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# Multisystem Inflammatory Syndrome of the Adults (MIS-A) - The undercover threat for young adults. A systematic review and meta-analysis of medical cases

**Christos Michailides[1], Konstantinos Papantoniou[1], Themistoklis Paraskevas[1], Maria Lagadinou[1], Markos Marangos[1], Michael Kavvousanos[1], Pinelopi Michailidou[2], Dimitrios Velissaris[1]**

[1]Department of Internal Medicine, Patras University Hospital, Patras, Greece;
[2]Department of Medicine, Leuven Catholic University, Leuven, Belgium

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## SUMMARY

*Background:* COVID-19 related syndromes are not yet well described and understood. Multisystem inflammatory syndrome of the adults (MIS-A) is a recently characterized syndrome affecting multiple organs of young adults, causing serious complications, even shock and death.
*Objectives:* To determine the clinical characteristics, course, and complications of MIS-A in a systematic way and summarize currently used treatments.
*Methods:* Literature search in March 2023 in PubMed and Scopus databases. Case reports and case-series that fulfilled the CDC criteria for MIS-A were eligible for inclusion.
*Results:* A total of 71 patients from 60 reports were included. 66% of the patients were male and the mean age of the synthetic cohort was 32.9 years old. The majority (70.4%) of the enrolled cases had no significant medical history. MIS-A was diagnosed after a median of 4 weeks period. All but two patients presented with cardiac symptoms, while the most common secondary diagnostic criterion was abdominal pain, vomiting or diarrhea followed by shock or hypotension. Heart failure therapy and immunomodulation were used as therapeutic options. Although more than half of the cohort was admitted to the Intensive Care Unit (ICU) (n=39) only 4 deaths were reported.
*Conclusion:* MIS-A can affect patients independently of age, sex, and co-morbidity status, resulting in serious complications, often including severe cardiac disease, shock, acute kidney injury and sometimes death. It can occur immediately after SARS-CoV-2 acute infection until two months later, usually manifesting four weeks after acute disease.

*Keywords:* COVID-19, MIS-A, acute cardiac disease, hyperinflammation, Kawasaki-like syndrome.

## INTRODUCTION

Four years after the initiation of COVID-19 pandemic, caused by SARS-CoV-2, the scientific community has achieved a satisfying level of understanding of the viral attacking mechanisms, clinical course, complications, effective treatments, and preventive measures. Meanwhile disease severity is mitigated and new variants that emerged result in respiratory failure less frequently. Notwithstanding, new clinical syndromes are emitted, and a variety of COVID-19 related syndromes has been recently described [1]. Multisystem inflammatory syndrome of the adults (MIS-A), firstly described as Kawasaki-like syndrome in children and later as Multisystem Inflammatory Syndrome

*Corresponding author*
Christos Michailides
E-mail: christos.mich1@gmail.com

of the Children (MIS-C), is a syndrome unexpectedly affecting multiple organs, including heart, kidneys, and eyes, even in previously healthy young patients, resulting in serious complications [1-3]. Its pathophysiology is not yet fully clarified, though exertion of IL-6, IFNγ, IL-10 and TNF distinguishes MIS-A related immune dysregulation, leading to T-cell overproduction and B cell deficiency. Activated T-cells may trigger MHC-II to release auto-antibodies that may lead to multi-organ damage. Hyperinflammation and hypercoagulation state occurs due to lasting cytokine response secondary to SARS-CoV-2 infection, thus MIS-A patients often present one month after the acute phase with positive anti-S IgG antibodies. Consequently, S-protein may act as superantigen causing MIS-A symptoms [4-7].This syndrome is not well studied yet and the association with SARS-CoV-2 is not concretely determined, therefore there are no guidelines for etiologic treatment. Currently, treatment approaches described in case reports and case series are based on clinical presentational and general COVID-19 treatment guidelines, including corticosteroids, IVIG and immunomodulating factors [8]. The aim of this study was to systematically review all the reported case reports fulfilling the CDC criteria for MIS-A diagnosis to determine its clinical course, complications and review all tested drugs [1].

