Clinical Infectious Diseases

MAJOR ARTICLE

Multisystem Inflammatory Syndrome in Adults: Case Finding Through Systematic Review of Electronic Medical Records

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Background. Multisystem inflammatory syndrome in adults (MIS-A) is a severe condition temporally associated with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection.

Methods. In this retrospective cohort study, we applied the US Centers for Disease Control and Prevention (CDC) case definition to identify diagnosed and undiagnosed MIS-A cases among adults discharged during April 2020–January 2021 from 4 Atlanta, Georgia hospitals affiliated with a single medical center. Non–MIS-A coronavirus disease 2019 (COVID-19) hospitalizations were identified using *International Classification of Diseases, Tenth Revision, Clinical Modification* encounter code U07.1. We calculated the ratio of MIS-A to COVID-19 hospitalizations, compared demographic characteristics of the 2 cohorts, and described clinical characteristics of MIS-A patients.

Results. We identified 11 MIS-A cases, none of which were diagnosed by the treatment team, and 5755 COVID-19 hospitalizations (ratio 1:523). Compared with patients with COVID-19, patients with MIS-A were more likely to be younger than 50 years (72.7% vs 26.1%, $P < .01$) and to be non-Hispanic Black (81.8% vs 50.0%, $P = .04$). Ten patients with MIS-A (90.9%) had at least 1 underlying medical condition. Two MIS-A patients (18.2%) had a previous episode of laboratory-confirmed COVID-19, occurring 37 and 55 days prior to admission. All MIS-A patients developed left ventricular systolic dysfunction. None had documented mucocutaneous involvement. All required intensive care, all received systemic corticosteroids, 8 (72.7%) required mechanical ventilation, 2 (18.2%) required mechanical cardiovascular circulatory support, and none received intravenous immunoglobulin. Two (18.2%) died or were discharged to hospice.

Conclusions. MIS-A is a severe but likely underrecognized complication of SARS-CoV-2 infection. Improved recognition of MIS-A is needed to quantify its burden and identify populations at highest risk.

Keywords. COVID-19; coronavirus; MIS-A; MIS-C; multisystem inflammatory syndrome in adults.

In June 2020, soon after the description of multisystem inflammatory syndrome in children (MIS-C) [1–4], reports first described a similar multisystem inflammatory syndrome in adults (MIS-A) temporally associated with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection [5, 6]. Most cases reported in the United States (US) have been among young adults, males, and non-Hispanic Black and Hispanic persons [6]. Both MIS-C and MIS-A have features overlapping with extrapulmonary manifestations of coronavirus disease 2019 (COVID-19) [6–8]. However, distinguishing MIS-A from COVID-19 is a greater diagnostic challenge; adults with COVID-19 are often hospitalized with a biphasic course of illness with clinical decompensation in the second week [9] and, like patients with MIS, may present with cardiomyopathy [10–16]. Exacerbation of underlying medical conditions may also supplant or obscure features of MIS-A. Most patients with MIS-A require intensive care, and mortality has been estimated to be 3%–10% [6].

MIS-A is infrequently reported. As of March 2022, the US Centers for Disease Control and Prevention (CDC) recorded nearly 7000 cases of MIS-C [17], while <300 cases of MIS-A have been described in scientific literature [6]. MIS-A may be underrecognized due to lack of provider awareness of the syndrome and intersection with other inflammatory consequences of COVID-19. On 13 May 2021, CDC released a case definition [18] informed by review of published MIS-A case reports to facilitate reporting from health departments and to better understand the public health burden, including among adults who

Received 22 November 2021; editorial decision 10 April 2022; published online 20 April 2022

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Clinical Infectious Diseases® 2022;75(11):1903–11

https://doi.org/10.1093/cid/ciac303

may have had mild, undiagnosed initial SARS-CoV-2 infection. Retrospectively applying the definition, US jurisdictional health departments reported 20 MIS-A cases occurring during 14 December 2020–30 April 2021 [19].

Here we describe the first effort to quantify MIS-A burden using the CDC definition, adapted for case finding using an electronic medical record (EMR). Our objectives were to identify diagnosed and undiagnosed cases meeting the CDC definition among hospitalized adults, to compare the relative frequency of MIS-A and adult COVID-19 hospitalizations, to describe demographic and clinical characteristics of patients with MIS-A, and to identify limitations in the CDC definition.

METHODS

This study was reviewed by CDC, was determined to meet the requirements of public health surveillance, and was conducted in consistence with federal law and CDC policy (45 Code of Federal Regulations [CFR] 46.102(l)(2), 21 CFR part 56; 42 US Code [USC] §241(d); 5 USC §552a; 44 USC §3501 et seq) [20, 21].

Design and Setting

In this retrospective cohort study, we identified patients hospitalized with MIS-A and COVID-19 through EMR review at 4 hospitals affiliated with a single academic center in metropolitan Atlanta, Georgia, with discharge dates during 1 April 2020–31 January 2021.

