological profiles highlight the main features of MIS-A$^-$ and MIS-A$^+$ fulminant COVID-19–related myocarditis phenotypes. CRP = C-reactive protein; LVEF = left ventricular ejection fraction; PCA = principal component analysis; RT-PCR = reverse transcription polymerase chain reaction; SOFA = Sequential Organ Failure Assessment; other abbreviations as in Figure 1.

requiring VA-ECMO, with infrequent concomitant COVID-19-associated pneumonia. All survivors recovered a near normal cardiac function at distant follow-up. To our knowledge, this study is the largest cohort of COVID-19-related fulminant myocarditis and extends prior reports of COVID-19-related myocarditis[9,12-15] and fulminant non-COVID-19 myocarditis.[7,16-19]

This analysis underscores the major clinical and immunological differences between patients with fulminant COVID-19-related myocarditis fulfilling or not MIS-A criteria. The original description of MIS-C was reported in May 2020,[8] and MIS-A, a few months afterwards.[9,20,21] This somewhat delayed description, together with the rarity of the disease, may have participated to an under-recognition of MIS in the adult population. Furthermore, whereas MIS-C is now well-defined with classification criteria established by the World Health Organization and the Centers for Disease Control and Prevention,[22,23] only the latter has adapted its criteria to the adult population.[10]

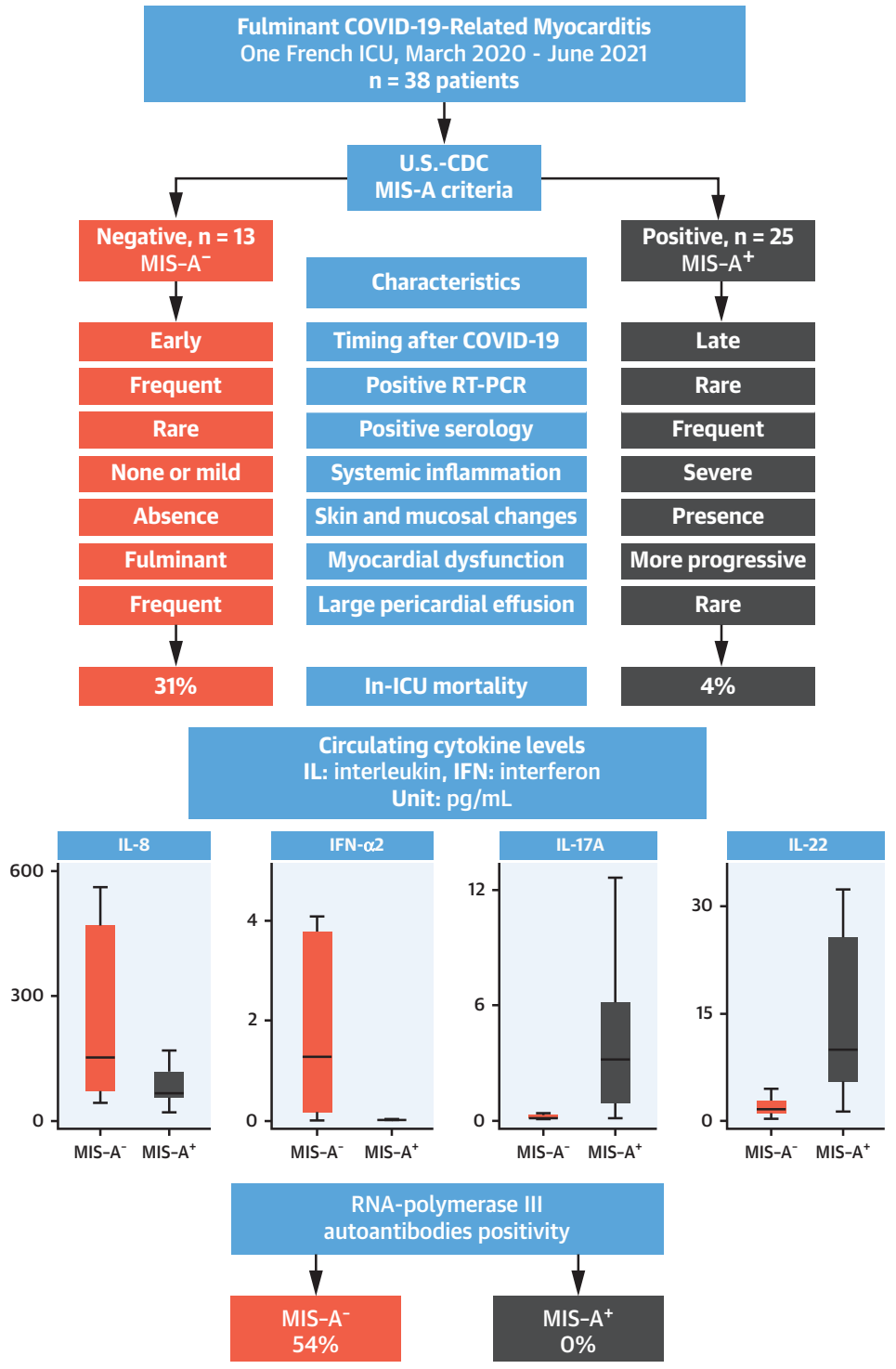
The main differences between the phenotypes of MIS-A$^+$ and MIS-A$^-$ patients are summarized in the **Central Illustration**. MIS-A$^+$ COVID-19-related myocarditis appears to be a postinfectious complication of SARS-CoV-2 infection, as suggested by the higher delay between COVID-19 symptoms and myocarditis, as well as by frequently positive serology and negative (or slightly positive) RT-PCR. Mucocutaneous manifestations are frequent in addition to laboratory evidence of severe systemic inflammation. Heart failure is more progressive, leading to fewer accounts of refractory cardiogenic shock, and is associated with a lower mortality rate. Conversely, MIS-A$^-$ fulminant COVID-19-related myocarditis occurred at the early phase of SARS-CoV-2 infection (negative or slightly positive serology and positive RT-PCR) with an explosive and refractory cardiogenic shock in nearly all patients leading to high morbidity and mortality.

