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Multisystem inflammatory syndrome in adults with COVID-19 requiring mechanical ventilation: A retrospective cohort study

Fumito Kato[1] | **Naofumi Bunya**[1,2] | **Ryuichi Nakayama**[1] | **Eichi Narimatsu**[1] | **Shinichiro Ohshimo**[3] | **Nobuaki Shime**[3] | **Shigeki Kushimoto**[2,4] | **Satoru Hashimoto**[2,5] | **Shinhiro Takeda**[2,6]

[1]Department of Emergency Medicine, Sapporo Medical University, Sapporo, Japan

[2]Nonprofit Organization, Japan ECMO Network, Kawaguchi, Japan

[3]Department of Emergency and Critical Care Medicine, Graduate School of Biomedical and Health Sciences, Hiroshima University, Hiroshima, Japan

[4]Division of Emergency and Critical Care Medicine, Tohoku University Graduate School of Medicine, Sendai, Japan

[5]Nonprofit Organization, ICU Collaboration Network, Tokyo, Japan

[6]Kawaguchi Cardiovascular and Respiratory Hospital, Kawaguchi, Japan

Correspondence
Naofumi Bunya, Department of Emergency Medicine, Sapporo Medical University, S1W16 Chuo-ku Sapporo, Hokkaido 060-8543, Japan.
Email: naobun1221@gmail.com

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Abstract

Aim: Multisystem inflammatory syndrome in adults (MIS-A) is a hyperinflammatory multisystem condition associated with coronavirus disease (COVID-19). Critically ill COVID-19 patients may develop multiorgan damage and elevated inflammatory responses, thus making it difficult to differentiate between progression to organ damage due to COVID-19 itself or MIS-A. This study aimed to explore the characteristics and complications of MIS-A in critical COVID-19 patients.

Methods: The Japan Extracorporeal Membrane Oxygenation (ECMO) Network and ICU Collaboration Network developed a web-based database system called the CRoss Intensive Care Unit Searchable Information System (CRISIS) to monitor critical COVID-19 patients throughout Japan. We retrospectively identified patients with MIS-A among critical COVID-19 patients enrolled from March 2020 to December 2021, using CRISIS. Our MIS-A definition required patients to be at least 18 years of age, have laboratory evidence of inflammation, severe dysfunction of at least two extrapulmonary organ systems, and no plausible alternative diagnoses.

Results: Of the 1052 patients, 26 (2.5%) were diagnosed with MIS-A. The MIS-A patients had a higher likelihood of using ECMO (13% vs. 46%, $p < 0.001$) and lower overall survival (77% vs. 42%, $p < 0.001$) than non-MIS-A patients. More than 80% of the MIS-A cases occurred 3 weeks after the COVID-19 onset.

Conclusion: Multisystem inflammatory syndrome in adults can occur in 2.5% of critically ill COVID-19 patients, and the mortality rate is high. Multisystem inflammatory syndrome in adults may be considered when there is a re-elevation of the unexplained inflammatory response and severe dysfunction of at least two extrapulmonary organ systems several weeks after the onset of COVID-19.

KEYWORDS
COVID-19, ECMO, inflammation, MIS-A, SARS-CoV-2

INTRODUCTION

Coronavirus disease (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), remains an important public health problem. Multisystem inflammatory syndrome in children (MIS-C) is a rare condition linked to SARS-CoV-2, which typically manifests itself 2–5 weeks following infection with SARS-CoV-2, and likely occurs as a consequence of a delayed immunologic response to the virus.[1] Multisystem inflammatory syndrome in children is similar to Kawasaki disease, and patients with MIS-C have a higher mortality rate than patients with COVID-19.[2] Likewise, a similar hyperinflammatory multisystem state temporally associated with COVID-19 has

been observed in adults, termed multisystem inflammatory syndrome in adults (MIS-A).[3] Multisystem inflammatory syndrome in adults also develops approximately 4 weeks after the onset of COVID-19.[4] Although the clinical course of patients with COVID-19 varies depending on the virus strain, COVID-19 infection induces respiratory disorders between days 5 and 8 and severe respiratory failure within 10–12 days in serious cases.[5] In other words, critical illness in COVID-19 patients may coincide with the emergence of MIS-A. Therefore, it can be difficult to distinguish between progression to organ damage due to acute respiratory distress syndrome of COVID-19 itself and due to MIS-A if multiorgan damage with elevated inflammatory response arises during the treatment of critically ill COVID-19 patients. How MIS-A develops in patients critically ill with COVID-19 is not known. The purpose of this study was to examine MIS-A complications and characteristics in critically ill patients with COVID-19.