**Table 1** - MIS-A clinical characteristics.

| *System* | *Manifestations* |
|---|---|
| *Cardiovascular* | Arrhythmias, cardiogenic shock, acute heart failure and pulmonary edema, dyspnoea, cardiomyopathy, pericardial effusion, cardiac arrest |
| *Renal* | Acute kidney injury, proteinuria, electrolyte disturbancies, |
| *Liver* | Ascites, liver failure, transaminasemia, hyperbilirubinemia, jaundice |
| *Respiratory* | Pulmonary embolism, pleural effusion, pulmonary hypertension |
| *Nervous* | Bell's pulsy, amnesia, delirium, neuromyelitis optica |
| *Gastrointestinal* | Diarrhea, abdominal pain |
| *Other* | Rabdomyolysis, myopathy, coagulopathy, thromboembolic events, lactate acidocis, thyrotoxicosis |

## METHODS

*Eligibility Criteria*

In this systematic review we included case series and case reports of patients that fulfill the MIS-A criteria by CDC, which include age ≥21 years, fever for ≥24 hours without alternative diagnosis, severe cardiac disease, rush, conjunctivitis, gastrointestinal tract symptoms, neuropathy, shock, thrombocytopenia, C-reactive protein, ferritin, IL-6, erythrocyte sedimentation rate, procalcitonin and recent or current positive SARS-CoV-2 test [1]. Cases that did not fulfill these criteria, cohorts, and other non-relevant article types, such as reviews and expert opinions were excluded (Table 1).

*Search Strategy*

In March 2023, we performed a systematic literature search in PubMed and Scopus libraries for relevant articles. The following search terms were used: (multisystem inflammatory syndrome and adult) OR (mis-a) and (covid-19 or sars-cov2 or coronavirus).

*Study Selection*

The titles and abstracts were screened firstly by two independent authors. Full-text screening was also performed by two independent authors and all potentially eligible cases were checked against the MIS-A diagnostic criteria. All conflicts were resolved after discussion with a third author.

*Data Extraction and Synthesis*

For each study the following information were extracted based on a pre-specified form (author, date, country, age, sex, co-morbidities, severity of COVID-19 diseases (based on the criteria of the World Health Organization], timing relating to infection, diagnostic criteria fulfilled, treatment, length of hospitalization, death, ICU admission, further complications). We used the data from all available cases to create a secondary cohort and reported its descriptive characteristics on the above variables. Chi square test was used to make comparisons for categorical data for the outcome of ICU admission. References were constructed via Mendeley.

## RESULTS

Through our search, we identified 1006 unique articles in Medbase and Scopus. After a two-step

screening process, a total of 71 patients described in 60 reports were included in our analysis [8-66] (Figure 1). 798 articles were excluded as the respective patients did not fulfill the current criteria for MIS-A diagnosis or the articles were not in the requested form.

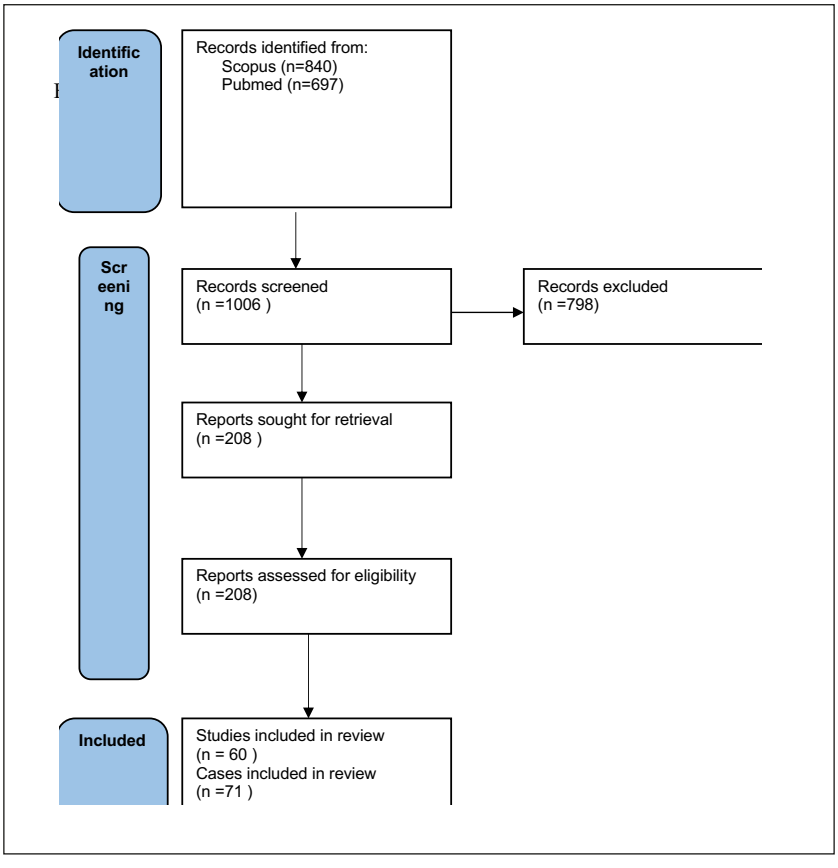
Forty-seven (66%) patients in our synthetic cohort were male and 24 were female with a mean age of 32.9 years (SD=10.8). The youngest enrolled patient was 21 years old and the oldest 63. Fifty patients (70.4%) had no significant past medical history. The most frequent co-morbidity was obesity (9/71, 12.68%). The majority (88.7%) of the patients had a previous non-severe course of COVID-19, while only 3 had a severe disease and 5 had a critical disease course as per the WHO standards [63]. MIS-A was diagnosed after a median 4 weeks (Q1-Q3: 2.63-5 weeks) time after COVID-19 (Table 2).