MIS-A Case Ascertainment

To establish inclusion criteria, the CDC MIS-A case definition [18] was adapted to facilitate systematic search of the EMR (Table 1). We required age ≥18 years and admission to an adult medicine service, hospitalization ≥24 hours or ending in death, measured fever (≥38.0 C) during the first 3 hospital days, ≥3 clinical criteria prior to or during the first 3 hospital days (including at least severe cardiac illness or rash with nonpurulent conjunctivitis), no more likely alternative diagnosis, ≥2 elevated laboratory markers of inflammation, and either a positive SARS-CoV-2 reverse-transcription polymerase chain reaction test (RT-PCR) or a positive serologic test for anti–spike protein immunoglobulin G during hospitalization. For this study, we lowered the MIS-A minimum age from 21 to 18 years to identify possibly undiagnosed MIS-C cases (defined in persons aged <21 years) [4] hospitalized in an adult medicine service.

We first queried the EMR to identify inpatient encounters meeting initial screening criteria: patient age ≥18 years, maximum recorded temperature ≥38.0°C, and the laboratory criteria for inflammation and SARS-CoV-2 testing (Table 1). Clinical notes, laboratory results, and imaging reports from encounters meeting the screening criteria were reviewed to determine whether full MIS-A inclusion criteria were met. The date of admission was considered hospital day zero. Inclusion criteria dependent on signs or symptoms (eg, rash, conjunctivitis) and those dependent on clinical diagnosis (eg, pericarditis, encephalopathy) were ascertained through text search in clinical notes. Myocarditis was ascertained through review of cardiac magnetic resonance imaging (MRI) or biopsy reports. Ventricular dysfunction and coronary artery abnormalities were identified using echocardiography or other cardiac imaging reports. Left ventricular ejection fraction (LVEF) <50% was considered reduced. Shock was determined by clinician diagnosis or use of vasopressors; hypotension was classified as systolic blood pressure <90 mm Hg on 2 consecutive measurements, or on a single measurement if followed by a resuscitative intervention. Alternative diagnoses were evaluated using microbiology results, imaging reports, and clinical notes. Diagnoses were not considered alternative if onset was delayed, consistent with a process secondary to the primary illness or an iatrogenic cause (eg, ventilator-associated pneumonia). *International Classification of Diseases, Tenth Revision, Clinical Modification* (*ICD-10-CM*) codes were not used to determine MIS-A inclusion or exclusion.

All cases determined to meet inclusion criteria underwent review by a second unblinded investigator. A third unblinded reviewer adjudicated the final classification if there were 2 discordant reviews.

Separately, we searched the EMR for adult inpatient encounters assigned the *ICD-10-CM* code M35.81 (first available 1 January 2021) to identify potential provider-diagnosed MIS-A cases that did not meet inclusion criteria.

Data Collection and Analysis

Demographic and clinical data from each case meeting MIS-A inclusion criteria were abstracted from the EMR and maintained using Research Electronic Data Capture (REDCap) tools [22, 23]. Underlying conditions and hospital complications were ascertained through text search and review of encounter *ICD-10-CM* codes. Obesity was classified either by clinician diagnosis or by body mass index ≥30.0 kg/m^2 using height and weight recorded at hospital admission. Nonpregnant, nonobese patients without chronic diagnoses were classified as having no underlying conditions. Patients with admission dates prior to 11 December 2020, the date of the first US Food and Drug Administration emergency use authorization for a COVID-19 vaccine [24], were assumed not to have received a COVID-19 vaccine. Vaccination status of patients admitted on or after this date was determined from text search of the EMR and verified using the Georgia Department of Public Health COVID-19 immunization registry. We considered MIS-A diagnosed during hospitalization either if *ICD-10-CM* code M35.81 was assigned or if the terms "multisystem inflammatory syndrome" or "MIS" were identified in provider notes.

Table 1. Application of Centers for Disease Control and Prevention Case Definition for Multisystem Inflammatory Syndrome in Adults for Case Finding Through Electronic Medical Record Search

Criterion[a]	CDC Case Definition	Inclusion Criteria for This Study Step 1: Automated EMR Query	Inclusion Criteria for This Study Step 2: Investigator Review of EMR
1	Age ≥21 y	Age ≥18 y	Admitted to adult medicine inpatient service
2	Illness requiring hospitalization for ≥24 h or resulting in death		Inpatient encounter with duration ≥24 h or ending in in-hospital death
3	No alternative plausible diagnosis is more likely		No alternative plausible diagnosis is more likely
4	Subjective fever or documented fever (≥38.0 C) for ≥24 h prior to or within 3 d of hospitalization[b]	Maximum recorded temperature ≥38.0 C at any time during hospitalization	Maximum recorded temperature ≥38.0 C during first 3 d of hospitalization[b]