METHODS

Study settings

The Japan Extracorporeal Membrane Oxygenation (ECMO) Network, a nonprofit organization, was established in February 2020.[6] The organization and the ICU Collaboration Network, also a nonprofit organization, developed a web-based database system, the CRoss Intensive Care Unit Searchable Information System (CRISIS), to enable real-time monitoring of critically ill COVID-19 patients receiving mechanical ventilation and veno-venous ECMO (VV-ECMO) in intensive care units (ICUs) throughout Japan during the pandemic. The CRISIS database covers more than 6600 ICU beds, accounting for approximately 90% of all ICU beds in Japan. Our research plan to collect data from ICUs throughout Japan for analysis and use the data for epidemiological studies was approved by the Ethical Review Committee of Hiroshima University (approval number: E-1965). The study was registered with the University Hospital Information Network Clinical Trials Registry, the Japanese clinical trial registry (registration number: UMIN000041450). Institutional review board approval and patient consent at each institution were not required for this study because only publicly available data were used. The ethics committees of the Japanese Society of Intensive Care Medicine, Japanese Association for Acute Medicine, and Japanese Society of Respiratory Care Medicine agreed to this waiver. In this retrospective cohort study, COVID-19 patients were defined as those who tested positive for SARS-CoV-2 using polymerase chain reaction or antigen testing. Using the CRISIS cases enrolled from March 2020 to December 2021, we identified patients with MIS-A as critically ill COVID-19 patients. There were five COVID-19 outbreaks in Japan until December 2021.[7] In the fourth wave (March 1, 2021 to June 20, 2021), the Alpha variant (B.1.1.7) was the main strain. In the fifth wave (June 21, 2021 to December 31, 2021), the Delta variant (B.1.617.2) was the main strain.[7] We examined the occurrence of MIS-A depending on the Alpha variant seasons and the Delta variant seasons.

Definition of MIS-A

Although the Centers for Disease Control and Prevention (CDC) recently defined the diagnostic criteria for MIS-A,[8] these criteria were not yet established when our study was designed. Therefore, the definition of MIS-A was developed based on the MIS-C criteria[1] and the case definition of Morris et al.[3] Our definition required the following criteria to be fulfilled: (1) the patient is aged at least 18 years old, (2) laboratory evidence of inflammation, (3) presence of severe dysfunction of at least two extrapulmonary organ systems, (4) no plausible alternative diagnoses, and (5) positive SARS-CoV-2 test results either during admission or in the past. We lowered the minimum age requirement from 21 to 18 years to identify potentially undiagnosed MIS-C cases in the adult population receiving medical services. As per the definition by Morris et al.[3] we selected extrapulmonary organ systems including hypotension or shock, heart, kidney, blood, liver, gastrointestinal tract, skin, and nerves. As the CRISIS database used in this study compiles information on critically ill COVID-19 patients admitted to the ICU, for a patient to be diagnosed with MIS-A, he/she had to meet all three criteria of laboratory evidence of inflammation, severe dysfunction of at least two extrapulmonary organ systems, and no plausible alternative diagnoses. We did not include a question regarding fever in our diagnostic criteria, as patients in the CRISIS database were more likely to have received fever-modifying treatments, such as steroids or antipyretic analgesics. To extract MIS-A information from the database, we developed two questions: the first is related to the diagnosis of MIS-A and the second is related to the timing of MIS-A onset.

The questions are listed below.

Question 1-1: During COVID-19 treatment, did the patient have a re-elevation of the inflammatory response that could not be explained by other diseases?

