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 supplement 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...
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 accordance 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).

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/m2 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.
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

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### 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 | 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 a | Maximum recorded temperature ≥38.0°C at any time during hospitalization | Maximum recorded temperature ≥38.0°C during first 3 d of hospitalization a |
| 5         | At least 3 of the following clinical criteria occurring prior to or within 3 d of hospitalization b | 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 |
| 6         | Laboratory evidence of severe inflammation c | Positive test for SARS-CoV-2 infection during hospitalization (by RT-PCR or serology d) |
| 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) |

Abbreviation: CDC, Centers for Disease Control and Prevention; CRP, C-reactive protein; 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.

aAll criteria must be met for study inclusion.
bCriterion must be met by the end of hospital day 3, where the date of hospital admission is hospital day 0.
cIncludes 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.
dIncludes encephalopathy in a patient without prior cognitive impairment, seizures, meningeal signs, or peripheral neuropathy (including Guillain-Barré syndrome).
eDocumented clinical diagnosis or administration of vasoactive medications to augment blood pressure or cardiac output (eg, norepinephrine, dobutamine, milrinone).
fSystolic blood pressure <90 mm Hg on ≥2 consecutive measurements or requiring intervention (eg, intravenous fluid administration).
gIncludes elevated levels of at least 2 of the following: CRP, ferritin, IL-6, ESR, PCT.
hAntigen testing was not systematically recorded in the EMR.
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%, \( P = .04 \)).

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

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**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 \( (n=11) \) | Patients With COVID-19 \( (n=5471) \) | \( P \) Value
|-----------------------------------------------------|-----------------------------------|----------------------------------------|---------------------
| 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. (%)                     |                                   |                                        | \(.04\)            |
| Black, non-Hispanic                                 | 9 (81.8)                          | 2738 (50.0)                            |                    |
| White, non-Hispanic                                 | 2 (18.2)                          | 1564 (28.6)                            | \(.73\)            |
| Hispanic                                            | 0 (0.0)                           | 456 (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.

6Full MIS-A inclusion criteria for this study after automated query of the electronic medical record and manual review (Table 1).

7International 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.

