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Multisystem Inflammatory Syndrome in Adults Among Critically Ill Patients With COVID-19: Frequency, Clinical Characteristics, and Exploratory Survival Analysis

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Short Report

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Abstract

Objective

Multisystem inflammatory syndrome in adults (MIS-A) is a post–SARS-CoV-2 inflammatory condition whose frequency and clinical relevance among critically ill patients remain poorly defined. We aimed to determine the frequency and clinical characteristics of MIS-A and explore its relationship with clinical outcomes and survival in critically ill adults with COVID-19.

Results

In this retrospective cohort of 266 adults with confirmed COVID-19 admitted to a tertiary-care intensive care unit, MIS-A was identified using an operationalized Centers for Disease Control and Prevention case definition. Thirteen patients (4.9%) fulfilled MIS-A criteria. No statistically significant differences in hospital mortality or ICU and hospital survival were observed between patients with and without MIS-A. Fever-associated hyperinflammatory states were frequent and associated with lower observed survival. These findings indicate that MIS-A was uncommon in this critically ill population and was not significantly associated with mortality; however, the small number of MIS-A cases limits definitive prognostic inference. The observed association between hyperinflammation and survival should be considered exploratory and may reflect residual confounding by illness severity.

INTRODUCTION

Multisystem inflammatory syndrome in adults (MIS-A) is a severe post-infectious complication of SARS-CoV-2 characterized by hyperinflammation, multisystem dysfunction, and prominent cardiovascular involvement occurring days to weeks after acute infection. Although MIS-A shares immunopathologic features with pediatric MIS-C, its presentation in adults is more heterogeneous and often overlaps with severe or critical COVID-19, septic shock, myocarditis, or other inflammatory states commonly encountered in the intensive care unit (ICU).[1–3]

Since its first description in 2020, MIS-A has been considered uncommon, with estimated incidences ranging from 0.02% to 0.15% depending on surveillance methodology and population studied in hospitalized cohorts and fewer than 1 case per 500 COVID-19 admissions in surveillance datasets.[4–6] However, these estimates are derived largely from administrative databases or mixed inpatient populations, where detailed clinical, laboratory, and imaging data needed for accurate case identification are often absent. Evidence on the epidemiology, diagnostic challenges, and outcomes of MIS-A in critically ill adults remains extremely limited. Most published data consist of small case series, retrospective reviews, or database surveillance studies lacking granularity on severity of illness, organ dysfunction, and ICU-specific outcomes.[5–8]

For intensivists, early recognition of MIS-A is clinically relevant because the syndrome may mimic refractory COVID-19, bacterial sepsis, or cardiogenic shock, potentially delaying immunomodulatory therapy. The diagnosis is further complicated in the ICU, where fever, elevated inflammatory markers, and multiorgan dysfunction are common but may reflect alternative etiologies such as secondary infection, cytokine storm, or progression of acute respiratory distress syndrome (ARDS).[9–11] This overlap raises concern that MIS-A may be underdiagnosed in critically ill populations, and its true incidence and clinical impact remain unknowable without detailed chart-level adjudication.

To address these knowledge gaps, we conducted a retrospective cohort study evaluating the frequency, clinical characteristics, and outcomes of MIS-A among adults with laboratory-confirmed COVID-19 admitted to a dedicated COVID-19 ICU at a tertiary referral center. By applying a prespecified operational definition and reviewing detailed clinical data, we aimed to determine the frequency and clinical characteristics of MIS-A and explore its associations with clinical outcomes in critically ill adults with COVID-19.

MATERIAL AND METHODS

Study Design and Setting

We conducted a retrospective cohort study of adults admitted to the Intensive Care Unit (ICU) of a tertiary public hospital referral center for COVID-19 care. The study period spanned from March 2020 to May 2021, covering the first major pandemic waves in the region.