Laboratory evidence of inflammation was defined as elevated C-reactive protein and interleukin-6 levels and high blood sedimentation rate. Patients with an initially elevated inflammatory response attributable to COVID-19 pneumonia before and after ventilator initiation were excluded.

Question 1-2: Select the impaired organ(s)

(a) Hypotension or shock, (b) Heart, (c) Kidney, (d) Blood, (e) Liver, (f) Gastrointestinal tract, (g) Skin, (h) Nerves.

Question 2: Select the time when the patients presented with a re-elevated inflammatory response or appearance of organ damage since the first symptoms of COVID-19

(a) 1–7 days, (b) 8–14 days, (c) 15–21 days, (d) 22–28 days, (e) 29–35 days, (f) 36–42 days, (g) After 43 days.

If the timing of the first symptoms of COVID-19 was unknown, the date of the positive SARS-CoV-2 test result was considered the first day of COVID-19.

We sent the above questions regarding MIS-A to facilities registered in CRISIS and included the patients whose data were provided. If the response to Question 1-1 was "No", the study enrollment was terminated; if the response was "Yes", the enrollment proceeded to Question 1-2. If "0" or "1" organ failure was selected in Question 1-2, the study enrollment was terminated. If failure of two or more organs was noted in Question 1-2, the study enrollment proceeded to Question 2.

Data collection

The data stored in CRISIS included patient demographic information, the duration of mechanical ventilation and VV-ECMO, occurrence of the prone position and other supplementary treatments, as well as all-cause mortality. The data were collected only up to the time of discharge or transfer from each facility. Furthermore, the answers to the above questions were extracted. The data used in this study were obtained between March 2020 and December 2021. The ICU Collaboration Network, a nonprofit organization, established the registry and carried out inspections to ensure complete data entry. Different personnel from those responsible for data analysis undertook the data extraction and cleaning processes.

Statistical analysis

Data related to patient characteristics were expressed as frequencies and percentages for categorical variables and as medians with interquartile ranges for continuous variables, as appropriate. Fisher's exact test was used for categorical variables, while the Mann–Whitney *U*-test was used to compare continuous variables. All *p* values were two-tailed, and a significance level of $p < 0.05$ was considered statistically significant. Statistical analyses were carried out using SPSS Statistics version 25 (IBM Corp.).

RESULTS

Diagnostic process of MIS-A

A total of 1052 patients whose data regarding MIS-A were provided at facilities in CRISIS during the study period were enrolled in the registry, and all received mechanical ventilation. During COVID-19 treatment, 55 patients experienced "a re-elevation of the inflammatory response that could not be explained by other diseases." Among these cases, 26 (2.5%) cases had "more than one organ system disorder" (Figure 1) and were diagnosed with MIS-A. Of the 1052 patients, there were two patients aged 18–21 years and they were not diagnosed with MIS-A.

Comparison of MIS-A and non-MIS-A

Table 1 shows the characteristics of the patients, including 1026 non-MIS-A patients and 26 MIS-A patients. Their overall survival (OS) rates were 77% (793/1026) and 42% (11/26), respectively ($p < 0.001$). Veno-venous ECMO was used in 135 (13%) non-MIS-A patients and 12 (46%) MIS-A patients ($p < 0.001$). Patients with MIS-A had a higher likelihood of receiving VV-ECMO and a lower OS rate than non-MIS-A patients.

Characteristics of MIS-A

Table 2 shows the number of impaired organs in the patients with MIS-A. Kidney impairment was present in 18 patients (69%), hypotension or shock in 16 (62%), and gastrointestinal tract involvement in 16 (62%). Table 3 shows the number of impaired organs and survival rates in patients with MIS-A. Patients with six or more organ failures exhibited a 0% survival rate. The majority of the patients had two impaired organs (eight patients); the highest survival rate was 88%. The most common organ failure combinations were kidney and hypotension/shock, kidney and blood, and hypotension/shock and blood, with 12 cases (46%) each. Among the 26 patients diagnosed with MIS-A (Figure 2); in more than 80% of the MIS-A patients, the time from symptom onset to MIS-A onset was more than 3 weeks after COVID-19 onset. Of the 26 MIS-A patients, 9 (34.6%) were infected with the Alpha variant and 5 (19.2%) with the Delta variant.

