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Original Research

Multisystem inflammatory syndrome in adults: Comparison with other inflammatory conditions during the Covid-19 pandemic

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ABSTRACT

Background: Multisystem inflammatory syndrome in adults (MIS-A) is an increasingly recognized complication of Covid-19. We assessed risk factors, clinical characteristics, and outcomes of patients with MIS-A compared with other inflammatory conditions.

Methods: We analyzed a cohort of patients ≥21 years hospitalized with MIS-A in Quebec, Canada between February 2020 and March 2021. We included comparison groups that share symptomatology or pathophysiology with MIS-A, including Kawasaki disease, toxic shock syndrome, and other Covid-19 complications. We examined characteristics of men and women at admission, and identified preexisting factors associated with MIS-A through odds ratios (OR) and 95% confidence intervals (CI) from adjusted logistic regression models.

Results: Among 22,251 patients in this study, 52 had MIS-A, 90 Kawasaki disease, 500 toxic shock syndrome, and 21,609 other Covid-19 complications. MIS-A was associated with an elevated risk of respiratory failure compared with Kawasaki disease (OR 7.22, 95% CI 1.26–41.24), toxic shock syndrome (OR 4.41, 95% CI 1.73–11.23), and other Covid-19 complications (OR 3.03, 95% CI 1.67–5.50). Patients with MIS-A had a greater risk of cardiac involvement, renal failure, and mortality. The data pointed towards sex-specific differences in presentation, with more respiratory involvement in women and cardiac involvement in men compared with patients that had other Covid-19 complications. Except for allergic disorders and cancer, prior medical risk factors were not associated with a greater likelihood of MIS-A.

Conclusions: Patients with MIS-A have an elevated risk of mortality compared with other inflammatory conditions, with women having a predominance of respiratory complications and men cardiovascular complications.

1. Introduction

Multisystem inflammatory syndrome was initially documented in children (MIS-C) at the start of the pandemic, but has since been found in adults (MIS-A) as well [1,2]. MIS-C is defined as fever accompanied by a combination of rash, conjunctivitis, hypotension, shock, myocardial dysfunction, coagulopathy, gastrointestinal manifestations, and markers of inflammation manifesting between two to six weeks after a SARS-CoV-2 infection among persons under 20 years of age [3]. Apart from obesity and chronic respiratory disorders, children with MIS-C tend to have few predisposing morbidities [4]. However, risk factors for MIS-A remain poorly characterized. While MIS-A is an increasingly recognized complication of SARS-CoV-2 infection in older patients [1,2], the clinical profile of these patients is less clearly understood.

The Centers for Disease Control and Prevention first issued a working case definition for MIS-A in October 2020 [5]. A few studies have since been published [2,6–8], with some suggesting that MIS-A has features of inflammatory diseases such as Kawasaki disease and toxic shock

Abbreviations: CI, confidence interval; ICD, International Classification of Diseases; MIS-A, multisystem inflammatory syndrome in adults; OR, odds ratio.

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syndrome [9]. Kawasaki disease is a systemic vasculitis characterized by coronary artery aneurysms and mucocutaneous complications in children [9,10], but adults may also present with this condition [11]. Toxic shock syndrome is an acute inflammatory reaction triggered by pathogenic toxins acting as superantigens that lead to shock and multiorgan failure [9,12]. MIS-A has signs and symptoms similar to Kawasaki disease and toxic shock syndrome [6,9,12]. These conditions have been comparison groups for pediatric MIS-C in previous research [13]. However, comparisons of MIS-A with these inflammatory conditions are lacking. In this exploratory study, we contrasted the risk factors and clinical characteristics of adults hospitalized for MIS-A against Kawasaki disease, toxic shock syndrome, and other Covid-19 complications in a Canadian population heavily affected by the pandemic.

2. Materials and methods

2.1. Population

We analyzed a cohort of 22,251 adults admitted to hospital for MIS-A, Kawasaki disease, toxic shock syndrome, or other Covid-19 complications between April 1, 2006 and March 31, 2021 in Quebec, Canada. We identified patients with these conditions in the Maintenance and Use of Data for the Study of Hospital Clientele repository, which contains discharge abstracts for all admissions and hospital-based procedures, excluding ambulatory or emergency care [14]. The data include patients with conditions severe enough to require in-hospital care anywhere in the province. We used encrypted health insurance numbers to trace patients back in time for their clinical history.