8Barnard exact test.
### 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     | 40–44     | 50–54     | 50–54     | ≥80        |
| Sex                                                 | Male      | Female    | Male      | Male      | Female    | Male      | Male      | Male      | Male      | Male       | Female     |
| Underlying medical condition(s)                      | None      | Obesity   | Asthma, tobacco smoker | Hypothyroidism | Obesity | Obesity | 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, myalgia | Fever, fatigue, myalgia | Fever, fatigue | Fever, fatigue | Fever, fatigue | Fever, fatigue |
| Gastrointestinal                                    | Abd. pain, diarrhea | Abd. pain, diarrhea, vomiting | Abd. pain, diarrhea, vomiting | Abd. pain, diarrhea | Abd. pain, diarrhea, vomiting | Abd. pain, diarrhea, vomiting | Abd. pain, diarrhea | Abd. pain, diarrhea | Abd. pain, diarrhea | Abd. pain, diarrhea |
| Lower respiratory                                    | Dyspnea   | Cough, dyspnea |           |           |           |           |           |           |           |            |            |
| Upper respiratory                                    | Anosmia    | Cervical lymphadenopathy |           |           |           |           |           |           |           |            |            |
| Neurologic                                          |           |           |           |           |           |           |           |           |           |            |            |
| Evidence of prior SARS-CoV-2 antigenic exposure      |           |           |           |           |           |           |           |           |           |            |            |
| Previous COVID-19 symptom onset                     | None      | None      | 55 d PTA  | None      | 37 d PTA  | None      | None      | None      | None      | None       | None       |
| Known COVID-19 exposure                             | None      | None      | None      | None      | None      | None      | None      | None      | None      | None       | None       |
| COVID-19 vaccination                                 | None      | None      | None      | None      | None      | None      | None      | None      | None      | 0–10 d PTA | None       |
| SARS-CoV-2 testing during present hospitalization   |           |           |           |           |           |           |           |           |           |            |            |
| RT-PCR                                              | ++        | +         | +         | +         | +         | ND        | +         | +         | +         | +          | +          |
| Anti–spike protein IgG                               | ND        | +         | ND        | ND        | +         | ND        | ND        | ND        | ND        | ND          |
| Clinical criteria met prior to or during hospital days 0–30 | ✓          | ✓          | ✓          | ✓          | ✓          | ✓          | ✓          | ✓          | ✓          | ✓          |
| Severe cardiac illness                               | ✓          | ✓          | ✓          | ✓          | ✓          | ✓          | ✓          | ✓          | ✓          | ✓          |
| Rash and nonpulmonary conjunctivitis                 | ✓          | ✓          | ✓          | ✓          | ✓          | ✓          | ✓          | ✓          | ✓          | ✓          |
| New-onset neurologic signs and symptoms               | ✓          | ✓          | ✓          | ✓          | ✓          | ✓          | ✓          | ✓          | ✓          | ✓          |
| Shock or hypotension not attributable to medical therapy | ✓        | ✓          | ✓          | ✓          | ✓          | ✓          | ✓          | ✓          | ✓          | ✓          |
| Abdominal pain, vomiting, or diarrhea                | ✓          | ✓          | ✓          | ✓          | ✓          | ✓          | ✓          | ✓          | ✓          | ✓          |
| Thrombocytopenia                                    | ✓          | ✓          | ✓          | ✓          | ✓          | ✓          | ✓          | ✓          | ✓          | ✓          |
| Evaluation of cardiomyopathy                         | ✓          | ✓          | ✓          | ✓          | ✓          | ✓          | ✓          | ✓          | ✓          | ✓          |
| LVEF nadir                                           | 40%, HD 2  | 10%, HD 3 | 26%, HD 2 | 15%, HD 1 | 35%, HD 0 | 40%, HD 3 | 25%, HD 1 | 30%, HD 1 | 46%, 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 |
| RV systolic dysfunction                              | Moderate  | Severe    | Severe    | Mild      | Mild      | Mild      | Moderate  | None      | Mild      | Severe     | None       |
| LVEF recovery or last measurement                    | 55%–60%, HD 8 | 65%, HD 14 | 55%–60%, HD 22 | 60%–65%, HD 3 | Not repeated | 70%–75%, HD 8 | 35%, HD 3 | 35%, HD 3 | 40%, HD 6 | Not repeated |
| 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                             | ND                             | ND                             | No evidence of myocarditis    | ND                             | ND                             | ND                             | ND                             |
| Complications                                                                 |                                 |                                |                                |                                |                                |                                |                                |                                |                                |                                |                                |
| Cardiac                                                                       | Mild MR                        | Moderate MR & TR, AF            | Severe MR & TR, VT             | Moderate MR                    | Moderate MR                    | AF                             | AF                             | AF                             | Mild MR                        |                                |
| Pulmonary                                                                     | Pleural effusion               | ARDS, pleural effusion         | ARDS, pleural effusion         | ARDS, pleural effusion         | ARDS, pleural effusion         | Pleural effusion               | ARDS, pleural effusion         |                                |                                |                                |
| Infectious                                                                    |                                 |                                |                                |                                |                                |                                |                                |                                |                                |                                |                                |
| Other                                                                          | AKI, pulmonary embolism, anoxic brain injury | AKI, rhabdomyolysis, critical illness neuropathy | AKI, primary adrenal insufficiency | AKI, rhabdomyolysis | AKI, DKA, acute liver failure | AKI                            | AKI                            | AKI                            | AKI                            | AKI                            |
| Treatments administered                                                        |                                 |                                |                                |                                |                                |                                |                                |                                |                                |                                |                                |
| Systemic corticosteroids                                                       | Dex.                           | Dex., Hydro.                    | Dex.                           | Dex.                           | Dex.                           | Dex.                           | Dex.                           | Dex.                           | Dex.                           | Dak                           |
| 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                             | No                             | 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.

Previous COVID-19 was laboratory confirmed.

Hospital day 0 is day of admission.

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

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

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).

Platelet count <150,000/μL.

Repeat LVEF was measured by position 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.