DISCUSSION

This study showed the prevalence of MIS-A complications in critically ill COVID-19 patients receiving mechanical ventilation using a nationwide registry that covers the majority of ICUs in Japan. Among the 1052 patients enrolled, 26 (2.5%) were diagnosed with MIS-A and had a low survival rate. Furthermore, more than 80% of the MIS-A cases occurred 3 weeks after the onset of COVID-19.

Multisystem inflammatory syndrome in adults is a rare but severe clinical condition.[9] DeCuir et al. found that 53 of 34,515 patients with mild-to-moderate COVID-19 had MIS-A (0.15%)[9] and Melgar et al. found that 11 of 3598 patients had MIS-A (0.3%).[10] The present study showed that approximately 2.5% of the critically ill COVID-19 patients requiring mechanical ventilation developed MIS-A,

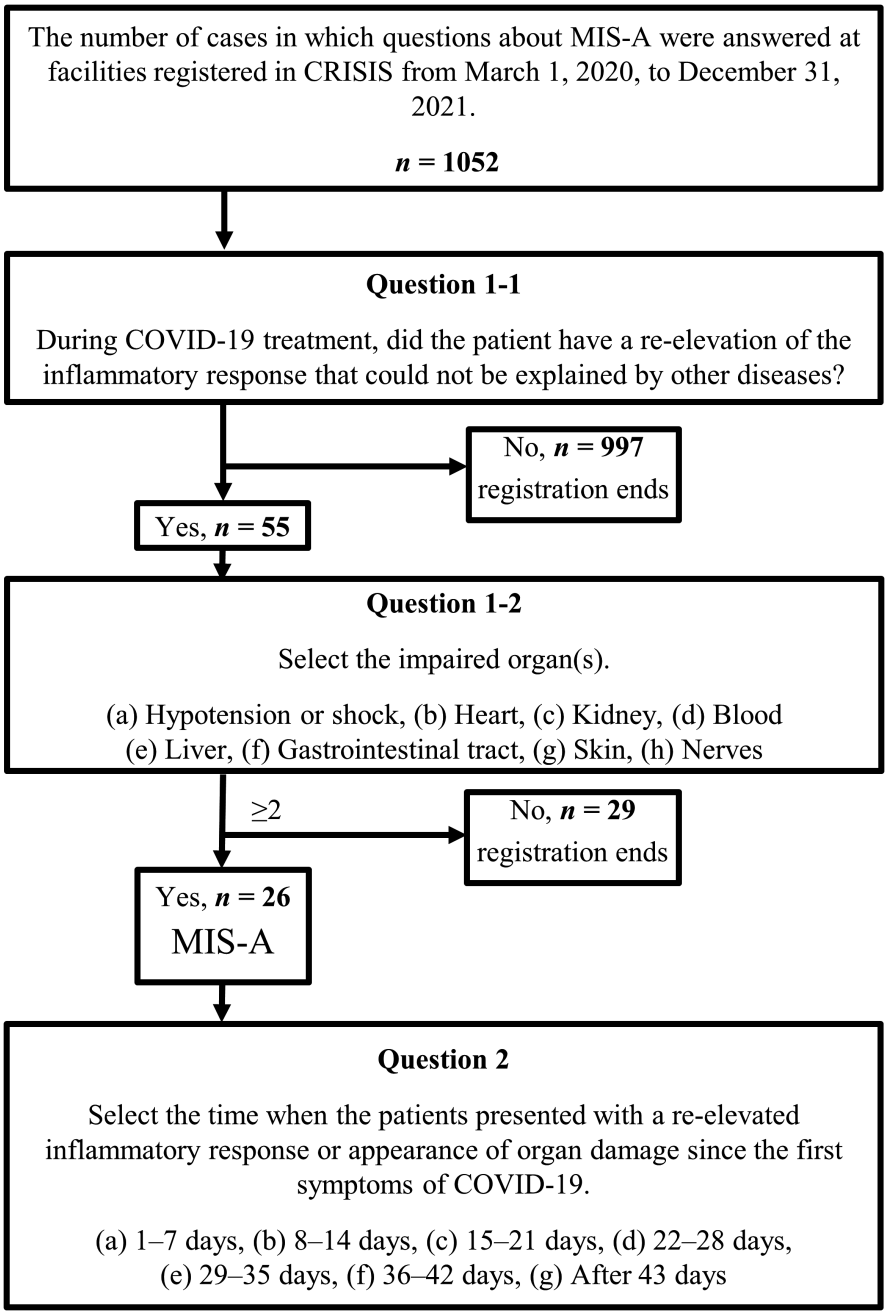

FIGURE 1 Flowchart of inclusion of Japanese patients with multisystem inflammatory syndrome in adults (MIS-A) and questions regarding MIS-A onset. COVID-19, coronavirus disease; CRISIS, CRoss Intensive Care Unit Searchable Information System.

TABLE 1 Demographic and clinical characteristics and outcomes of patients.

	Non-MIS-A ($n = 1026$)	MIS-A ($n = 26$)	p value
Age, years (IQR)	64 (54–72)	67 (56–73)	0.390
Male sex, n (%)	782 (76)	25 (96)	0.130
BMI, kg/m^2 (IQR)	26 (23.3–29.2)	26 (22.8–29.3)	0.910
Prone position, n (%)	410 (40)	14 (54)	0.110
VV-ECMO, n (%)	135 (13)	12 (46)	<0.001
Overall survival, n (%)	793 (77)	11 (42)	<0.001

Note: Data are presented as the median (interquartile range [IQR]) or number (percentage).
Abbreviations: BMI, body mass index; MIS-A, multisystem inflammatory syndrome in adults; VV-ECMO, veno-venous extracorporeal membrane oxygenation.

resulting in higher mortality rates. Physicians treating critically ill COVID-19 patients should be aware of the risk of MIS-A development. Although the clinical course varies with the virus strain, critically ill patients with COVID-19 generally develop respiratory disorders on days 5–8, followed by severe respiratory failure on days 10–12.