5	At least 3 of the following clinical criteria occurring prior to or within 3 d of hospitalization[b]. At least 1 must be a primary clinical criterion.
	• Primary clinical criteria
	  • Severe cardiac illness[c]
	  • Rash AND nonpurulent conjunctivitis
	• Secondary clinical criteria
	  • New-onset neurologic signs and symptoms[d]
	  • Shock or hypotension not attributable to medical therapy (eg, sedation, RRT)
	  • Abdominal pain, vomiting, or diarrhea
	  • Thrombocytopenia (platelet count <150 000/μL)
			At least 3 of the following clinical criteria occurring prior to or within 3 d of hospitalization[b]. At least 1 must be a primary clinical criterion.
			• Primary clinical criteria
			  • Severe cardiac illness[c]
			  • Rash AND nonpurulent conjunctivitis
			• Secondary clinical criteria
			  • New-onset neurologic signs and symptoms[d]
			  • Shock[e] or hypotension[f] not attributable to medical therapy (eg, sedation, RRT)
			  • Abdominal pain, vomiting, or diarrhea
			  • Thrombocytopenia (platelet count <150 000/μL)

6	Laboratory evidence of severe inflammation[g]	At least 2 of the following during hospitalization: • CRP >10 mg/L • IL-6 >2 pg/mL • ESR >40 mm/h • Ferritin >307 ng/mL • PCT >0.25 ng/mL	
7	Positive SARS-CoV-2 test for current or recent infection (by RT-PCR, serology, or antigen detection)	Positive test for SARS-CoV-2 infection during hospitalization (by RT-PCR or serology)[h]	

Abbreviation: CDC, Centers for Disease Control and Prevention; CRP, C-reactive protein; EMR, electronic medical record, ESR, erythrocyte sedimentation rate; IL-6, interleukin 6; PCT, procalcitonin; RRT, renal replacement therapy; RT-PCR, reverse-transcription polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

[a]All criteria must be met for study inclusion.

[b]Criterion must be met by the end of hospital day 3, where the date of hospital admission is hospital day 0.

[c]Includes myocarditis, pericarditis, coronary artery dilatation or aneurysm, new-onset right or left ventricular dysfunction (left ventricular ejection fraction <50%), new-onset second- or third-degree atrioventricular block, or ventricular tachycardia. Cardiac arrest alone does not meet this criterion.

[d]Includes encephalopathy in a patient without prior cognitive impairment, seizures, meningeal signs, or peripheral neuropathy (including Guillain-Barré syndrome).

[e]Documented clinical diagnosis or administration of vasoactive medications to augment blood pressure or cardiac output (eg, norepinephrine, dobutamine, milrinone).

[f]Systolic blood pressure <90 mm Hg on ≥2 consecutive measurements or requiring intervention (eg, intravenous fluid administration).

[g]Elevated levels of at least 2 of the following: CRP, ferritin, IL-6, ESR, PCT.

[h]Antigen testing was not systematically recorded in the EMR.

We calculated descriptive statistics of epidemiologic and clinical characteristics of MIS-A patients.

The EMR was also used to identify COVID-19 hospitalizations (defined as hospital encounters in which the *ICD-10-CM* code U07.1 was assigned [25] and which did not meet MIS-A inclusion criteria) among adults (aged ≥18 years) with discharge dates 1 April 2020–31 January 2021. Because some patients may have undergone SARS-CoV-2 testing prior to admission, a positive RT-PCR result was not required to identify COVID-19 hospitalizations. We calculated the ratio of MIS-A hospitalizations to adult COVID-19 hospitalizations. Patient age (18–49 years, ≥50 years), sex, and race/ethnicity (Hispanic, non-Hispanic) were compared between the MIS-A and COVID-19 cohorts using Barnard exact test (2-tailed) [26]. *P* values <.05 were considered significant. Analyses were performed using R software version 4.1.2.

RESULTS

Retrospective query of the EMR identified 3598 adult inpatient encounters with positive SARS-CoV-2 laboratory testing, of which 1336 (37.1%) met the initial MIS-A screening criteria (Figure 1). Review of this cohort identified 11 inpatient encounters among 11 unique patients who met full MIS-A inclusion criteria. None were diagnosed with MIS-A during hospitalization; all were diagnosed as having manifestations of acute COVID-19. Ten patients who otherwise met inclusion criteria had more likely alternative diagnoses, the most

