State of the art paper

Multisystem inflammatory syndrome in adults hospitalizations in the United States; evaluating patient characteristics, COVID-19 associations, and mortality

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Abstract

Introduction: Multisystem inflammatory syndrome in adults (MIS-A) is thought to be closely linked with COVID-19 infection. This study aims to elucidate the demographics and clinical characteristics of MIS-A, aiding in timely diagnosis and management.
Methods: Utilizing the National Inpatient Sample (NIS) database (2021), patients were stratified into MIS-A and non-MIS-A groups. Baseline characteristics and comorbidities, the association with COVID-19, post-COVID-19 syndrome, and personal history of COVID-19, as well as impact on mortality were studied.
Results: We identified 2,730 adults with MIS-A. MIS-A was linked with active COVID-19 infection (aOR = 27.436, $p < 0.001$), post-COVID-19 syndrome (aOR = 32.766, $p < 0.001$), personal history of COVID-19 (aOR = 2.963, $p < 0.001$), and an increased mortality (aOR = 3.743, $p < 0.001$).
Conclusions: Using data adjusted for confounding variables, MIS-A was found to be associated with active and past COVID-19, and a greater mortality rate when compared to non-MIS-A patients.

Key words: multisystem inflammatory syndrome in adults, COVID-19, comorbidities.

Introduction

Multisystem inflammatory syndrome (MIS) is a hyper-inflammatory event that impacts multiple organ systems within the body [1]. Initial-

ly, the condition was discovered as a post-infectious complication of SARS-CoV2 in pediatric age groups exclusively and was labeled Multisystem inflammatory syndrome in children (MIS-C) [2]. Later, this syndrome was found to affect adults as well, and this variety was termed multisystem inflammatory syndrome in adults (MIS-A).

The pathophysiology of MIS involves an overactive immune system, as also seen in Kawasaki disease, while having distinct clinical characteristics that set them apart [3]. While a dysregulated immune response following infection by SARS-CoV2 plays a significant role, MIS is believed to be multifactorial, whereby both genetic and environmental factors may also impact its pathophysiology [4].

MIS-A often presents with a wide range of symptoms, including, but not limited to, fever, hypotension, dyspnea, diarrhea, signs of heart failure, and coagulation abnormalities. In their review, Patel *et al.* estimated that the median number of systems involved was 5 among 221 patients studied [5]. As these clinical manifestations can overlap with other conditions, and MIS-A is associated with high mortality that might also be impacted by underlying diseases and predisposing factors, a timely diagnosis and management are critical for their prognosis [1, 6, 7].

Nevertheless, there is fairly little information available regarding the demographics, risk factors, and clinical outcomes among MIS-A patients. As such, this study aims to elucidate the patient characteristics, comorbidities, and clinical outcomes associated with MIS-A to provide a better understanding of the syndrome.

Methods

We performed a retrospective study utilising data from the 2021 National Inpatient Sample (NIS) database. As per the recommendations of the CDC, we only retained patients aged ≥ 21 years [8]. The NIS is compiled each year by the Healthcare Cost and Utilization Project (HCUP), with non-federal hospitalizations, which can be extrapolated to cover 35 million national records annually. Users can study various conditions and procedures via the respective International Classification of Diseases (ICD) codes. Records before 1 October 2015 required the use of ICD-9 codes, after which the NIS transitioned to ICD-10 codes [9].

Our sample of admissions between 1 January 2021 and 31 December 2021 was stratified into groups of individuals with and without MIS-A, via the ICD-10 code "M35.81" [10]. Further patient characteristics, comorbidities, and complications were added based on recommendations from prior studies [11–14].

Baseline patient demographics and characteristics were evaluated. We used χ^2 tests for categorical groups, and Mann-Whitney *U* tests for continuous variables based on the non-parametric nature of the NIS. We further explored the presence of active COVID-19 infection, post-COVID-19 syndrome, and personal history of COVID-19 [15, 16], and multivariable regression models were used to estimate the odds of MIS-A in the presence of such risk factors. Finally, we estimated the odds of mortality associated with MIS-A and the median length of stay (LOS), as well as the hospital charge (USD).

Statistical analysis

Statistical analysis were carried out using SPSS 29.0 (IBM Corp, Armonk, NY, USA).