We restricted the analysis to individuals age 21 years and over, following the current case definition for MIS-A [15]. We used diagnostic codes from the 9th and 10th revision of the International Classification of Diseases (ICD-9 and ICD-10) to identify patient characteristics. We used codes from the Canadian Classification of Health Interventions to identify interventions during admission.

2.2. MIS-A

Cases included all admissions for MIS-A after February 25, 2020 (ICD-10 U07.3) [16]. The first case of acute Covid-19 infection was identified in Quebec on that date [17]. The Centers for Disease Control and Prevention currently defines MIS-A as the presence of 1) elevated inflammatory biomarkers, 2) positive test for SARS-CoV-2 infection at or prior to symptom onset, and 3) fever lasting at least 24 h or emerging in the first 72 h of admission [15]. Patients must have at least three of the following symptoms: severe cardiac illness; rash or conjunctivitis; neurological signs; shock or hypotension; gastrointestinal symptoms; and thrombocytopenia [15].

2.3. Comparison groups

We included patients hospitalized for Kawasaki disease (ICD-10 M30.3) and toxic shock syndrome (ICD-10 A48.3) as comparison groups. As these inflammatory conditions are rare, we identified patients with these conditions any time between April 2006 and March 2021. In addition, we included a comparison group of patients hospitalized for other Covid-19 complications during the pandemic (ICD-10 U07.1, U07.2, U07.4, U07.5) [16]. Patients with MIS-A, Kawasaki disease, toxic shock syndrome, and other Covid-19 complications were mutually exclusive and included only once in the analysis.

2.4. Clinical characteristics

We assessed the clinical presentation, management, and outcomes of patients during admission using diagnostic and intervention codes (Table S1). Physicians used criteria in the literature to diagnose clinical complications. Each patient could have up to 41 diagnoses and 35 treatments during a given admission [14]. We identified outcomes such as respiratory failure, respiratory distress syndrome, pleural effusion, pneumothorax, pulmonary embolism, myocardial infarction, heart failure, carditis, coronary aneurysm, cardiac arrhythmia, cardiogenic shock, hypotension, renal failure, electrolyte imbalance, septic shock, and death. For management, we identified patients who required intubation, dialysis, blood transfusion, admission to an intensive care unit, lengthy hospital stays (≥14 days), or had an adverse drug reaction or other medical and surgical complication during admission.

2.5. Risk factors

To investigate potential risk factors, we examined prior hospitalization records between 1989 and the date of admission for MIS-A or other inflammatory conditions. Risk factors included any Charlson morbidity [18], metabolic disorder (diabetes, obesity, hypertension, dyslipidemia), cardiovascular disease (myocardial infarction, heart failure, cerebrovascular disease), pulmonary disease (chronic obstructive, pneumonia), asthma and allergic disorder, other infection, autoimmune disease, cancer, renal disease, digestive/liver disease, anemia/blood disorder, skin disorder, nervous system disorder, sensory organ disorder, mental illness, and tobacco or other substance use disorder. We identified these conditions using diagnostic codes (Table S2).

2.6. Covariates

We considered the following covariates as potential confounders: age (21–54, 55–64, 65–74, ≥75 years), sex, location prior to admission (home; hospital transfer; long-term care, seniors home, other), rural residence (rural, urban, unknown), and socioeconomic deprivation (yes, no, unknown). Socioeconomic deprivation was defined as the lowest quintile of a population index for average income, education level, and employment rates within neighborhoods [19].

2.7. Data analysis

We calculated descriptive statistics using frequencies and percentages and applied multivariable logistic regression models to estimate odds ratios (OR) and 95% confidence intervals (CI). For the analysis of clinical presentation, we considered MIS-A the exposure and computed the odds of adverse outcomes for MIS-A relative to each inflammatory condition separately. For the analysis of risk factors for MIS-A, we considered prior medical conditions the exposure and computed the odds of developing of MIS-A as opposed to Kawasaki disease, toxic shock syndrome, or other Covid-19 complications. We stratified the analysis by sex to determine if the pattern of associations differed between men and women. In sensitivity analyses, we stratified toxic shock syndrome by type (streptococcal, non-streptococcal). We also stratified other Covid-19 complications by symptom severity.