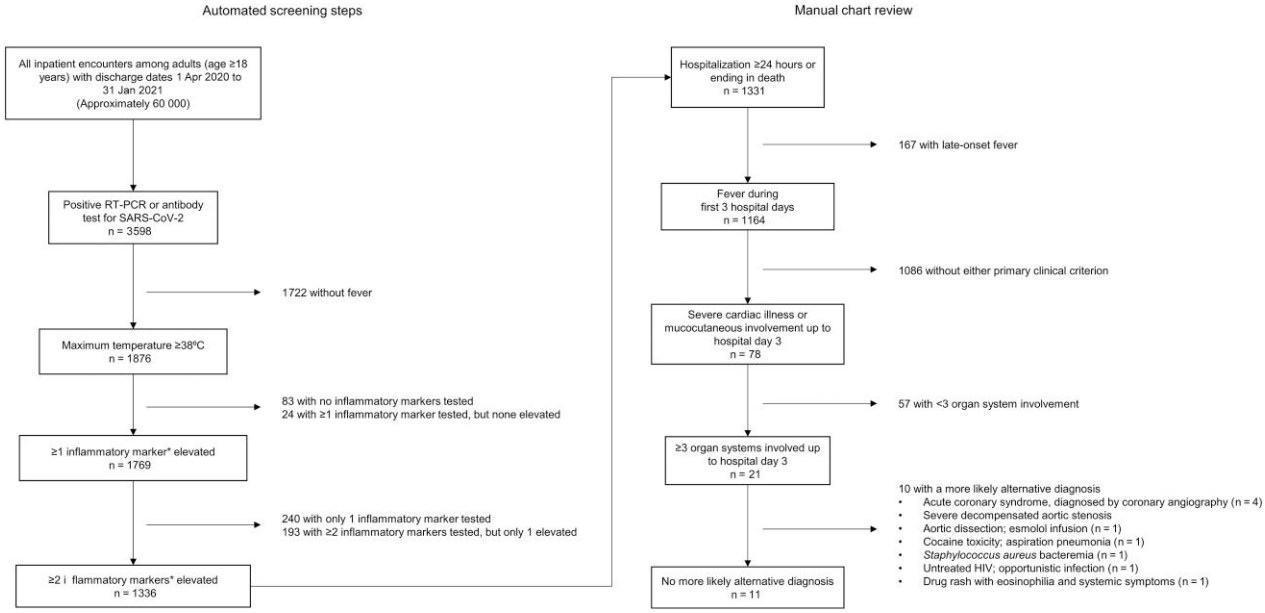

Figure 1. Flowchart of inclusion of patients with multisystem inflammatory syndrome in adults. *C-reactive protein >10 mg/L, erythrocyte sedimentation rate >40 mm/hour, ferritin >307 ng/mL, procalcitonin >0.25 ng/mL, interleukin 6 >2 pg/mL. Abbreviations: HIV, human immunodeficiency virus; RT-PCR, reverse-transcription polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

common of which was acute coronary syndrome with myocardial infarction. There were no provider-diagnosed MIS-A cases assigned *ICD-10-CM* code M35.81.

Over the same period, there were 5755 COVID-19 hospitalizations (*ICD-10-CM* code U07.1 assigned) among 5471 unique adult patients, resulting in a ratio of MIS-A to COVID-19 hospitalizations of 1:523. Although 63.6% of MIS-A patients were male, the percentage was not significantly different from that of COVID-19 patients (49.8%, $P = .37$; Table 2). Compared with COVID-19 patients, MIS-A patients were more likely to be younger than 50 years (72.7% vs 26.1%, $P < .01$) and to be non-Hispanic Black (81.8% vs 50.0%, $P = .04$).

Table 2. Multisystem Inflammatory Syndrome in Adults and Coronavirus Disease 2019 Hospitalizations Among Adults Aged ≥18 Years at 4 Acute Care Hospitals in Atlanta, Georgia, United States, With Discharge Dates During 1 April 2020–31 January 2021

Characteristic	Patients With MIS-A[a] (n = 11)	Patients With COVID-19[b] (n = 5471)	*P* Value[c]
Patient age, No. (%)			<.01
18–49 y	8 (72.7)	1429 (26.1)	
≥50 y	3 (27.3)	4042 (73.9)	
Patient sex, No. (%)			.37
Female	4 (36.4)	2746 (50.2)	
Male	7 (63.6)	2725 (49.8)	
Patient race/ethnicity, No. (%)			
Black, non-Hispanic	9 (81.8)	2738 (50.0)	.04
White, non-Hispanic	2 (18.2)	1564 (28.6)	.73
Hispanic	0 (0.0)	455 (8.3)	>.99
Other, non-Hispanic	0 (0.0)	714 (13.1)	.61

Abbreviations: COVID-19, coronavirus disease 2019; MIS-A, multisystem inflammatory syndrome in adults.

[a]Met full MIS-A inclusion criteria for this study after automated query of the electronic medical record and manual review (Table 1).

[b]*International Classification of Diseases, Tenth Revision, Clinical Modification* code U07.1 was assigned as a primary or secondary diagnosis and did not meet MIS-A inclusion criteria.

[c]Barnard exact test.

The median age of MIS-A patients was 37 years (range, 18–83 years). Ten (90.9%) had at least 1 underlying condition, of which obesity was the most common (Table 3). The most common presenting signs and symptoms were fever (81.8%), diarrhea (72.7%), and dyspnea (54.5%). Seven (63.6%) patients had lower respiratory symptoms.