Results

Among the total cohort of 27,948,054 patients enrolled in this investigation, 2,730 individuals were admitted with MIS-A. Several differences in characteristics about demographics and comorbidities were reported between patients with and without MIS-A (Table I). Notably, the median age of patients diagnosed with MIS-A was 58.00 years, slightly lower than the median age of 62.00 years observed in non-MIS-A admissions. In terms of age distribution, we found that 27.5% of MIS-A hospitalizations occurred in the 21–45 age group, 25.8% in the 46–60 group, and 46.7% were over 60 years old, while, amongst non-MIS-A admissions, the distribution was 28.3%, 19.5%, and 52.2%, respectively ($p < 0.01$). Furthermore, we also found differences in the sex, with a higher proportion of MIS-A patients being males (58.6%, $p < 0.01$). Additionally, there were significant differences in the racial distribution, where 56.0% of MIS-A patients were White, 20.6% Black, 16.1% Hispanic, and 3.4% Asian/Pacific Islander, compared to 65.7%, 15.5%, 12.2%, and 2.9%, respectively, in non-MIS-A admissions ($p < 0.01$). We also found that MIS-A hospitalizations were associated with a lower proportion of Medicare (37.1% vs. 46.8%) and a higher proportion of private medical insurance (38.2% vs. 26.9%) as opposed to those hospitalized without MIS-A ($p < 0.01$). MIS-A hospitalizations involved mostly urban teaching hospitals (68.9%) and hospitals in the South region (45.6%).

Patients hospitalized with MIS-A had significantly different comorbidity profiles as compared to those hospitalized without the condition, with a higher prevalence of diabetes (33.5% vs. 29.0%, $p < 0.01$), chronic kidney disease (CKD) (23.4% vs. 18.2%, $p < 0.01$), obesity (31.3% vs. 19.9%, $p < 0.01$) and heart failure (21.2% vs. 19.5%, $p = 0.018$). MIS-A had an especially strong association with autoimmune conditions (90.5% vs. 3.3%, $p < 0.01$). On the other hand, certain comorbid conditions were observed to report a lower prevalence in the MIS-A cohort in comparison

Table I. Baseline characteristics of adult patients with vs without MIS-A in 2021

Variable	All non-MIS-A hospitalizations (*n* = 27945324) (%)	MIS-A hospitalization (*n* = 2730) (%)	*P*-value
Median age (IQR)	62.00 (42.00-74.00)	58.00 (42.00-69.00)	
Age group:			< 0.01
21–45	28.3	27.5	
46–60	19.5	25.8	
> 60	52.2	46.7	
Sex:			< 0.01
Male	44.2	58.6	
Female	55.8	41.4	
Race:			< 0.01
White	65.7	56.0	
Black	15.5	20.6	
Hispanic	12.2	16.1	
Asian/Pacific Islander	2.9	3.4	
Insurance form:			< 0.01
Medicare	46.8	37.1	
Medicaid	18.6	15.6	
Private	26.9	38.2	
Hospital location:			< 0.01
Rural	8.5	6.8	
Urban non-teaching	17.6	24.4	
Urban teaching	73.9	68.9	
Region of hospital:			< 0.01
Northeast	18.4	15.0	
Midwest	21.8	10.6	
South	40.4	45.6	
West	19.4	28.8	
Hypertension	31.4	31.3	0.904
Diabetes	29.0	33.5	< 0.01
Dyslipidemia	36.9	30.6	< 0.01
Smoking	36.1	23.1	< 0.01
CKD	18.2	23.4	< 0.01
Obesity	19.9	31.3	< 0.01
Alcohol abuse	5.9	2.0	< 0.01
Autoimmune conditions	3.3	90.5	< 0.01
Cancer	7.7	4.2	< 0.01
Chronic lung disease	20.6	18.5	< 0.01
Perivascular disease	6.1	3.8	< 0.01
Hypothyroidism	13.0	8.6	< 0.01
Heart failure	19.5	21.2	0.018
COVID-19 related:			
COVID-19 (active)	8.5	71.8	< 0.01
Post-COVID-19	0.1	2.0	< 0.01
Personal history of COVID-19	3.3	5.3	< 0.01
Outcomes:			
Death	3.6	26.9	< 0.01
Median hospital charge [USD] (IQR)	40075 (21353–78747)	120891 (55528–272775)	< 0.01
Median length of stay [days] (IQR)	3.00 (2.00–6.00)	9.00 (4.00-–16.00)	< 0.01