Interestingly, these different clinical phenotypes are supported by immunological findings. The frequency of RNA polymerase III autoantibodies is high in MIS-A$^-$, whereas it is absent in MIS-A$^+$ patients. The presence of these rare autoantibodies, usually associated with severe systemic sclerosis, has been previously reported by Pineton de Chambrun et al[24] in patients with severe recurrent myocarditis and/or pericarditis, especially related to influenza virus. The role of these autoantibodies in the susceptibility to viral myocarditis is not yet elucidated. Their presence might reflect altered immune defenses toward viral infections or, alternatively, exaggerated antiviral responses leading to organ damage. Another patient with recurrent viral myocarditis, including COVID-19-related myocarditis, has been recently reported.[25]

The cytokine profiles of these patients were also found definitely different in the 2 clinical phenotypes (**Figure 2**). In MIS-A$^-$ patients, high levels of systemic circulating antiviral IFN-α2 likely arise from the ongoing viral infection, in relation to detectable viral replication and yet undetectable anti-SARS-CoV-2 IgG humoral responses. Levels of IL-8, a proinflammatory cytokine, were also more elevated in MIS-A$^-$, as compared with MIS-A$^+$ patients, further underlining the dominance of an innate type of immune response in the former group. Conversely, elevated IL-17 and IL-22 levels were found particularly associated with the MIS-A$^+$ phenotype, in agreement with the mucocutaneous manifestations observed in these patients. IL-17 and IL-22 shape innate defenses at mucosal and epithelial surfaces, IL-17 being proinflammatory and involved in the pathogenesis of several autoimmune diseases, whereas the latter cytokine is playing an important role in tissue regeneration.[26] Of note, the extremely high serum IL-10 levels observed in both MIS-A$^-$ and MIS-A$^+$ patients have been previously associated with severe myocardial injury[27] and increased risk of death in severe COVID-19 patients.[28]

MIS pathogenesis is not fully understood, but the delay between SARS-CoV-2 infection and disease onset, and overexpression of mucosal T cell cytokines (IL-22 and IL-17) suggest a role for the adaptive immune response in MIS-A$^+$ patients. Conversely, in MIS-A$^-$ cases, innate antiviral immunity and/or direct toxicity of the virus are more likely involved in heart tissue injury. In our series, SARS-CoV-2 RT-PCR on 2 MIS-A$^-$ endomyocardial biopsies (EMBs) were negative. This is in line with previous cases reports,[2,29] even if positive SARS-CoV-2 RT-PCR in myocardial samples has also been sporadically reported.[3,30] To the best of our knowledge, only 1 study demonstrated the presence of viral particles in cardiomyocytes by electronical microscopy,[31] with only mild interstitial inflammatory infiltrate and no necrosis or microthrombosis, thereby suggesting that the underlying mechanism of myocarditis development was mainly related to a virus-mediated immune response. The EMBs published results from fulminant COVID-19-related myocarditis often reported important myocardial edema with no or mild inflammatory infiltrate or necrosis,[2,32] a finding that is also consistent with CMR observations.[2,5]

CENTRAL ILLUSTRATION **Main Phenotypic Differences Between Fulminant COVID-19-Related Myocarditis With and Without Multisystem Inflammatory Syndrome in Adults**



Barhoum P, et al. J Am Coll Cardiol. 2022;80(4):299-312.