All 10 MIS-A patients who underwent SARS-CoV-2 RT-PCR testing had positive results, and all 5 who underwent serologic testing had positive results (Table 3). Two patients had a history of prior laboratory-confirmed COVID-19, occurring 37 and 55 days prior to admission. One patient without preceding COVID-19 had a documented exposure to a laboratory-confirmed COVID-19 case 30 days prior to admission. Another had ongoing exposure to a household member with COVID-19 beginning 10 days prior to admission. No patient had received a COVID-19 vaccine.

All MIS-A patients met inclusion criteria through development of severe cardiac illness (Table 3). Neither rash nor conjunctivitis were documented in MIS-A patients. Of the secondary clinical criteria in the case definition, shock or

Table 3. Clinical Characteristics of Patients With Multisystem Inflammatory Syndrome in Adults Discharged from 4 Acute Care Hospitals, Atlanta, Georgia, United States, 1 April 2020–31 January 2021

Characteristic	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8	Patient 9	Patient 10	Patient 11
Age group, y	18–24	18–24	25–29	30–34	35–39	35–39	35–39	40–44	50–54	50–54	≥80
Sex	Male	Female	Male	Male	Female	Female	Male	Male	Male	Male	Female
Underlying medical condition(s)	None	Obesity	Asthma, tobacco smoker	Hypothyroidism	Obesity	Obesity	T2DM	Obesity, HTN, CKD, chronic pancreatitis	Obesity	HTN, T2DM, peripheral neuropathy	HTN, CKD, RA, history of VTE, dementia
Signs/symptoms on presentation											
Symptom duration PTA	7 d	3 d	5 d	5 d	6 d	3 d	4 d	6 d	3 d	8 d	13 d
Constitutional	Fever, headache, myalgia	Fever, fatigue, myalgia	Fever, headache	Fever, fatigue	Fever, fatigue, headache	Fever, fatigue, myalgia			Fatigue	Fever, fatigue	Fever
Gastrointestinal	Abd. pain, diarrhea	Abd. pain, diarrhea, vomiting	Abd. pain, diarrhea, vomiting	Diarrhea, vomiting	Diarrhea	Abd. pain, diarrhea, vomiting	Abd. pain, diarrhea	Vomiting	Diarrhea		
Lower respiratory	Dyspnea		Cough, dyspnea		Dyspnea		Cough, dyspnea	Cough, dyspnea	Cough, dyspnea	Cough	
Upper respiratory				Sore throat	Cervical lymphadenopathy						
Neurologic		Anosmia, ageusia		Altered mental status				Altered mental status	Anosmia	Altered mental status	Altered mental status
Other	Chest pain, neck pain		Chest pain		Chest pain, joint pain		Chest pain			Chest pain	
Evidence of prior SARS-CoV-2 antigenic exposure											
Previous COVID-19 symptom onset	None	None	55 d PTA[a]	None	37 d PTA[a]	None	None	None	None	None	None
Known COVID-19 exposure	None	None	None	None	None	None	30 d PTA	None	None	0–10 d PTA	None
COVID-19 vaccination	None	None	None	None	None	None	None	None	None	None	None
SARS-CoV-2 testing during present hospitalization											
RT-PCR	+	+	+	+	+	ND	+	+	+	+	+
Anti–spike protein IgG	ND	+	+	ND	ND	+	+	ND	ND	+	ND
Clinical criteria met prior to or during hospital days 0–3[b]											
Severe cardiac illness[c]	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Rash and nonpurulent conjunctivitis											
New-onset neurologic signs and symptoms[d]			✓	✓				✓	✓	✓	
Shock or hypotension not attributable to medical therapy[e]	✓	✓	✓	✓	✓	✓	✓		✓	✓	✓
Abdominal pain, vomiting, or diarrhea	✓	✓	✓	✓	✓	✓	✓	✓	✓		
Thrombocytopenia[f]	✓		✓	✓		✓	✓	✓			✓
Evaluation of cardiomyopathy											
LVEF nadir	40%, HD 2	10%, HD 3	35%, HD 2	15%, HD 1	35%, HD 0	40%, HD 3	25%, HD 1	30%, HD 1	45%, HD 1	10%, HD 2	45%, HD 1
Regional wall motion abnormalities	None	Global hypokinesis	None	Global hypokinesis	Global hypokinesis	None	Global hypokinesis	None	Anterior wall hypokinesis	Global hypokinesis	Mild apical septal hypokinesis
RV systolic dysfunction	Moderate	Severe	Severe	Mild	Mild	Mild	Moderate	None	Mild	Severe	None
LVEF recovery or last measurement	55%–60%, HD 8	55%, HD 8	65%, HD 14	55%–60%, HD 22	60%–65%, HD 3	Not repeated	70%–75%, HD 8	35%, HD 3	68%, HD 27[g]	40%, HD 6	Not repeated