All statistical models were adjusted for age, location prior to admission, rural residence, and socioeconomic deprivation. We conducted the analysis in SAS version 9.4 (SAS Institute Inc., Cary, NC). The institutional review board of our hospital research center issued an ethics waiver for this study, since the data were anonymized and informed consent was not required.

3. Results

Among 22,251 patients who were hospitalized, 52 (0.2%) were admissions for MIS-A, 90 (0.4%) for Kawasaki disease, 500 (2.2%) for toxic shock syndrome, and 21,609 (97.1%) for other Covid-19 complications (Table 1). The majority of MIS-A patients were men, age 75 years and older, from urban areas, and hospitalized during the second wave of the pandemic. In contrast, patients with Kawasaki disease and toxic shock syndrome were mainly between 21 and 54 years of age. Most patients with Kawasaki disease were male, whereas patients with toxic shock

Table 1
Demographic characteristics of patients with MIS-A, Kawasaki, toxic shock syndrome, and other Covid-19 complications.

	No. patients (%)			
	MIS-A	Kawasaki	Toxic shock syndrome	Other Covid-19 complications
Covid-19 wave[a]				
Prepandemic	–	80 (88.9)	470 (94.0)	–
Wave 1	8 (15.4)	<5	19 (3.8)	7,509 (34.8)
Wave 2	44 (84.6)	6 (6.7)	11 (2.2)	14,100 (65.3)
Age at first admission, years				
21-54	5 (9.6)	64 (71.1)	370 (74.0)	3,922 (18.2)
55-64	10 (19.2)	7 (7.8)	58 (11.6)	2,850 (13.2)
65-74	14 (26.9)	10 (11.1)	43 (8.6)	3,839 (17.8)
≥75	23 (44.2)	9 (10.0)	29 (5.8)	10,998 (50.9)
Sex				
Male	37 (71.2)	56 (62.2)	197 (39.4)	10,690 (49.5)
Female	15 (28.9)	34 (37.8)	303 (60.6)	10,919 (50.5)
Location prior to admission				
Home	28 (53.9)	75 (83.3)	457 (91.4)	13,094 (60.6)
Hospital transfer	14 (26.9)	12 (13.3)	31 (6.2)	2,682 (12.4)
Long-term care, seniors home, other	10 (19.2)	<5	12 (2.4)	5,833 (27.0)
Rural residence				
Rural	<5	15 (16.7)	101 (20.2)	2,039 (9.4)
Urban	48 (92.3)	57 (63.3)	395 (79.0)	19,316 (89.4)
Socioeconomic deprivation				
Yes	11 (21.2)	18 (20.0)	92 (18.4)	4,360 (20.2)
No	35 (67.3)	63 (70.0)	381 (76.2)	12,312 (57.0)
Total	52 (100)	90 (100)	500 (100)	21,609 (100)

[a] Prepandemic: April 1, 2006 to February 24, 2020; Wave 1: February 25, 2020 to August 22, 2020; Wave 2: August 23, 2020 to March 31, 2021.

syndrome were predominantly female.

3.1. Clinical presentation of MIS-A

Patients with MIS-A had a considerably elevated risk of mortality compared with Kawasaki disease (OR 31.08, 95% CI 3.01–321.21), toxic shock syndrome (OR 2.96, 95% CI 1.31–6.66), and other Covid-19 complications (OR 4.03, 95% CI 2.21–7.34) (Table 2). These patients were at risk of respiratory failure compared with Kawasaki (OR 7.22, 95% CI 1.26–41.24), toxic shock syndrome (OR 4.41, 95% CI 1.73–11.23), and other Covid-19 complications (OR 3.03, 95% CI 1.67–5.50). MIS-A was associated with a generally higher risk of respiratory distress syndrome, pulmonary embolism, carditis, renal failure, electrolyte imbalance, admission to an intensive care unit, intubation, and blood transfusion. Patients with MIS-A were also more likely to require a hospital stay ≥14 days.