All data were obtained through review of electronic medical records. The study protocol was approved by the institutional Research Ethics Committee (approval No. 5.187.336; Certificate of Ethical Appreciation No. 52553721.0.0000.0071). Given that the study used de-identified retrospective data, informed consent was waived by the Institutional Review Board.

Patient Eligibility

Eligible participants were adults aged ≥ 18 years, with laboratory-confirmed SARS-CoV-2 infection by reverse transcription polymerase chain reaction (RT-PCR) or serology, admitted to the ICU during the study period. We excluded patients with suspected but unconfirmed COVID-19; ICU admission for reasons unrelated to COVID-19 infection; transfer to another facility before a final outcome (death or discharge) could be determined. This resulted in 266 patients included in the final analysis. A sensitivity assessment excluding patients aged 18–20 years was performed to verify that adaptation of the CDC age criterion did not materially affect case classification.

Case Identification and Operational Definition of MIS-A

MIS-A was identified retrospectively through structured review of clinical, laboratory, and imaging data using a prespecified operational definition based on CDC criteria available at the time the study protocol was developed. The classification algorithm comprised four mandatory criteria: (1) fever associated with elevated inflammatory markers; (2) laboratory-confirmed recent SARS-CoV-2 infection by RT-PCR or serology, with onset of the inflammatory syndrome within 12 weeks of confirmed infection; (3) exclusion of other potential causative conditions; and (4) absence of severe respiratory disease sufficient to explain organ dysfunction through tissue hypoxia. Patients fulfilling all four mandatory criteria were subsequently assessed for five additional clinical manifestations: mucocutaneous involvement, hypotension or shock, cardiovascular involvement, coagulation abnormalities and/or liver injury, and new-onset gastrointestinal symptoms.

Patients were classified as having MIS-A when all four mandatory criteria and at least two of the five additional clinical criteria were fulfilled. Criteria were assessed sequentially during chart review; therefore, not all downstream criteria were available for patients who failed an earlier step of the diagnostic algorithm. The complete operational definitions used for classification are provided in Supplementary Table S1.

Because the study population included adults aged ≥ 18 years, whereas the original CDC working definition used an age threshold of ≥ 21 years, a sensitivity analysis excluding patients aged 18–20 years was performed.

Data Collection

Data extracted for the 266 included patients comprised demographic characteristics, comorbidities, COVID-19 timeline, ICU interventions, and clinical outcomes. MIS-A diagnostic criteria were assessed according to the sequential classification algorithm described above. Consequently, availability of individual diagnostic criteria varied according to the stage reached in the diagnostic assessment.

Outcomes

The primary outcome was the frequency of MIS-A among critically ill adults with confirmed COVID-19. Outcome analyses were considered exploratory given the limited number of patients fulfilling MIS-A criteria. Secondary outcomes included hospital length of stay, ICU length of stay, in-hospital mortality, and transition to exclusive palliative care. We also evaluated survival differences according to fulfillment of individual mandatory MIS-A diagnostic criteria.

Statistical Analysis

Continuous variables were summarized using means and standard deviations or medians with interquartile ranges, depending on normality assessed by the Shapiro-Wilk test. Categorical variables were compared using Fisher’s exact test when appropriate. Survival analyses were performed using the

Kaplan-Meier method, with comparisons between groups using the log-rank test. To explore associations between MIS-A and time to death, univariate Cox proportional hazards models were fitted. Because the number of MIS-A cases was small (n = 13), all survival analyses were considered exploratory, and no multivariable models were performed. All statistical analyses were conducted using R version 4.1.1 (R Foundation for Statistical Computing). All statistical tests were interpreted cautiously given the exploratory nature of the analyses.

Given the small number of MIS-A cases, the study was not powered to detect modest differences in mortality between MIS-A and non–MIS-A groups. Therefore, absence of statistical significance should not be interpreted as evidence of equivalence.