Fever was present in all the included patients. Cardiac symptoms were present in all but 2 patients. Rash and conjunctivitis were reported in 23 (32.4%) cases. Cardiac symptoms presented among others as acute heart failure, arrhythmias, myocarditis, pericarditis, or pericardial effusion and troponinemia.

Regarding the secondary clinical criteria, the most reported criterion was "abdominal pain, vomiting or diarrhea" (87.3%), followed by "shock or hypotension not attributable to medical therapy" (80.3%), thrombocytopenia (51%) and ''new-onset neurological signs and symptoms'' (12.7%). Neurological sign and symptoms included headache, neck stiffness, hallucinations, cognitive status alteration, seizures, and peripheral nervous system abnormalities. ESR: Mean: 75.41, SD: 34.75 (reported in 31% of the studies)PCT: Median: 8.32, IQR 13.26 (reported in 64.8% of the studies) Ferritin: Median 1014, IQR: 1619.55 (reported in 85.9% of the studies)CRP: Median 28.2, IQR: 14.65 (reported in 93% of the studies)IL-6: Median 86, IQR: 296 (reported in 21.1% of the studies).

Heart failure therapy (beta-blockers, diuretics,

**Figure 1**
Study searching flowchart.



ACE inhibitors etc.), anticoagulation and antibiotics were mainly used as therapeutic options. Regarding immunomodulation, corticosteroids and regiments, including methylprednisolone, prednisone and dexamethasone were employed in the majority of the included cases. Additionally, IVIG was used in 42 patients, eculizumab, a monoclonal antibody that targets complement protein C5 was used in 1 patient, anakinra (anti IL-1α) was used in 8 patients and tocilizumab (anti IL-6 receptor) was used in 5 cases. Plasmapheresis was used in 2 patients.

**Table 2** - Demographics and clinical characteristics of MIS-A patient.

| | *Total number of Patients n=71* |
|---|---|
| Male Gender | 66% (n=47) |
| Age (years) * | 32.9 (10.8) |
| *Co-morbidities* | |
| None | 70.4% (n=50) |
| Obesity | 12.68% (n=9) |
| *Previous Course of COVID-19* | |
| Non-Severe | 88.7% (n=63) |
| Severe | 4.2% (n=3) |
| Critical | 7% (n=5) |
| *MISA Criteria* | |
| Fever | 100% (n=71) |
| Cardiac symptoms | 97.1% (n=69) |
| Rash and Conjunctivitis | 32.4% (n=23) |
| Abdominal pain, vomiting and or diarrhea | 87.3% (n=62) |
| Shock or hypotension not attributable to medical therapy | 80.3% (n=57) |
| Thrombocytopenia | 51% (n=36) |
| New-onset neurological signs and symptoms | 12.7% (n=9) |
| *Inflammatory Biomarkers* | |
| ESR * | 75.41 (34.75) |
| PCT ** | 8.32 (13.26) |
| Ferritin ** | 1014 (1619.55) |
| CRP ** | 28.2 (14.65) |
| IL-6 ** | 86 (296) |
| *Outcomes* | |
| Hospitalization (days) ** | 10 (7) |
| ICU admission | 54.9% (n=39) |
| Death | 5.6% (n=4) |
| Acute Kidney Injury | 21.1% (n=15) |

*Mean, SD
**Median, IQR

The median duration of hospitalization was 10 days (Q1-Q3: 7-14 days), but it was only properly reported in 52 of the 71 included cases. Although more than half of the cohort was admitted to the ICU (n=39) only 4 deaths were reported. The non-survivors were 23, 28, 31 and 50 years old, 2 of them were male and 2 were female and all had a non-severe previous COVID-19. Severe sepsis and cardiovascular complications were reported in these patients, including severe systolic heart failure with low ejection fracture (15%) and arrhythmias. One of these patients died during initial evaluation at the emergency department. Additionally to the expected complications per definition, kidney injury was reported in a high proportion of patients (15/71, 21.13%).

Although more than half of the cohort was admitted to the ICU (n=39) only 4 deaths were reported. ICU admission was independent of age, sex, comorbidities, and time since COVID-19 development (p values 0.723, 1.000, 1.000 and 0.283 respectively).