Table 3. Continued

Characteristic	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8	Patient 9	Patient 10	Patient 11
Cardiac MRI	Hyperemia, myocardial edema	ND	Hyperemia, myocardial edema	ND	No evidence of myocarditis	ND	ND	ND	ND	ND	ND
Complications											
Cardiac	Mild MR	Moderate MR & TR, AF	Severe MR & TR, VT	Moderate MR		Moderate MR	AF		AF		Mild MR
Pulmonary			Pleural effusion			ARDS, pleural effusion	ARDS, pleural effusion	ARDS, pleural effusion	Pleural effusion	ARDS, pleural effusion	
Infectious		*Staphylococcus lugdunensis* bacteremia		*Staphylococcus aureus* VAP						*Staphylococcus aureus* VAP	
Other	AKI	AKI, pulmonary embolism, anoxic brain injury	AKI, rhabdomyolysis, critical illness neuropathy	AKI, primary adrenal insufficiency	AKI	AKI, rhabdomyolysis	AKI, DKA, acute liver failure	AKI	AKI	AKI, DKA, acute liver failure	AKI
Treatments administered											
Systemic corticosteroids	Dex.	Dex., Hydro.	Dex.	Dex., Hydro.	Dex.	Dex., Hydro.	Dex., Hydro.	Hydro.	Dex.	Dex., Hydro.	Dex.
Vasopressors	✓	✓	✓	✓		✓	✓	✓		✓	
Mechanical ventilation		✓	✓	✓		✓	✓	✓	✓	✓	
RRT		✓	✓	✓			✓	✓	✓	✓	
Plasmapheresis							✓			✓	
Mechanical circulatory support		VAD, V-A ECMO	VAD								
Remdesivir	✓										✓
Convalescent plasma						✓					
Outcomes											
Length of hospitalization, d	11	23	17	27	5	17	15	23	34	12	14
ICU admission	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Died in hospital or discharged to hospice	No	Yes	No	No	No	No	No	No	No	Yes	No

Abbreviations: Abd., abdominal; AF, atrial fibrillation; AKI, acute kidney injury; ARDS, acute respiratory distress syndrome; CKD, chronic kidney disease; COVID-19, coronavirus disease 2019; Dex., dexamethasone; DKA, diabetic ketoacidosis; ECMO, extracorporeal membrane oxygenation; HD, hospital day; HTN, hypertension; Hydro., hydrocortisone; ICU, intensive care unit; IgG, immunoglobulin G; LVEF, left ventricular ejection fraction; MR, mitral regurgitation; MRI, magnetic resonance imaging; ND, not done; PTA, prior to admission; RA, rheumatoid arthritis; RRT, renal replacement therapy; RT-PCR, reverse-transcription polymerase chain reaction; RV, right ventricle; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; T2DM, type 2 diabetes mellitus; TR, tricuspid regurgitation; V-A, venoarterial; VAD, ventricular assist device; VAP, ventilator-associated pneumonia; VT, ventricular tachycardia; VTE, venous thromboembolism.

[a]Previous COVID-19 was laboratory confirmed.

[b]Hospital day 0 is day of admission.

[c]Includes myocarditis, pericarditis, coronary artery dilatation or aneurysm, new-onset right or left ventricular dysfunction (LVEF <50%), new-onset second- or third-degree atrioventricular block, or ventricular tachycardia.

[d]Includes encephalopathy in a patient without prior cognitive impairment, seizures, meningeal signs, or peripheral neuropathy.

[e]Documented clinical diagnosis of shock, administration of vasoactive medications to augment blood pressure or cardiac output (eg, norepinephrine, dobutamine, milrinone), or systolic blood pressure <90 mm Hg on ≥2 consecutive measurements or on a single measurement requiring intervention (eg, intravenous fluid administration).

[f]Platelet count <150 000/μL.

[g]Repeat LVEF was measured by positron emission tomography prior to pharmacologic cardiac stress testing.

hypotension occurred in 10 patients (90.9%), gastrointestinal symptoms in 9 (81.8%), thrombocytopenia in 7 (63.6%), and neurologic signs or symptoms in 5 (45.5%). Laboratory findings were remarkable for neutrophilia with lymphopenia and elevated troponin I, brain natriuretic peptide, D-dimer, and laboratory markers of inflammation (Table 4).

Reduced LVEF was detected by echocardiography in all MIS-A patients (median LVEF nadir 35%) and right ventricular systolic dysfunction in 9 (81.8%) (Table 3). Regional wall motion abnormalities other than global hypokinesis were present in 2 patients (18.2%). None had apical akinesis characteristic of stress cardiomyopathy. Myocarditis was diagnosed by cardiac MRI in 2 patients (18.2%). Nine patients underwent repeat LVEF measurement during hospitalization, demonstrating improvement in systolic function (median LVEF, 55%–60%). In 7 patients, biventricular function normalized (median 7 days from LVEF nadir to LVEF ≥50%). Two patients were diagnosed with pericarditis. None had coronary artery aneurysm or dilatation.