RESULTS

Study population

A total of 266 adult patients with confirmed COVID-19 admitted to the intensive care unit were included in the study (Fig. 1). Among the 266 included patients, 13 (4.9%) fulfilled the prespecified operational MIS-A definition (Supplementary Table S1). Sensitivity analysis excluding patients aged 18–20 years did not alter MIS-A classification.

Baseline demographic characteristics and comorbidities of patients with and without MIS-A are summarized descriptively in Table 1. Overall, both groups comprised predominantly older adults with a substantial burden of chronic comorbid conditions.

Table 1
Baseline characteristics of patients with and without MIS-A (N = 266).

Characteristic	MIS-A (n = 13)	Non–MIS-A (n = 253)
Age, years, median (IQR)	63(55–70)	62(52–71)
TS, days, median (IQR)	8(4–10)	7(3–10)
Male sex, n (%)	7(53.8)	153(60.5)
Hypertension, n (%)	7(53.8)	160(63.2)
Diabetes mellitus, n (%)	4(30.8)	92(36.4)
Obesity, n (%)	0(0)	57(22.5)
Cancer, n (%)	3(23.1)	71(28.1)
Chronic lung disease, n (%)	2(15.4)	18(7.11)
Heart Failure, n(%)	2(15.4)	12(4.74)
Chronic kidney disease, n (%)	2(15.4)	20(7.91)
No comorbidities, n (%)	1(7.69)	19(7.51)
Data presented as median (IQR) or n (%).		
MIS-A = Multisystem Inflammatory Syndrome in Adults.		
TS: Time between onset of symptoms and hospital admission.		

Distribution of MIS-A diagnostic criteria

The distribution of individual diagnostic criteria for MIS-A is detailed in Table 2. Although several patients met one or more components of the operational MIS-A definition, fulfillment of the complete classification criteria was uncommon. Evidence of a fever-associated hyperinflammatory state (Criterion 1) was frequently observed in the cohort, whereas other mandatory and supportive criteria were less consistently present.

Table 2
Distribution of operational MIS-A diagnostic criteria according to MIS-A status.

Operational criterion	MIS-A (n = 13), n/N (%)	Non–MIS-A (n = 253), n/N (%)
Mandatory criteria		
1. Fever and systemic inflammation	13/13 (100%)	170/252 (67.5%)
2. Recent SARS-CoV-2 infection and timing criterion	13/13 (100%)	167/170 (98.2%)
3. Exclusion of alternative causes	13/13 (100%)	35/170 (20.6%)
4. Absence of severe respiratory disease	13/13 (100%)	61/170 (35.9%)
Additional clinical criteria		
5. Mucocutaneous involvement	1/13 (7.7%)	0/20 (0%)
6. Hypotension or shock	6/13 (46.2%)	0/20 (0%)
7. Cardiovascular involvement	8/13 (61.5%)	0/20 (0%)
8. Coagulation abnormalities and/or liver injury	10/13 (76.9%)	1/20 (5.0%)
9. New-onset gastrointestinal symptoms	5/13 (38.5%)	1/20 (5.0%)
Fulfilled complete operational MIS-A definition	**13/13 (100%)**	**0/253 (0%)**

Among the additional clinical criteria, cardiovascular involvement and coagulation abnormalities and/or liver injury were the most frequently observed manifestations among patients classified as MIS-A, whereas mucocutaneous involvement was uncommon.

Clinical outcomes

Clinical outcomes of patients with and without MIS-A are summarized in Table 3. Crude in-hospital mortality was similar numerically between groups (53.8% vs 53.0%). Hospital and ICU length of stay are presented descriptively in Table 3. Transition to palliative care occurred more frequently among patients with MIS-A (46.2% vs 20.6%; p = 0.040), although this finding should be interpreted cautiously given the small number of MIS-A cases and the exploratory nature of the comparison.

Table 3
Clinical outcomes of MIS-A and non–MIS-A patients.