MIS-A$^+$ and MIS-A$^-$ fulminant COVID-19-related myocarditis patients have 2 distinct phenotypes with different clinical presentations, prognosis and immunological profiles. For **box and whisker plots:** the **center line** denotes the median value (50th percentile), whereas the **box** contains the 25th to 75th percentiles of dataset. The **whiskers** mark the 5th and 95th percentiles. ICU = intensive care unit; MIS-A = multisystem inflammatory syndrome in adults; RT-PCR = reverse transcription polymerase chain reaction; U.S.-CDC = U.S. Centers for Disease Control and Protection.

The phenotypic clustering of patients with fulminant COVID-19-related myocarditis seems relevant for their management. Indeed, MIS-A$^-$ cases, owing to the high risk of evolution toward refractory cardiogenic shock, should be urgently referred to a center with VA-ECMO capability and closely monitored to avoid a too-late cannulation, especially under cardiopulmonary resuscitation, known to be associated with poor outcome.[33] The 5 patients who died in our series had late VA-ECMO implantation, while having multiple organ failure or under resuscitation. Conversely, the risk of evolution toward refractory cardiogenic shock is lower in MIS-A$^+$ cases. Our results are consistent with those of a large series of 186 MIS-C from the United States, where only 8 patients required VA-ECMO and 4 died.[34] MIS-A$^+$ patient identification is all the more important given that numerous data support the efficacy of corticosteroids and/or intravenous immunoglobulins in MIS-C.[35] Best treatment regimen is yet to be determined because conflicting results have been reported with standalone or combination treatment.[36,37] However, one should take with caution the results of nonrandomized/nonblinded therapeutic intervention in a disease where spontaneous recovery occurs in most patients in a few days.

STUDY LIMITATIONS. First, the external validity is limited by its monocentric and retrospective nature. Notably, as an ECMO center, there might be a selection bias toward the inclusion of the most severe patients. Second, although being the largest series of fulminant COVID-19-related myocarditis, the sample size remains small, limiting the power of the study. Lastly, EMBs were performed in only 3 patients, whereas expert consensus and guidelines recommend to consider EMB in fulminant presentation for its diagnostic and therapeutic implications.[38-40] However, coagulation disorders are frequent in COVID-19-related myocarditis and VA-ECMO patients. The benefit/risk ratio was evaluated against EMB in all but 3 cases, especially given the known diagnosis of SARS-CoV-2 infection. It is nevertheless unfortunate that we cannot provide a more extensive characterization of COVID-19-related myocarditis histopathological findings in MIS-A$^+$ and MIS-A$^-$ patients.

CONCLUSIONS

We identified 2 phenotypes of fulminant COVID-19-related myocarditis harboring distinct clinical and laboratory manifestations, evolutions, and outcomes. Differentiating these patients seems relevant for their management and for further pathophysiological studies. The role of RNA polymerase III autoantibodies in fulminant myocarditis requires further investigation.

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PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: MIS-A criteria distinguish phenotypes of patients who develop fulminant myocarditis related to COVID-19, with different clinical presentations, immunological profiles, and outcomes. Those with MIS-A criteria more often have elevated serum levels of IL-17 and IL-22 while those without are frequently positive for serum RNA polymerase III autoantibodies, have high serum level of IFN-α and more often require ECMO.

TRANSLATIONAL OUTLOOK: Further investigation is needed to characterize the role of RNA-polymerase-III antibodies in the pathophysiology of MIS-A COVID-19–related fulminant myocarditis.

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KEY WORDS COVID-19, cytokines, fulminant myocarditis, multisystem inflammatory syndrome, RNA polymerase III autoantibodies, SARS-CoV-2, VA-ECMO

APPENDIX For an expanded Methods section and a supplemental table, please see the online version of this paper.