Median length of MIS-A hospitalization was 17 days (range, 5–34 days) (Table 3). All patients were admitted to intensive care and 2 (18.2%) either died or were discharged to hospice. All patients developed acute kidney injury, requiring renal replacement therapy in 7 (63.6%). Two (18.2%) had rhabdomyolysis. Delayed-onset bacterial infection was confirmed in 3 patients (27.3%). All patients received systemic corticosteroids, but none received intravenous immunoglobulin or interleukin receptor antagonists. Six (54.5%) received stress dose hydrocortisone, including 1 patient diagnosed with primary adrenal insufficiency. Eight patients (72.7%) received vasopressors, 8 (72.7%) required mechanical ventilation, and 2 (18.2%) required mechanical cardiovascular circulatory support.

Table 4. Laboratory Testing Results of Patients With Multisystem Inflammatory Syndrome in Adults Discharged From 4 Acute Care Hospitals, Atlanta, Georgia, United States, 1 April 2020–31 January 2021

Laboratory Test	No. With Data Available	Result, Median (Range)
ANC peak, 10^3 cells/μL (normal range 0.9–5.5)	11	22.7 (12.9–45.9)
ALC nadir, 10^3 cells/μL (normal range 0.8–5.0)	11	0.4 (0.0–1.6)
Platelet count nadir, 10^3 cells/μL (normal range 150–450)	11	116 (41–304)
Troponin I peak, ng/mL (normal range ≤0.04)	11	2.60 (0.07–17.84)
BNP peak, pg/mL (normal range ≤99)	11	704 (40–4700)
D-dimer peak, ng/mL (normal range ≤574)	11	11 639 (4579–60 000)
CRP peak, mg/dL (normal range ≤1.0)	11	38.5 (10.3–48.0)
Ferritin peak, ng/mL (normal range 11–307)	9	1683 (153–37 580)
IL-6 peak, pg/mL (normal range ≤2)	8	141 (4–3172)
PCT peak, ng/mL (normal range ≤0.25)	6	11.15 (0.71–100.00)
ESR peak, mm/h (normal range ≤40)	4	126 (117–130)

Abbreviations: ALC, absolute lymphocyte count; ANC, absolute neutrophil count; BNP, brain natriuretic peptide; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; IL-6, interleukin 6; PCT, procalcitonin.

DISCUSSION

MIS-A is an infrequently reported condition hypothesized to represent postacute hyperinflammation occurring after SARS-CoV-2 infection. In the present single-center study, we found that MIS-A is remarkably rare; 1 case meeting the CDC MIS-A definition was identified for every 523 COVID-19 hospitalizations among adults discharged during 1 April 2020–31 January 2021. However, despite occurring mostly in young adults, outcomes were severe among the 11 identified cases: most patients required vasopressors, mechanical ventilation, and renal replacement therapy; 2 required mechanical cardiovascular circulatory support; and 2 died or were discharged to hospice. None were diagnosed with MIS-A during hospitalization, suggesting that although rare, MIS-A is an underrecognized condition.

Our estimate of MIS-A frequency relative to COVID-19 hospitalizations (1:523) is substantially lower than that of another retrospective cohort study at a single medical center in the southeastern US, which identified 15 patients with MIS-A among 839 adult patients with an admission surrounding or after a positive SARS-CoV-2 test [27]. This may be because the case definition used in the present study required more specific organ system involvement than that in the prior study. Furthermore, unlike the prior study, our comparison group included all adult inpatients with an *ICD-10-CM* code indicating COVID-19, not limited to those with a corresponding laboratory test in the EMR. Similar to prior results, however, none of the MIS-A cases identified in the present study were diagnosed during hospitalization, including those with documented SARS-CoV-2 infection >14 days prior [27]. In each case, the working diagnosis of the treatment team indicated complications of acute COVID-19. Also similar to prior results, MIS-A patients were younger compared with COVID-19 patients, and more likely to be non-Hispanic Black persons [5, 6, 19, 27]. Unlike prior reports, we did not identify MIS-A cases among Hispanic persons. Hispanic persons accounted for a low proportion of COVID-19 hospitalizations, likely reflecting the demographics of the catchment areas. Although most MIS-A patients were male, male patients were not significantly overrepresented compared with COVID-19 patients. Future studies with broader geographic representation are needed to elucidate demographic risk factors for MIS-A.

Although incidence remains unknown, MIS-A appears to be much rarer than MIS-C. An early retrospective cohort study identified 14 cases of MIS-C in Georgia during 1 April–30 June 2020, compared with 2840 reported cases of COVID-19 among persons younger than 21 years, including both hospitalized and nonhospitalized persons, during 1 March–31 May

2020 [28]. Despite the inclusion of nonhospitalized persons with COVID-19, which reduces the ratio of MIS-C to COVID-19, this ratio (1:203) is still higher than that for MIS-A in the present study. The relative rarity of MIS-A is consistent with the observation that MIS-C incidence decreases with age beginning in adolescence; the same study estimated population-based incidence of MIS-C to be 52% lower among adolescents and young adults aged 16–20 years than among children 5 years or younger [28].