**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 nonhospitized persons, during 1 March–31 May

| 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 | 11639 (4579–60000) |
| 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 (153–37580) |
| 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, mmmh (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.
Although 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
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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.

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References
1. Riphagen S, Gomez X, Gonzalez-Martinez C, Wilkinson N, Theocharis P. Hyperinflammatory shock in children during COVID-19 pandemic. Lancet 2020; 395:1607–8.
2. Feldstein LR, Rose EB, Horwitz SM, et al. Multisystem inflammatory syndrome in U.S. children and adolescents. N Engl J Med 2020; 383:334–46.
3. DuFort EM, Koumans EH, Chow EJ, et al. Multisystem inflammatory syndrome in children in New York state. N Engl J Med 2020; 383:347–58.
4. Centers for Disease Control and Prevention. Multisystem inflammatory syndrome in children (MIS-C) associated with coronavirus disease 2019 (COVID-19): HAN00432. Available at: https://emergency.cdc.gov/han/2020/han0432.asp. Accessed 1 March 2022.
5. Morris SB, Schwartz NG, Patel P, et al. Case series of multisystem inflammatory syndrome in adults associated with SARS-CoV-2 infection—United Kingdom and United States, March–August 2020. MMWR Morb Mortal Wkly Rep 2020; 69:1450–6.
6. Patel P, DeCuir J, Abrams J, Campbell AP, Godfred-Cato S, Belay ED. Clinical characteristics of multisystem inflammatory syndrome in adults: a systematic review. JAMA Netw Open 2021; 4:e2126456.
7. Gupta A, Madhavan MV, Sehgal K, et al. Extrapulmonary manifestations of COVID-19. Nat Med 2020; 26:1017–32.
8. Webb BJ, Peltan ID, Jensen P, et al. Clinical criteria for COVID-19-associated hyperinflammatory syndrome: a cohort study. Lancet Rheumatol 2020; 2:e754–63.
9. Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet 2020; 395:1054–62.
10. Tavazzi G, Pellegriini C, Maurelli M, et al. Myocardial localization of coronavirus in COVID-19 cardiogenic shock. Eur J Heart Fail 2020; 22:911–5.
11. Mele D, Flamigni F, Rapezzi C, Ferrari R. Myocarditis in COVID-19 patients: current problems. Intern Emerg Med 2021; 16:1123–9.
12. Haussner W, DeRosa AP, Haussner D, et al. COVID-19 associated myocarditis: a systematic review. Am J Emerg Med 2022; 51:150–5.
13. Castiello T, Georgiopoulos G, Finocchiaro G, et al. COVID-19 and myocarditis: a systematic review and overview of current challenges. Heart Fail Rev 2022; 27: 251–61.
14. Rathore SS, Rojas GA, Sondhi M, et al. Myocarditis associated with Covid-19 disease: a systematic review of published case reports and case series. Int J Clin Pract 2021; 75:e14470.
15. Maiers A, Frati P, Del Duca F, et al. Myocardial pathology in COVID-19-associated cardiac injury: a systematic review. Diagnostics (Basel) 2021; 11:1647.
16. Diaz-Arocita C, Torres-Valencia J, Saucedo-Chinchay J, Cueva S. ST-segment elevation in patients with COVID-19: a systematic review. J Thromb Thrombolysis 2021; 52:738–45.
17. Centers for Disease Control and Prevention. Centers for Disease Control and Prevention COVID data tracker. Available at: https://covid.cdc.gov/covid-data-tracker/. Accessed 1 March 2022.
18. Centers for Disease Control and Prevention. Multisystem inflammatory syndrome in adults (MIS-A) – case definition. Available at: https://www.cdc.gov/mis-a/hcp.html. Accessed 1 March 2022.
19. Belay E, Godfred-Cato S, Rao A, et al. Multisystem inflammatory syndrome in adults after SARS-CoV-2 infection and COVID-19 vaccination. Clin Infect Dis 2021. doi:10.1093/cid/ciaa936.