Clinical profiles appeared to be sex-dependent (Table 3). Men and women with MIS-A both had increased odds of respiratory failure. Among women, MIS-A was strongly associated with adult respiratory distress syndrome (OR 8.06, 95% CI 1.71–37.98), intubation (OR 6.76, 95% CI 1.70–26.99), and hospital stays of 14 days or more (OR 4.66, 95% CI 1.26–17.26) compared with toxic shock syndrome. Men with MIS-A had a greater prevalence of adverse cardiovascular events such as pulmonary embolism and cardiogenic shock than men with Kawasaki disease, whereas women with MIS-A did not appear to be at risk of cardiovascular events. Among men, MIS-A was associated with 7.62 times the odds of renal failure (95% CI 1.73–33.54), 25.03 times the odds of electrolyte imbalance (95% CI 3.61–173.38), and 4.56 times the odds of admission to an intensive care unit (95% CI 1.24–16.86).

The tendency for cardiovascular events in men and respiratory events in women persisted when we compared MIS-A with other Covid-19 complications (Table 4). Men with MIS-A had increased odds of cardiovascular complications such as myocardial infarction (OR 3.14, 95% CI 1.35–7.31), carditis (OR 9.15, 95% CI 2.72–30.83), cardiogenic shock (OR 18.14, 95% CI 6.11–53.91), and pulmonary embolism (OR 4.42, 95% CI 1.80–10.86) compared with other Covid-19 complications. Men with MIS-A were also more likely to require dialysis (OR 4.71, 95% CI 1.92–11.55). Although men and women both had an increased risk of respiratory complications, women with MIS-A had greater odds of respiratory distress syndrome (OR 13.26, 95% CI 4.35–40.45), pneumothorax (OR 15.51, 95% CI 1.92–125.13), intubation (OR 23.97, 95% CI 7.79–73.74), and death (OR 9.19, 95% CI 3.02–28.03). Women with MIS-A were also more likely to experience complications during admission (OR 3.42, 95% CI 1.21–9.69) and remain in hospital for 14 days or longer (OR 4.89, 95% CI 1.47–16.25).

In sensitivity analyses, MIS-A remained associated with adverse outcomes compared with both streptococcal and non-streptococcal toxic shock syndrome (Table S3). Adverse outcomes were greater when MIS-A was compared with nonsevere than severe Covid-19 (Table S4).

3.2. Risk factors

We did not find strong associations between prior medical history and MIS-A (Table 5). MIS-A patients were more likely to have a prior history of asthma, allergic disorders, and cancer relative to Kawasaki disease, toxic shock syndrome, and other Covid-19 complications, although the difference was not statistically significant.

4. Discussion

In this preliminary study of severe inflammatory disorders, adults hospitalized for MIS-A had an elevated risk of morbidity and mortality compared with Kawasaki disease, toxic shock syndrome, and other Covid-19 complications. Relative to toxic shock syndrome, women with MIS-A were more likely to develop respiratory complications, including respiratory failure and adult respiratory distress syndrome. Men with MIS-A presented more frequently with respiratory and renal failure than men with Kawasaki disease. When compared with other Covid-19 complications, MIS-A was associated with an elevated risk of respiratory complications among women and cardiovascular complications among men. The findings suggest that the clinical outcomes of MIS-A differ from other inflammatory disorders, with men potentially at greater risk of cardiac complications than women. Risk factors for MIS-A did not appear to differ significantly from that of Kawasaki disease, toxic shock syndrome, or other Covid-19 complications.

Previous studies of the demographic and clinical presentation of patients with MIS-A are conflicting [2,5–8]. In existing studies, MIS-A patients were young with a median age of 21–45 years [2,7,8].

Table 2
Clinical presentation of MIS-A compared with Kawasaki, toxic shock syndrome, and other Covid-19 complications.