Outcome	MIS-A (n = 13)	Non–MIS-A (n = 253)	p-value
In-hospital mortality	7 (53.8%)	134 (53%)	0.999
Palliative care transition	6 (46.2%)	52 (20.6%)	0.040
Hospital length of stay, days, median (IQR)	14 (11–25)	18 (10–31)	—
ICU length of stay, days, median (IQR)	12 (5–17)	10 (5–22)	—

Survival analyses

Kaplan–Meier survival analyses stratified by MIS-A status are shown in Supplemental Figs. 1 and 2. No statistically significant differences in ICU or hospital survival were observed between patients with and without MIS-A; however, effect estimates were imprecise because only 13 patients fulfilled MIS-A criteria. Survival curves crossed over time, suggesting non-proportional hazards. In contrast, when survival was analyzed according to fulfillment of Criterion 1 (fever-associated hyperinflammatory state), patients meeting this criterion demonstrated significantly lower survival compared with those who did not, as illustrated in Supplemental Fig. 3. Estimated survival probabilities at clinically relevant time points are presented in Supplemental Table S3.

Exploratory univariate Cox proportional hazards regression analyses are summarized in Supplemental Table S2. While MIS-A diagnosis was not associated with mortality, fulfillment of Criterion 1 was associated with an increased hazard of death. Given the small number of MIS-A cases and evidence of non-proportional hazards, Cox regression estimates were considered exploratory and no multivariable Cox model was fitted.

DISCUSSION

This study provides new insight into the occurrence and clinical characteristics of multisystem inflammatory syndrome in adults (MIS-A) among critically ill patients hospitalized with COVID-19. MIS-A was uncommon, and no statistically significant association with mortality or survival was observed. However, the small number of MIS-A cases limits the precision of these estimates and precludes definitive prognostic conclusions. In contrast, the fever-associated hyperinflammatory state represented by Criterion 1 was frequently observed and was associated with poorer survival in exploratory analyses.

Previous reports have emphasized the severity of MIS-A and its frequent need for hospitalization and intensive care.[1–5] However, much of the existing evidence derives from case series, surveillance reports, or heterogeneous cohorts with limited representation of patients who are already critically ill at presentation.[2, 3, 7] Within this context, our findings suggest that distinguishing MIS-A from other

hyperinflammatory manifestations of critical COVID-19 may be challenging in the ICU setting, where systemic inflammation and multiorgan dysfunction are common.[6, 8, 11]

Importantly, the present study was designed primarily to estimate the occurrence of MIS-A in a critically ill COVID-19 population rather than to establish prognostic effects. Only 13 patients fulfilled the complete MIS-A definition, resulting in limited statistical precision. Consequently, the absence of statistically significant survival differences should not be interpreted as evidence that MIS-A has no prognostic relevance. Larger multicenter cohorts are needed to evaluate this question adequately.

An important observation was the distinction between MIS-A as a categorical diagnosis and the presence of hyperinflammation. While fulfillment of the complete MIS-A definition was uncommon, fever-associated hyperinflammatory states were frequently observed and were associated with poorer survival in exploratory analyses. This observation is consistent with previous studies identifying immune dysregulation and excessive inflammatory responses as important features of severe COVID-19.[12, 13] The demonstrated benefit of anti-inflammatory therapies, particularly corticosteroids, further supports the biological relevance of inflammation in severe COVID-19.[10, 14] However, the association observed in our cohort should not be interpreted as evidence that hyperinflammation independently predicts mortality or that inflammatory phenotyping is superior to syndromic MIS-A classification, because residual confounding by severity of illness cannot be excluded.