[5] The duration of mechanical ventilation for such patients is approximately 9 days.[11] Reportedly, the onset of MIS-A is more common 4 weeks after the onset of COVID-19.[4] Although, to the best of our knowledge, there is no study of MIS-A, the severity of MIS-C has been found to decrease with each subsequent SARS-CoV-2 variant, especially the Omicron variant.[12] In this study, MIS-A complications were observed several

weeks after the onset of COVID-19. In other words, the timing of MIS-A onset and the treatment of patients critically ill with COVID-19 may overlap. The important of MIS-A is underrecognized,[13] and the risk of MIS-A complications should be recognized when a re-elevation of the inflammatory response that cannot be explained by other diseases is observed during the treatment of patients critically ill with COVID-19.

TABLE 2 Impaired organs of 26 Japanese patients with multisystem inflammatory syndrome in adults.

Impaired organs	*n* = 26
Kidney, *n* (%)	18 (69)
Hypotension or shock, *n* (%)	16 (62)
Gastrointestinal tract, *n* (%)	16 (62)
Blood, *n* (%)	15 (58)
Liver, *n* (%)	12 (46)
Heart, *n* (%)	9 (35)
Skin, *n* (%)	6 (23)
Nerves, *n* (%)	3 (2)

TABLE 3 Number of impaired organs and survival rate in 26 Japanese patients with multisystem inflammatory syndrome in adults.

Number of impaired organs	*n* = 26	Survival (%)
2	8	7/8 (88)
3	5	2/5 (40)
4	6	1/6 (17)
5	2	1/2 (50)
6	5	0/5 (0)

Reportedly, MIS-A has been treated using steroids and intravenous immunoglobulin (IVIG).[4,9] In contrast, secondary bacterial or fungal infections can occur during the treatment of patients critically ill with COVID-19, and the mortality rate increases when secondary infections occur.[14] Considering the possibility of organ damage due to a new infection, the use of immunosuppressive drugs is discouraged. When MIS-A is not recognized, treatment with steroids or IVIG is not initiated. Early intervention for MIS-A is crucial when an elevated inflammatory response that cannot be explained by other diseases is observed.