20. United States Department of Health and Human Services. Code of Federal Regulations; 45 C.F.R. part 46.102(d)(2); 21 C.F.R. part 56. Available at: https://ecfr.federalregister.gov/. Accessed 1 March 2022.
21. United States House of Representatives. United States Code; 42 USC §241(d); 5 USC §552a; 44 USC §3501 et seq. Office of the Law Revision Counsel. Available at: https://uscode.house.gov/. Accessed 1 March 2022.
22. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)—a metadata-driven methodology and workflow process for providing translational research informatics support. J Biomed Inform 2009; 42:377–81.
23. Harris PA, Taylor R, Minor BL, et al. The REDCap consortium: building an international community of software platform partners. J Biomed Inform 2019; 95:103208.
24. United States Department of Food and Drug Administration. Emergency Use Authorization (EUA) for an unapproved product review memorandum. Available at: https://www.fda.gov/media/144416/download. Accessed 1 March 2022.
25. Kadri SS, Gundrum J, Warner S, et al. Uptake and accuracy of the diagnosis code for COVID-19 among US hospitalizations. JAMA 2020; 324:2553–4.
26. Barnard GA. A new test for 2+2 tables. Nature 1945; 156:177.
27. Davogutso GE, Clark DE, Hardison E, et al. Characteristics associated with multisystem inflammatory syndrome among adults with SARS-CoV-2 infection. JAMA Netw Open 2021; 4:e2110323.
28. Payne AB, Gillani Z, Godfred-Cato S, et al. Incidence of multisystem inflammatory syndrome in children among US persons infected with SARS-CoV-2. JAMA Netw Open 2021; 4:e2116420.
29. Belay ED, Abrams J, Oster ME, et al. Trends in geographic and temporal distribution of US children with multisystem inflammatory syndrome during the COVID-19 pandemic. JAMA Pediatr 2021; 175:837–45.
30. Gao Z, Xu Y, Sun C, et al. A systematic review of asymptomatic infections with COVID-19. J Microbiol Immunol Infect 2021; 54:12–6.
31. Blaser MJ, Barrett ES, Gennaro ML, Horton DB. Cohort and biomarkers for COVID-19 severity, natural history, and reinfection. National Institutes of Health, 2021. Available at: https://reporter.nih.gov/search/v-czdl/USKENVPnWcYBNw/project-details/10375868. Accessed 1 March 2022.
32. Kaufman KM. COVID-19: anti-SARS-CoV-2 antibodies and infection severity. National Institutes of Health, 2021. Available at: https://reporter.nih.gov/search/3ml3yiHGeCaCpFrb6UOGj/project-details/10512299. Accessed 1 March 2022.
33. Most ZM, Hendren N, Drazner MH, Perl TM. Sticking similarities of multisystem inflammatory syndrome in children and a myocarditis-like syndrome in adults: overlapping manifestations of COVID-19. Circulation 2021; 143:4–6.
34. Kawakami R, Sakamoto A, Kawai K, et al. Pathological evidence for SARS-CoV-2 as a cause of myocarditis: JACC review topic of the week. J Am Coll Cardiol 2021; 77:314–25.
35. Wenzel P, Kopp S, Gobel S, et al. Evidence of SARS-CoV-2 mRNA in endomyocardial biopsies of patients with clinically suspected myocarditis tested negative for COVID-19 in nasopharyngeal swab. Cardiovasc Res 2020; 116:1661–3.
36. Escher F, Pietsh E, Aleshcheva G, et al. Detection of viral SARS-CoV-2 genomes and histopathological changes in endomyocardial biopsies. ESC Heart Fail 2020; 7:2440–7.
37. Ishikura H, Maruyama J, Hoshino K, et al. Coronavirus disease (COVID-19) associated delayed-onset fulminant myocarditis in patient with a history of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. J Infect Chemother 2021; 27:1760–4.
38. Feldstein LR, Tenforde MW, Friedman KG, et al. Characteristics and outcomes of US children and adolescents with multisystem inflammatory syndrome in children (MIS-C) compared with severe acute COVID-19. JAMA 2021; 325:1074–87.
39. Cadieux G, Buckeridge DL, Jacques A, Libman M, Dendukuri N, Tamlyn R. Accuracy of syndrome definitions based on diagnoses in physician claims. BMC Public Health 2011; 11:37.