Survival analyses should be interpreted as exploratory. Although no statistically significant differences in ICU or hospital survival were observed according to MIS-A status, poorer survival was observed among patients fulfilling the hyperinflammatory criterion. Given the small number of patients with MIS-A and evidence of non-proportional hazards, Cox regression estimates were considered exploratory and no multivariable Cox model was fitted. Consequently, these analyses should be interpreted as descriptive associations rather than estimates of independent prognostic effects.[15]

This study has several strengths. It evaluates MIS-A in a well-defined cohort of critically ill patients with COVID-19, applies a prespecified operationalized CDC-based case definition, and integrates detailed clinical characterization with exploratory time-to-event analyses. The systematic assessment of MIS-A within an exclusively ICU-based cohort provides data from a population that has been underrepresented in previous reports.

LIMITATIONS

This study has several limitations. First, its retrospective, single-center design limits causal inference and generalizability to other critically ill populations. MIS-A classification relied on routinely collected clinical and laboratory data, and incomplete ascertainment or variation in the timing of inflammatory measurements may have resulted in misclassification. In addition, the cohort was restricted to the early phase of the COVID-19 pandemic, before widespread vaccination and the emergence of later SARS-CoV-2 variants, which limits applicability to contemporary populations.

Second, only 13 patients fulfilled the complete MIS-A criteria, resulting in limited statistical precision and low power to detect modest differences in clinical outcomes. Accordingly, the absence of statistically significant differences in mortality or survival should not be interpreted as evidence of equivalence or absence of prognostic relevance. The small number of MIS-A cases also limited the feasibility of robust multivariable adjustment. Survival analyses were therefore exploratory, and residual confounding—particularly by severity of illness—cannot be excluded. Finally, the observed association between hyperinflammation and poorer survival should not be interpreted as an independent prognostic effect, as inflammatory abnormalities may partly reflect the severity of the underlying critical illness.

The operational MIS-A definition required exclusion of severe respiratory disease as the primary explanation for organ dysfunction; however, retrospective differentiation between MIS-A and severe acute COVID-19 may be challenging in an ICU population and remains susceptible to classification error. Exclusion of patients transferred before ascertainment of the final hospital outcome may also have introduced selection bias.

CONCLUSION

In this cohort of critically ill adults with COVID-19, MIS-A was uncommon, affecting approximately 5% of patients. No statistically significant association between MIS-A and mortality was observed, although the limited number of MIS-A cases restricts definitive prognostic inference. Fever-associated hyperinflammatory states were frequent and associated with lower observed survival; however, residual confounding by illness severity cannot be excluded. Larger multicenter studies are required to clarify the prognostic implications of MIS-A and the clinical relevance of inflammatory phenotypes in critically ill patients.

Abbreviations

AKI — Acute kidney injury

ARDS — Acute respiratory distress syndrome

CDC — Centers for Disease Control and Prevention

COVID-19 — Coronavirus disease 2019

CRP — C-reactive protein

ICU — Intensive care unit

IL-6 — Interleukin-6

IQR — Interquartile range

KM — Kaplan–Meier

LOS — Length of stay

MIS-A — Multisystem inflammatory syndrome in adults

OR — Odds ratio

RRT — Renal replacement therapy

SARS-CoV-2 — Severe acute respiratory syndrome coronavirus 2

SOFA — Sequential Organ Failure Assessment

WHO — World Health Organization

Declarations

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Consent to participate: Given that the study used de-identified retrospective data, informed consent was waived by the Institutional Review Board.

Written Consent for publication: Not applicable

Availability of data and material (data transparency): The datasets analyzed during the current study are available from the corresponding author upon reasonable request.

Code availability (software application or custom code): Not applicable.

Authors' contributions:

LMMM, LGP: Conceptualization, Methodology, Data curation, Original draft preparation. **LMMM, ELF**: Data curation, Writing, Software. **LGP, CCGP, SERP**: Visualization, Methodology, Validation, Supervision. **LGP, CCGP, SERP**: Validation, Supervision, Reviewing and Editing.