Several reports have indicated that MIS-A onset is more common in adolescents.[4] However, in our study, the median age of patients with MIS-A was 67 years, which was not lower than that of patients without MIS-A. The selection criteria in this study focused only on critically ill COVID-19 patients requiring ICU admission, which might have resulted in a higher age group. Therefore, the possibility of MIS-A development in older critically ill patients with COVID-19 should also be considered.

This study has several limitations. First, the diagnostic criteria for MIS-A were not established at the time of the study, and the diagnostic criteria used were based on the diagnostic criteria for MIS-C and prior published reports. The current CDC diagnostic criteria for MIS-A differ from those used in this study. Although MIS-A is a new disease concept, a report from the UK used diagnostic criteria similar to those used in this study.[15] This study captures the essence of MIS-A, namely the pathophysiology of some immune responses after SARS-CoV-2 infection, and will be useful for understanding the pathophysiology of MIS-A in the future. Second, this study was question oriented and did not provide a clear definition of organ failure and a re-elevation of the inflammatory response. Therefore, the definition of organ failure depended on the judgment of each respondent. Third, the final survival outcome remained indeterminate because

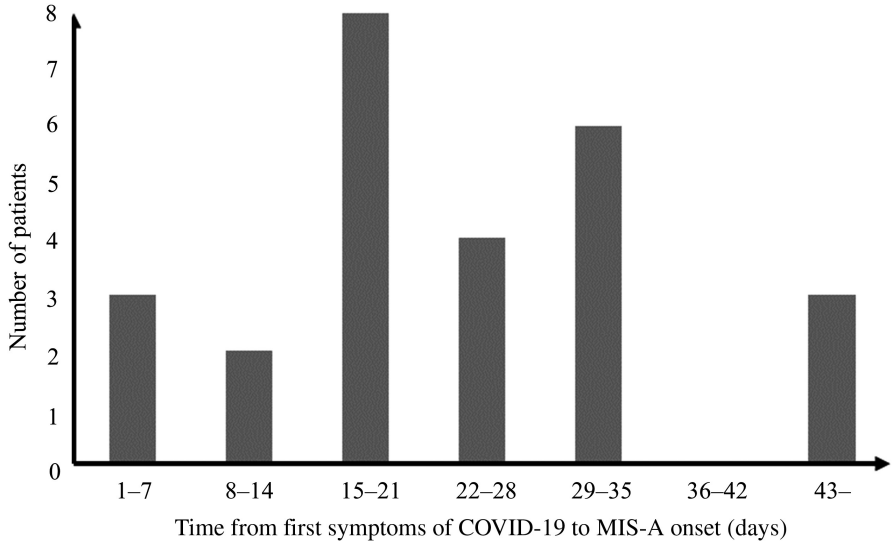

FIGURE 2 Time from first symptoms of coronavirus disease (COVID-19) to multisystem inflammatory syndrome in adults (MIS-A) onset in 26 Japanese patients.

the data were collected only up to the point of discharge or transfer from each facility.

In conclusion, we showed that MIS-A can occur in 2.5% of critically ill COVID-19 patients requiring mechanical ventilation, and the mortality rate was high. Multisystem inflammatory syndrome in adults may be considered when there is a re-elevation of the unexplained inflammatory response and severe dysfunction of at least two extrapulmonary organ systems several weeks after the onset of COVID-19. It is important to be aware of MIS-A because the diagnosis of MIS-A can be missed during critical COVID-19 treatment. Nonetheless, further studies of MIS-A in critically ill COVID-19 patients are needed.

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CONFLICT OF INTEREST STATEMENT

Authors declare no conflict of interest for this article. Dr. Shigeki Kushimoto is an Editorial Board member of *Acute Medicine and Surgery* and a co-author of this article. To minimize bias, they were excluded from all editorial decision-making related to the acceptance of this article for publication.

DATA AVAILABILITY STATEMENT

Non-profit organization Japan ECMO Network. URL: https://crisis.ecmonet.jp/.