Outcome	No. MIS-A (%)	No. Kawasaki (%)	No. Toxic shock syndrome (%)	No. Covid-19 (%)	Odds ratio (95% confidence interval)[a]		
					MIS-A vs Kawasaki	MIS-A vs Toxic shock syndrome	MIS-A vs Covid-19
Clinical							
Respiratory failure	16 (30.8)	<5	26 (5.2)	2,556 (11.8)	7.22 (1.26–41.24)	4.41 (1.73–11.23)	3.03 (1.67–5.50)
Adult respiratory distress syndrome	16 (30.8)	0	32 (6.4)	900 (4.2)	–	7.00 (2.68–18.25)	8.52 (4.60–15.75)
Pleural effusion	<5	0	40 (8.0)	651 (3.0)	–	0.77 (0.18–3.36)	1.86 (0.57–6.01)
Pneumothorax	<5	0	0	131 (0.6)	–	–	7.25 (2.19–24.02)
Pulmonary embolism	6 (11.5)	0	<5	761 (3.5)	–	24.37 (3.65–162.91)	2.98 (1.26–7.06)
Myocardial infarction	8 (15.4)	17 (18.9)	24 (4.8)	1,283 (5.9)	0.30 (0.08–1.16)	2.25 (0.72–7.04)	2.64 (1.23–5.71)
No ST elevation	7 (13.5)	11 (12.2)	23 (4.6)	1,162 (5.4)	0.51 (0.12–2.19)	2.10 (0.63–6.98)	2.52 (1.12–5.68)
Heart failure	9 (17.3)	9 (10.0)	30 (6.0)	2,494 (11.5)	1.14 (0.25–5.21)	0.97 (0.34–2.77)	1.56 (0.74–3.27)
Carditis	<5	<5	8 (1.6)	175 (0.8)	–	41.20 (5.34–317.84)	6.58 (2.02–21.47)
Coronary aneurysm	0	27 (30.0)	0	<5	–	–	–
Cardiac arrhythmia	17 (32.7)	9 (10.0)	56 (11.2)	4,709 (21.8)	4.02 (1.08–14.89)	0.92 (0.41–2.09)	1.71 (0.92–3.16)
Cardiogenic shock	<5	0	<5	83 (0.4)	–	–	14.91 (5.13–43.30)
Hypotension	5 (9.6)	<5	30 (6.0)	1,801 (8.3)	3.65 (0.28–47.01)	1.30 (0.35–4.76)	1.08 (0.43–2.74)
Renal failure	31 (59.6)	7 (7.8)	217 (43.4)	7,262 (33.6)	13.94 (3.56–54.61)	0.90 (0.44–1.82)	2.93 (1.62–5.30)
Septic shock	8 (15.4)	0	73 (14.6)	359 (1.7)	–	0.86 (0.34–2.21)	8.50 (3.93–18.38)
Electrolyte imbalance	22 (42.3)	5 (5.6)	150 (30.0)	5,075 (23.5)	9.42 (2.25–39.46)	1.54 (0.77–3.10)	2.30 (1.32–4.01)
Death	26 (50.0)	<5	40 (8.0)	4,847 (22.4)	31.08 (3.01–321.21)	2.96 (1.31–6.66)	4.03 (2.21–7.34)
Management							
ICU admission	36 (69.2)	29 (32.2)	363 (72.6)	3,931 (18.2)	5.77 (1.93–17.31)	1.32 (0.60–2.88)	9.65 (5.18–17.97)
Intubation	22 (42.3)	13 (14.4)	118 (23.6)	1,541 (7.1)	3.99 (1.27–12.49)	1.63 (0.78–3.42)	8.50 (4.69–15.40)
Dialysis	7 (13.5)	0	30 (6.0)	597 (2.8)	–	1.09 (0.36–3.31)	4.23 (1.87–9.60)
Blood transfusion	14 (26.9)	7 (7.8)	89 (17.8)	1,690 (7.8)	7.97 (1.68–37.92)	0.68 (0.30–1.55)	3.81 (2.04–7.12)
Medical complication	15 (28.9)	17 (18.9)	129 (25.8)	3,443 (15.9)	2.02 (0.60–6.79)	0.68 (0.31–1.47)	1.85 (1.01–3.40)
Length of stay, ≥14 days	29 (55.8)	23 (25.6)	110 (22.0)	8,531 (39.5)	3.68 (1.32–10.32)	2.38 (1.17–4.84)	1.73 (0.98–3.05)

[a] Odds ratio for patients exposed to MIS-A vs. other inflammatory conditions, adjusted for sex, age at first admission, location prior to admission, rural residence, and socioeconomic deprivation.

Table 3
Clinical presentation of MIS-A in men and women, compared with Kawasaki and toxic shock syndrome.