## DISCUSSION

This is a systematic review of all reported cases diagnosed with MIS-A syndrome according to CDC criteria. This syndrome belongs to COVID-19 related and post-COVID-19 syndromes [1, 3]. Our results demonstrate that this syndrome is not such a rare COVID-19 complication among previously healthy young adults. It predominantly affects male patients independently of their COVID-19 disease severity and their co-morbidity status. MIS-A can occur during COVID-19 acute infection, but it seems to emerge more often approximately one month later. Fever in combination with new-onset cardiac disease, gastro-intestinal tract (GIT) symptoms, shock and increased inflammatory markers usually set the diagnosis. Although the incidence of intubation was high, it has not been observed an increased death frequency among MIS-A patients (4/71, 5.63%). Death mostly complicated severe cardiac disease, such as ventricular tachycardia and acute heart failure with

decreased ejection fracture [32, 47]. Acute kidney injury (AKI) was the most frequent complication excluding those of the definition. Except heart failure, infection and hemodynamic instability treatment, MIS-A related inflammation was mostly treated with corticosteroids and IVIG at an indicative dose of 0.4 g/kg/d [57]. In two patients presented with fever, pericardial effusion and shock, Anakinra combined with IVIG or corticosteroids prevented death, ICU admission and other serious complications [17]. A patient who presented with fever and acute heart failure had a short, uncomplicated course after IVIG plus tocilizumab treatment [63].

Our data are in line with three other systematic reviews on MIS-A, by Kunal et al., Patel et al. and Qamar et al., that were carried through the two previous years, regarding median age of occurrence (31.67, 21 and 32.52 years of age, respectively), males increased representation and fever and cardiac involvement predominance compared to other symptoms [68-70]. Regarding inflammatory biomarkers, IL-6 and ferritin were found to peak at similar values in our study compared to the study of Patel et al. (86 both and 1014 vs 1029 median respectively) [65]. Kunal et al. found significantly higher median values for IL-6, PCT, ferritin, ESR compared to our investigation (219.04 pg/ml, 24.21 ng/ml, 3062 ng/ml, vs 86 pg/ml, 8.32 ng/ml and 1014 ng/ml respectively), but similar ESR (75.85 mm/h vs 75.41 mm/h respectively) [68]. Kunal et al. and Patel et al. also included antibiotics, anticoagulants, corticosteroids, immunomodulating factors and IVIG as possible therapeutic options [68, 69]. Another interesting ascertainment is that in a retrospective cohort study that included patients with a similar median age to that estimated in our systematic review (37 vs 32.9 years), the most frequent identified co-morbidity was also obesity. Correspondingly to our findings, patients were usually diagnosed with MIS-A due to fever combined with severe cardiac disease, shock, GIT symptoms and elevated inflammatory markers [71].

Limitations of our study include the encompassing of case reports and not larger study because of the lack of observational studies in this field, the deprivation of some cases that were reported as Kawasaki-like syndrome or multi-inflammatory syndrome, without mentioning the CDC criteria for MIS-A for establishing the diagnosis and the exclusion of case reports described as MIS-A without strictly fulfill CDC criteria despite the compatible clinical presentation and course. Additionally, limitations and bias arising from the publication process might have influenced the results of our synthetic analysis. It should be noted that there might be a higher probability of patients with positive outcomes being published as case reports. Also, lack of physicians' awareness for this new syndrome may have limited the availability of case reports. Lastly, the prognostic ability of clinical and laboratory factors cannot be properly explored in our analysis and should be further investigated by observational studies and registries.

The importance of this systematic review is the disambiguation that MIS-A syndrome is an inflammatory condition that can lead to severe complications patients who were COVID-19 positive independently of age, sex, co-morbidities, and time since COVID-19 was confirmed. Clinicians need to be alerted to identify patients in danger, as multisystem complications occur due to severe hyper-inflammation induced by SARS-CoV-2 and the syndrome can mimic other conditions that need different approach [68]. COVID-19 induced cytokine storm, microthrombosis and endothelial dysfunction along with ACEII receptor presence in cardiac endothelium and cytokine induced viral sepsis could be the underline mechanisms of severe cardiac disease, hypotension and multi-organ injury [72, 73]. The understanding of this condition will lead to testify treatment options to target disease process, underline mechanisms and susceptible organs. Pharmaceutical agents with established position in treatment of COVID-19 induced respiratory failure, such as dexamethasone, tocilizumab and anakinra, may be efficient for targeting the pathway of this under-recognized condition [74, 75].

**Authors' contribution**

CM and TP conceptualized and designed this work, CM, ML, TP, KP, reviewed the literature and wrote the paper, PM wrote the paper, MM supervised the paper, DV wrote, supervised and edited the paper.

**Availability of data and materials**

Available upon reasonable request.

**Ethics approval**

This systematic review was conducted in line with the Helsinki Declaration.

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**Conflicts of interest**
The authors declare that there are not any conflicts of interest.

**Consent of publication**
All authors gave consent for publication.

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