ETHICS STATEMENT

Approval of the research protocol: The study protocol was approved by the Ethical Review Committee of Hiroshima University (approval number: E-1965). Institutional review board approval at each institution was not required because only publicly available data were used.

Informed consent: Patient consent was not required because only publicly available data were used.

Registry and the registration no. of the study/trial: The study was registered with the University Hospital Information Network Clinical Trials Registry (registration number: UMIN000041450).

Animal studies: N/A.

ORCID

Fumito Kato https://orcid.org/0000-0002-6552-2243
Naofumi Bunya https://orcid.org/0000-0003-3605-402X
Ryuichi Nakayama https://orcid.org/0000-0002-3272-7680
Shinichiro Ohshimo https://orcid.org/0000-0003-1119-3322
Shigeki Kushimoto https://orcid.org/0000-0001-9232-5782

REFERENCES

1. Payne AB, Gilani Z, Godfred-Cato S, Belay ED, Feldstein LR, Patel MM, et al. Incidence of multisystem inflammatory syndrome in children among US persons infected with SARS-CoV-2. JAMA Netw Open. 2021;4:e2116420.
2. Long F, Zhu S, Wang Z, Zhang S, He J, Ge X, et al. Update on the treatment of multisystem inflammatory syndrome in children associated with COVID-19. Future Virol. 2022;18:63–74.
3. Morris SB, Schwartz NG, Patel P, Abbo L, Beauchamps L, Balan S, 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.
4. 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.
5. 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.
6. Ogura T, Ohshimo S, Liu K, Iwashita Y, Hashimoto S, Takeda S. Establishment of a disaster management-like system for COVID-19 patients requiring veno-venous extracorporeal membrane oxygenation in Japan. Membranes (Basel). 2021;11:11.
7. Lee H, Chubachi S, Namkoong H, Asakura T, Tanaka H, Otake S, et al. Japan COVID-19 task force. Characteristics of hospitalized patients with COVID-19 during the first to fifth waves of infection: a report from the Japan COVID-19 task force. BMC Infect Dis. 2022;22(1):935.
8. Prevention CfDCa. Multisystem Inflammatory Syndrome in Adults (MIS-A)—Case Definition. Cited 3 March 2023. Available from: https://www.cdc.gov/mis/mis-a/hcp.html
9. DeCuir J, Baggs J, Melgar M, Patel P, Wong KK, Schwartz NG, et al. Identification and description of patients with multisystem inflammatory syndrome in adults associated with SARS-CoV-2 infection using the premier healthcare database. Epidemiol Infect. 2022;150:e26.
10. Melgar M, Haston J, DeCuir J, Cheng Q, Arnold KE, Meng L, et al. Multisystem inflammatory syndrome in adults: case finding through systematic review of electronic medical records. Clin Infect Dis. 2022;75(11):1903–11.
11. Ohshimo S, Liu K, Ogura T, Iwashita Y, Kushimoto S, Shime N, et al. Trends in survival during the pandemic in patients with critical COVID-19 receiving mechanical ventilation with or without ECMO: analysis of the Japanese national registry data. Crit Care. 2022;26:354.
12. McCrindle BW, Harahsheh AS, Handoko R, Raghuveer G, Portman MA, Khoury M. SARS-CoV-2 variants and multisystem inflammatory syndrome in children. N Engl J Med. 2023;388(17):1624–6.
13. Davogustto GE, Clark DE, Hardison E, Yanis AH, Lowery BD, Halasa NB, et al. Characteristics associated with multisystem inflammatory syndrome among adults with SARS-CoV-2 infection. JAMA Netw Open. 2021;4:e2110323.
14. Baskaran V, Lawrence H, Lansbury LE, Webb K, Safavi S, Zainuddin NI, et al. Co-infection in critically ill patients with COVID-19: an observational cohort study from England. J Med Microbiol. 2021;70(40):001350.
15. Hookham L, Fisher C, Manson JJ, Morgan M, O'Hara G, Riley P, et al. Understanding the diagnosis and management of multisystem inflammatory syndrome in adults (MIS-A) in the UK: results of a national Delphi process. Clin Med. 2022;22:266–70.

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