As has been documented for MIS-C, most patients with MIS-A in the present study were not reported to have had prior COVID-19–like illness or SARS-CoV-2 infection [29]. Many young adults with acute SARS-CoV-2 infection have mild or no symptoms, so this history may be absent [30]. On the other hand, there may not have been clinical suspicion of MIS-A, so this history may not have been elicited. Patients in this study who did have prior COVID-19 or SARS-CoV-2 exposure did so primarily 4–7 weeks before MIS-A onset, consistent with recent surveillance [19]. One patient had ongoing household exposure at the time of presentation, which suggests that the multisystem illness was attributable to acute SARS-CoV-2 infection. Given phenotypic overlap between MIS-A and severe COVID-19 in adults, not requiring a documented prior SARS-CoV-2 infection is a limitation of the CDC case definition which, when applied in the absence of clinical judgment, may result in misclassification of some patients with COVID-19. However, small sample size notwithstanding, there was no clear distinction in organ system involvement or disease manifestation between the 3 identified MIS-A patients with SARS-CoV-2 infection or exposure >14 days prior to presentation and the other 8 patients. Ongoing prospective cohort studies may better elucidate the timing of MIS-A and other inflammatory consequences of COVID-19 relative to SARS-CoV-2 infection [31, 32].

Cardiomyopathy was uniformly present among patients with MIS-A in the present study, consistent with recent surveillance [19] and with a systematic review, which found that 77% of published MIS-A cases had cardiac dysfunction [6]. However, cardiomyopathy has also been described in acute COVID-19, complicating the diagnosis of MIS-A [33]. Indeed, myocarditis has been described in conjunction with COVID-19 [10] and SARS-CoV-2 RNA has been detected in endomyocardial biopsy specimens of hospitalized patients with impaired cardiac function and illnesses that may meet MIS-A criteria [34]. However, systematic reviews of COVID-19 myocarditis have reported a median/mean age of adult patients of approximately 50–60 years [11–15], similar to that of patients with other cardiac complications of COVID-19 [16] but unlike patients in the present study. Furthermore, although severe myocarditis may manifest shock and multiorgan dysfunction, fever has been reported in only 37%–54% of adult COVID-19 myocarditis cases, gastrointestinal symptoms in 11%–23%, and neurologic signs in 6%–11% [12–14]. By contrast, fever is nearly universally present in MIS-A patients and gastrointestinal and neurologic involvement much more common [6, 19]. That being said, the present study supports the phenotypic overlap between MIS-A and COVID-19 cardiovascular disease. Interestingly, even when SARS-CoV-2 RNA is detected in endomyocardial biopsy specimens, onset of cardiomyopathy may occur 3–4 weeks after recovery from acute COVID-19 [35–37]. Additional studies are needed to determine whether extrapulmonary organ dysfunction, including cardiomyopathy, makes up a spectrum of disease including MIS-A and acute COVID-19 hyperinflammation.

Similar proportions of MIS-A patients in this study manifested gastrointestinal, hematologic, and neurologic organ system dysfunction as previously reported [6, 19]. Mucocutaneous involvement, however, although common among MIS-C patients [29, 38] and described in MIS-A case reports [6], was absent in this study. Rashes and skin eruptions are underreported in EMRs, which may limit the sensitivity of our search strategy in identifying these manifestations [39]. Moreover, patients with mucocutaneous inflammation and illnesses compatible with MIS-A may not have undergone SARS-CoV-2 laboratory testing if clinical suspicion for a SARS-CoV-2–related illness was low. It remains unclear whether mucocutaneous manifestations of MIS-A are underrecognized.

Our results are subject to at least 3 limitations in addition to those previously discussed. First, most MIS-A patients did not undergo serologic testing and had positive RT-PCR results. In contrast, 25%–60% of MIS-A patients in recent literature who underwent RT-PCR tested negative [6, 19]. We may have underdetected MIS-A due to infrequent serologic testing of patients with a compatible illness. Early during the pandemic, serologic testing may not have been available. Second, although most encounters screened in the automated step had at least 2 inflammatory marker results, some MIS-A patients may have had only 1 performed and would have been missed. Third, workup for alternative diagnoses may have been incomplete, missing rheumatologic or cardiovascular causes. Not all patients had baseline cardiac imaging and some may have had undiagnosed cardiomyopathy preceding the present illness, leading to misclassification.

We applied the CDC case definition to identify MIS-A cases through EMR search. Our results demonstrate that MIS-A is an uncommon, but severe and likely underrecognized complication of SARS-CoV-2 infection. It is more common among younger and non-Hispanic Black adults. Providers should combine clinical judgement with application of the CDC case definition to identify patients with MIS-A. Increased provider awareness of MIS-A may increase diagnosis and reporting, help to quantify its epidemiologic burden, and identify populations at highest risk.

Notes

Acknowledgments. The authors thank the staff from the Georgia Department of Public Health and Emory Healthcare Information and Technical Services for their support of this study.

Disclaimer. The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

Potential conflicts of interest. The authors: No reported conflicts of interest. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest.

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