Outcome	Men			Women		
	No. MIS-A (%)	No. Kawasaki (%)	Odds ratio (95% confidence interval)[a]	No. MIS-A (%)	No. Toxic shock syndrome (%)	Odds ratio (95% confidence interval)[a]
Clinical						
Respiratory failure	12 (32.4)	<5	12.09 (1.12–130.31)	<5	13 (4.3)	10.22 (1.63–64.13)
Adult respiratory distress syndrome	11 (29.7)	0	–	5 (33.3)	22 (7.3)	8.06 (1.71–37.98)
Pleural effusion	<5	0	–	<5	30 (9.9)	0.53 (0.04–6.56)
Pneumothorax	<5	0	–	<5	0	–
Pulmonary embolism	6 (16.2)	0	–	0	<5	–
Myocardial infarction	7 (18.9)	15 (26.8)	0.32 (0.07–1.48)	<5	10 (3.3)	0.80 (0.05–12.32)
No ST elevation	6 (16.2)	9 (16.1)	0.61 (0.11–3.53)	<5	10 (3.3)	0.80 (0.05–12.32)
Heart failure	8 (21.6)	8 (14.3)	1.26 (0.25–6.31)	<5	16 (5.3)	0.16 (0.01–2.35)
Carditis	<5	<5	–	0	5 (1.7)	–
Coronary aneurysm	0	21 (37.5)	–	0	0	–
Cardiac arrhythmia	12 (32.4)	7 (12.5)	2.40 (0.52–11.14)	5 (33.3)	22 (7.3)	1.51 (0.37–6.12)
Cardiogenic shock	<5	0	–	0	0	–
Hypotension	<5	<5	–	<5	18 (5.9)	1.54 (0.22–10.93)
Renal failure	23 (62.2)	7 (12.5)	7.62 (1.73–33.54)	8 (53.3)	104 (34.3)	1.32 (0.40–4.40)
Septic shock	5 (13.5)	0	–	<5	37 (12.2)	1.46 (0.33–6.48)
Electrolyte imbalance	18 (48.7)	<5	25.03 (3.61–173.38)	<5	88 (29.0)	0.58 (0.16–2.14)
Death	17 (46.0)	0	–	9 (60.0)	15 (5.0)	8.81 (1.99–39.03)
Management						
ICU admission	26 (70.3)	23 (41.1)	4.56 (1.24–16.86)	10 (66.7)	220 (72.6)	1.27 (0.34–4.72)
Intubation	13 (35.1)	11 (19.6)	1.78 (0.45–7.11)	9 (60.0)	59 (19.5)	6.76 (1.70–26.99)
Dialysis	6 (16.2)	0	–	<5	11 (3.6)	1.50 (0.14–16.45)
Blood transfusion	10 (27.0)	<5	7.02 (0.88–56.05)	<5	47 (15.5)	1.10 (0.27–4.41)
Medical complication	9 (24.3)	12 (21.4)	2.20 (0.50–9.65)	6 (40.0)	77 (25.4)	1.03 (0.30–3.55)
Length of stay, ≥14 days	18 (48.7)	16 (28.6)	2.80 (0.80–9.87)	11 (73.3)	55 (18.2)	4.66 (1.26–17.26)

[a] Odds ratio for patients exposed to MIS-A vs. other inflammatory conditions, adjusted for age at first admission, location prior to admission, rural residence, and socioeconomic deprivation.

Table 4
Clinical presentation of MIS-A in men and women, compared with other Covid-19 complications.