with the non-MIS-A population. This included dyslipidemia (30.6% vs. 36.9%, $p < 0.01$), smoking (23.1% vs. 36.1%, $p < 0.01$), alcohol abuse (2.0% vs. 5.9%, $p < 0.01$), cancer (4.2% vs. 7.7%, $p < 0.01$), chronic lung disease (18.5% vs. 20.6%, $p < 0.01$), perivascular disease (6.1% vs. 3.8%, $p < 0.01$) and hypothyroidism (8.6% vs. 13.0%, $p < 0.01$). Hypertension was found to be marginally lower in MIS-A patients (31.3% vs. 31.4%), and this difference was observed to be statistically insignificant ($p = 0.904$). Our study also discovered a very strong association between active COVID-19 infection and the development of MIS-A (71.8% vs. 8.5%, aOR = 27.436, 95% CI: 25.082–30.011, $p < 0.001$). Interestingly, a larger number of patients with MIS-A also had a previous history of COVID-19 infection (5.3% vs. 3.3%, aOR = 2.963, 95% CI: 2.485–3.534, $p < 0.01$), and those with post-COVID-19-syndrome (2.0% vs. 0.1%, aOR = 32.766, 95% CI: 24.316–44.153, $p < 0.001$) when compared to those without MIS-A (Table II).

Regarding outcomes, MIS-A hospitalizations were significantly more likely to result in death compared to non-MIS-A hospitalizations (26.9% vs. 3.6%, aOR = 3.743, 95% CI: 3.399–4.121, $p < 0.001$) (Table II). Additionally, MIS-A patients tended to have longer hospital stays. The median length of hospital stays for MIS-A patients was 9.00 days (IQR: 4.00–16.00), whereas for non-MIS-A patients, it was only 3.00 days (2.00–6.00, $p < 0.01$). Similarly, the median hospital charge for MIS-A admissions was significantly higher than for non-MIS-A hospitalizations ($120,891, IQR: $55,528–$272,775; $40,075, IQR: $21,353–$78,747; $p < 0.01$).

Discussion

The primary findings from our analysis are as follows:

(1) COVID-19-related findings indicate a strong association between MIS-A hospitalizations and active COVID-19 status, with a notably higher prevalence compared to non-MIS-A hospitalizations. Post-COVID-19 status was also more prevalent among MIS-A patients compared to non-MIS-A patients.
(2) MIS-A patients were younger than our non-MIS-A cohort and involved more males.
(3) The comorbidity profile of MIS-A hospitalizations differed significantly from non-MIS-A hospitalizations, with some conditions positively and others negatively associated with MIS-A.
(4) Analysis of the outcomes revealed higher mortality, increased length of hospital stay, as well as increased hospital charges among the MIS-A cohort.

The findings of our study indicate a significant relationship between active, as well as prior COVID-19 infection and the development of MIS-A. This relationship held even after adjusting for confounding factors. This indicates that the suggested correlation is likely a true cause-and-effect relationship. These observations concur with an emerging literature that highlights MIS as a consequence of COVID-19 [4, 17, 18]. One major limitation of our study involves the lack of data on the type of COVID-19 virus involved. It is, therefore, vital to promote additional retrospective studies so that the genomic roles of the different variants and their roles in the pathogenesis of MIS can be better understood [19, 20].

To date, data on MIS-A have involved smaller samples, with a median age of 21 in a study by Patel *et al.* [5] and a mean age of 33 years by Lawrensia *et al.* [21], which is lower than our reported median age of 58.00. However, our sample size has allowed us to explore a wider range of patients, as compared to the 28 cases by Lawrensia *et al.* and 221 cases by Patel *et al.* [5, 21]. We also noted that our MIS-A sample was younger compared to our non-MIS-A control cohort. To evaluate the age-related immunological response and the pathophysiology of MIS-A additional studies should be encouraged.

Furthermore, the higher presence of males in our MIS-A group matches previous smaller studies of MIS-A [5]. Patel *et al.* associated such differences with biological risk factors as well as behavioral differences between the two sexes [5]. While past studies have associated females with a higher immune response, which predisposes them to various autoimmune conditions, the opposite differences seen among MIS-A patients warrant deeper understanding and studies [22, 23].