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Figures

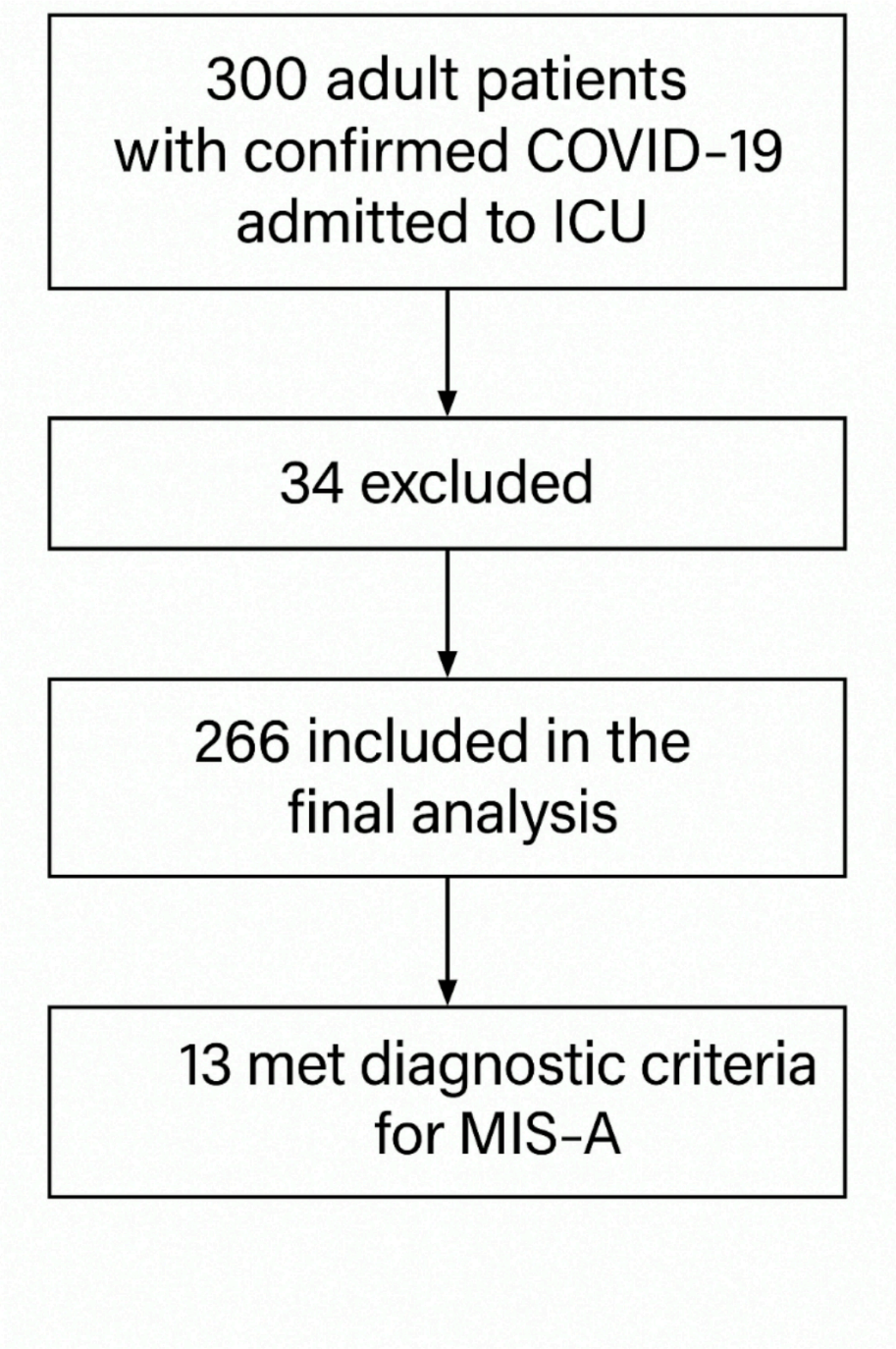


Figure 1

Study Flowchart showing patient selection and MIS-A classification.

Supplementary Files

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