Outcome	Men			Women		
	No. MIS-A (%)	No. Covid-19 (%)	Odds ratio (95% confidence interval)[a]	No. MIS-A (%)	No. Covid-19 (%)	Odds ratio (95% confidence interval)[a]
Clinical						
Respiratory failure	12 (32.4)	1,405 (13.1)	3.12 (1.56–6.23)	<5	1,151 (10.5)	2.75 (0.87–8.74)
Respiratory distress syndrome	11 (29.7)	623 (5.8)	7.16 (3.43–14.96)	5 (33.3)	277 (2.5)	13.26 (4.35–40.45)
Pleural effusion	<5	335 (3.1)	1.77 (0.42–7.42)	<5	316 (2.9)	2.22 (0.29–17.23)
Pneumothorax	<5	102 (1.0)	5.55 (1.29–23.85)	<5	29 (0.3)	15.51 (1.92–125.13)
Pulmonary embolism	6 (16.2)	471 (4.4)	4.42 (1.80–10.86)	0	290 (2.7)	–
Myocardial infarction	7 (18.9)	700 (6.6)	3.14 (1.35–7.31)	<5	583 (5.3)	1.29 (0.17–9.96)
No ST elevation	6 (16.2)	628 (5.9)	2.88 (1.17–7.06)	<5	534 (4.9)	1.45 (0.19–11.26)
Heart failure	8 (21.6)	1,230 (11.5)	1.94 (0.86–4.35)	<5	1,264 (11.6)	0.62 (0.08–4.88)
Carditis	<5	99 (0.9)	9.15 (2.72–30.83)	0	76 (0.7)	–
Coronary aneurysm	0	<5	–	0	0	–
Cardiac arrhythmia	12 (32.4)	2,454 (23.0)	1.48 (0.72–3.05)	5 (33.3)	2,255 (20.7)	2.64 (0.83–8.39)
Cardiogenic shock	<5	64 (0.6)	18.14 (6.11–53.91)	0	19 (0.2)	–
Hypotension	<5	935 (8.8)	0.53 (0.13–2.21)	<5	866 (7.9)	3.21 (0.88–11.64)
Renal failure	23 (62.2)	4,026 (37.7)	2.65 (1.32–5.33)	8 (53.3)	3,236 (29.6)	3.67 (1.25–10.76)
Septic shock	5 (13.5)	225 (2.1)	6.58 (2.51–17.25)	<5	134 (1.2)	14.92 (4.04–55.09)
Electrolyte imbalance	18 (48.7)	2,482 (23.2)	3.02 (1.57–5.79)	<5	2,593 (23.8)	1.10 (0.35–3.48)
Death	17 (46.0)	2,583 (24.2)	2.83 (1.39–5.77)	9 (60.0)	2,264 (20.7)	9.19 (3.02–28.03)
Management						
ICU admission	26 (70.3)	2,465 (23.1)	9.78 (4.63–20.65)	10 (66.7)	1,466 (13.4)	9.79 (3.18–30.15)
Intubation	13 (35.1)	1,036 (9.7)	5.60 (2.72–11.52)	9 (60.0)	505 (4.6)	23.97 (7.79–73.74)
Dialysis	6 (16.2)	405 (3.8)	4.71 (1.92–11.55)	<5	192 (1.8)	2.79 (0.35–22.11)
Blood transfusion	10 (27.0)	942 (8.8)	3.82 (1.82–8.03)	<5	748 (6.9)	4.01 (1.25–12.80)
Medical complication	9 (24.3)	1,869 (17.5)	1.42 (0.66–3.02)	6 (40.0)	1,574 (14.4)	3.42 (1.21–9.69)
Length of stay, ≥14 days	18 (48.7)	4,255 (39.8)	1.23 (0.64–2.39)	11 (73.3)	4,276 (39.2)	4.89 (1.47–16.25)

[a] Odds ratio for patients exposed to MIS-A vs. other inflammatory conditions, adjusted for age at first admission, location prior to admission, rural residence, and socioeconomic deprivation.

Table 5
Association of prior medical history with MIS-A, compared with Kawasaki, toxic shock syndrome, and other Covid-19 complications.