While a bigger sample of MIS-A patients were Whites, in comparison to non-MIS-A hospitalizations, the racial composition of patients hospitalized with

Table II. Adjusted odds ratio (aOR) of MIS-A and impact on mortality

Parameter	*P*-value	aOR	Lower 95% CI	Upper 95% CI
COVID-19 (active)	< 0.001	27.436	25.082	30.011
Post-COVID-19	< 0.001	32.766	24.316	44.153
Personal history of COVID-19	< 0.001	2.963	2.485	3.534
Odds of mortality among MIS-A patients vs. non-MIS-A admissions	< 0.001	3.743	3.399	4.121

MIS-A suggests a decline in the number of White patients and an increase in the numbers of Black and Hispanic patients. This study concurs with the findings of Javalkar *et al*., Middelburg *et al*., and Stierman *et al*. that there is a predilection for MIS among Black and Hispanic populations [24, 25]. Multiple autoimmune conditions such as SLE [26] are more common and severe in Blacks, and while a potential genetic predisposition may exist, extensive research may help bridge the gap in knowledge on the racial roles in pathogenesis and help in the treatment plans as preventive and curative measures. Finally, the higher presence of private insurance among MIS-A patients as compared to Medicare reflects the younger age in our MIS-A sample vs. our control group.

The lower presence of multiple comorbidities in our MIS-A group, such as dyslipidemia, chronic lung disease, cancer, and peripheral vascular disease, is linked with the younger age group as compared to the control cohort used. Several comorbidities seen, such as diabetes, CKD, obesity, and heart failure, have previously been strongly linked with more severe outcomes among COVID-19 patients [27–29]. In addition, 90.5% of patients with MIS-A in our study had some form of autoimmune condition. As the pathophysiology of MIS-A involves an immune dysregulation, the co-existing presence of such autoimmune conditions may put them at a much higher risk of an excessive immune response triggering MIS-A [30].

Finally, the mortality rate (26.9%) seen in MIS-A admissions in our study was higher than in past studies, such as Patel *et al.* who reported a mortality rate of 7% only [5]. However, our sample involved a bigger cohort, with a higher median age. Unfortunately, the NIS does not report the cause of death. Therefore, it is vital to conduct additional retrospective studies through hospital records based on various age groups and their causes of mortality.

In conclusion, we presented one of the most extensive samples of MIS-A patients and found differences in comorbidities compared to a non-MIS-A control group. Active and past COVID-19 exposures were strongly linked with a higher risk of MIS-A. Finally, MIS-A led to higher odds of all-cause in-hospital death.

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Ethical approval

The de-identified nature of the NIS waives the need for ethics and Institutional Review Board evaluations.

Conflict of interest

The authors declare no conflict of interest.

References

1. 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.
2. Rafferty MS, Burrows H, Joseph JP, Leveille J, Nihtianova S, Amirian ES. Multisystem inflammatory syndrome in children (MIS-C) and the coronavirus pandemic: current knowledge and implications for public health. J Infect Public Health 2021; 14: 484-94.
3. Loke YH, Berul CI, Harahsheh AS. Multisystem inflammatory syndrome in children: Is there a linkage to Kawasaki disease? Trends Cardiovasc Med 2020; 30: 389-96.
4. Martinez OM, Bridges ND, Goldmuntz E, Pascual V. The immune roadmap for understanding multi-system inflammatory syndrome in children: opportunities and challenges. Nat Med 2020; 26: 1819-24.
5. 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.
6. Lazova S, Gerenska D, Slabakova Y, Velikova T. Immunological features of the multisystem inflammatory syndrome associated with SARS-CoV-2 in children. Am J Clin Exp Immunol 2022; 11: 64-71.
7. Lai C, Hsu C, Hsueh S, Yen M, Ko W, Hsueh P. Multisystem inflammatory syndrome in adults: characteristics, treatment, and outcomes. J Med Virol 2023; 95: e28426.
8. CDC. Multisystem inflammatory syndrome (MIS) 2023 available from:https://www.cdc.gov/mis/index.html.
9. HCUP National Inpatient Sample (NIS). Healthcare Cost and Utilization Project (HCUP). 2021. Agency for Healthcare Research and Quality, Rockville, MD. 2024 [Available from: www.hcup-us.ahrq.gov/nisoverview.jsp.
10. Melgar M, Haston J, DeCuir J, et al. Multisystem inflammatory syndrome in adults: case finding through systematic review of electronic medical records. Clin Infect Dis 2022; 75: 1903-11.
11. Ahmed R, Shahbaz H, Ramphul K, et al. Racial disparities among patients with cardiac sarcoidosis and arrhythmias in the United States: a propensity matched-analysis from the national inpatient sample database 2016-2020. Curr Probl Cardiol 2024; 49: 102450.
12. Dhaliwal JS, Sekhon MS, Rajotia A, et al. Disparities and outcomes in the first and second year of the pandemic on events of acute myocardial infarction in coronavirus disease 2019 patients. Medicina (Mex) 2024; 60: 597.
13. Elixhauser Comorbidity Software Refined For ICD-10-CM. Available from: https://hcup-us.ahrq.gov/toolssoftware/comorbidityicd10/comorbidity_icd10.jsp.
14. Glasheen WP, Cordier T, Gumpina R, Haugh G, Davis J, Renda A. Charlson Comorbidity Index: ICD-9 update and ICD-10 translation. Am Health Drug Benefits 2019; 12: 188-97.
15. Dhaliwal JS, Kumar N, Mactaggart S, et al. Cardiovascular complications in young adults with postacute sequelae of COVID-19: a perspective from the United States. Am J Cardiol 2024; 217: 169-70.
16. Ramphul K, Dhaliwal JS, Sombans S, et al. Trends in admissions for COVID-19 in the United States between

April 2020 and December 2021 and cardiovascular events. Arch Med Sci Atheroscler Dis 2024; 9: 60-5.
17. 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.
18. Davogustto 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.
19. Malik YA. Covid-19 variants: impact on transmissibility and virulence. Malays J Pathol 2022; 44: 387-96.
20. Reis BCSD, Soares Faccion R, de Carvalho FAA, et al. Rare genetic variants involved in multisystem inflammatory syndrome in children: a multicenter Brazilian cohort study. Front Cell Infect Microbiol 2023; 13: 1182257.
21. Lawrensia S, Henrina J, Cahyadi A. Multisystem inflammatory syndrome in adults: a systematic review and meta-analysis of the rheumatological spectrum of complications post COVID-19 infection. Rev Colomb Reumatol 2022; 29: S17-24.
22. Kelly CD, Stoehr AM, Nunn C, Smyth KN, Prokop ZM. Sexual dimorphism in immunity across animals: a meta-analysis. Ecol Lett 2018; 21: 1885-94.
23. Kronzer VL, Bridges SL, Davis JM. Why women have more autoimmune diseases than men: an evolutionary perspective. Evol Appl 2021; 14: 629-33.
24. Javalkar K, Robson VK, Gaffney L, et al. Socioeconomic and racial and/or ethnic disparities in multisystem inflammatory syndrome. Pediatrics 2021; 147: e2020039933.
25. Middelburg JG, Crijnen TEM, D'Antiga L, et al. Association of ethnicity with multisystem inflammatory syndrome in children related to SARS-CoV-2 infection: an international case-referent study. Front Pediatr 2021; 9: 707650.
26. Parodis I, Lanata C, Nikolopoulos D, Blazer A, Yazdany J. Reframing health disparities in SLE: a critical reassessment of racial and ethnic differences in lupus disease outcomes. Best Pract Res Clin Rheumatol 2023; 37: 101894.
27. Singh J, Malik P, Patel N, et al. Kidney disease and COVID-19 disease severity – systematic review and meta-analysis. Clin Exp Med 2022; 22: 125-35.
28. Abumweis S, Alrefai W, Alzoughool F. Association of obesity with COVID-19 diseases severity and mortality: a meta-analysis of studies. Obes Med 2022; 33: 100431.
29. COVID-19 and Heart Failure 2023 [cited 2024 1st May]. Available from: https://www.heart.org/en/health-topics/heart-failure/living-with-heart-failure-and-managing-advanced-hf/covid-19-and-heart-failure#:~:text=The%20most%20important%20thing%20to,stay%20informed%20and%20stay%20cautious.
30. Sher EK, Ćosović A, Džidić-Krivić A, Farhat EK, Pinjić E, Sher F. Covid-19 a triggering factor of autoimmune and multi-inflammatory diseases. Life Sci 2023; 319: 121531.