Exposure	No. MIS-A (%)	No. Kawasaki (%)	Odds ratio (95% confidence interval)[a]	No. Toxic shock syndrome (%)	Odds ratio (95% confidence interval)[a]	No. Covid-19 (%)	Odds ratio (95% confidence interval)[a]
Charlson morbidity	33 (63.5)	38 (42.2)	0.50 (0.16–1.59)	144 (28.8)	0.49 (0.20–1.19)	13,867 (64.2)	0.85 (0.46–1.60)
Metabolic disorder	41 (78.9)	43 (47.8)	0.18 (0.03–1.19)	154 (30.8)	0.94 (0.35–2.53)	17,122 (79.2)	0.77 (0.37–1.58)
Diabetes	21 (40.4)	11 (12.2)	1.22 (0.37–4.05)	67 (13.4)	0.61 (0.27–1.40)	7,684 (35.6)	1.04 (0.60–1.83)
Obesity	10 (19.2)	13 (14.4)	0.61 (0.18–2.14)	54 (10.8)	1.00 (0.40–2.52)	4,308 (19.9)	0.95 (0.47–1.91)
Hypertension	35 (67.3)	34 (37.8)	0.27 (0.06–1.18)	107 (21.4)	0.99 (0.41–2.38)	14,694 (68.0)	0.83 (0.44–1.56)
Dyslipidemia	35 (67.3)	29 (32.2)	0.50 (0.13–1.87)	80 (16.0)	1.63 (0.72–3.67)	11,485 (53.2)	1.58 (0.85–2.94)
Cardiovascular disease	29 (55.8)	49 (54.4)	0.09 (0.02–0.40)	119 (23.8)	0.27 (0.10–0.70)	13,188 (61.0)	0.66 (0.36–1.23)
Myocardial infarction	13 (25.0)	17 (18.9)	0.64 (0.18–2.27)	21 (4.2)	1.52 (0.59–3.94)	3,268 (15.1)	1.67 (0.87–3.21)
Heart failure	8 (15.4)	6 (6.7)	0.49 (0.11–2.29)	24 (4.8)	0.76 (0.25–2.31)	3,108 (14.4)	1.03 (0.48–2.24)
Cerebrovascular disease	6 (11.5)	5 (5.6)	1.02 (0.17–6.17)	20 (4.0)	0.49 (0.14–1.71)	2,781 (12.9)	0.80 (0.34–1.92)
Pulmonary disease	25 (48.1)	26 (28.9)	1.41 (0.49–4.10)	139 (27.8)	0.85 (0.39–1.84)	9,454 (43.8)	1.16 (0.66–2.04)
Pneumonia	10 (19.2)	5 (5.6)	2.36 (0.42–13.33)	32 (6.4)	0.99 (0.37–2.67)	3,928 (18.2)	1.03 (0.51–2.08)
Chronic obstructive	15 (28.9)	<5	1.54 (0.33–7.24)	36 (7.2)	1.10 (0.46–2.67)	4,224 (19.6)	1.59 (0.86–2.97)
Asthma	11 (21.2)	6 (6.7)	1.79 (0.34–9.37)	43 (8.6)	1.12 (0.42–3.01)	2,811 (13.0)	1.98 (1.01–3.87)
Allergic disorder (except asthma)	<5	<5	3.13 (0.24–41.72)	24 (4.8)	1.06 (0.27–4.16)	1,308 (6.1)	1.39 (0.50–3.88)
Common allergies[b]	<5	<5	3.13 (0.24–41.72)	16 (3.2)	1.79 (0.41–7.85)	1,052 (4.9)	1.78 (0.64–4.97)
Severe and rare allergies[c]	<5	<5	–	10 (2.0)	0.79 (0.11–5.59)	318 (1.5)	2.88 (0.69–12.00)
Infection[d]	24 (46.2)	30 (33.3)	0.88 (0.30–2.56)	158 (31.6)	0.60 (0.27–1.35)	9,328 (43.2)	1.14 (0.65–2.00)
Autoimmune disease	<5	38 (42.2)	0.15 (0.04–0.60)	44 (8.8)	0.46 (0.14–1.58)	2,271 (10.5)	0.74 (0.26–2.05)
Cancer	13 (25.0)	<5	4.72 (0.79–28.32)	35 (7.0)	1.65 (0.67–4.06)	3,833 (17.7)	1.45 (0.76–2.76)
Renal disease	16 (30.8)	6 (6.7)	1.89 (0.42–8.61)	49 (9.8)	0.83 (0.34–2.03)	5,970 (27.6)	1.08 (0.58–2.00)
Digestive/liver disease	29 (55.8)	45 (50.0)	0.17 (0.05–0.66)	162 (32.4)	0.95 (0.44–2.04)	12,227 (56.6)	0.90 (0.51–1.58)
Anemia/blood disorder	21 (40.4)	17 (18.9)	1.86 (0.59–5.86)	94 (18.8)	1.19 (0.53–2.64)	8,300 (38.4)	1.09 (0.61–1.94)
Skin disorder	7 (13.5)	12 (13.3)	0.54 (0.12–2.40)	95 (19.0)	0.29 (0.11–0.80)	4,779 (22.1)	0.52 (0.23–1.16)
Nervous system disorder	18 (34.6)	19 (21.1)	0.39 (0.11–1.39)	117 (23.4)	0.43 (0.19–1.01)	9,032 (41.8)	0.68 (0.38–1.24)
Sensory organ disorder	25 (48.1)	21 (23.3)	0.92 (0.29–2.90)	83 (16.6)	1.50 (0.67–3.33)	10,492 (48.6)	1.11 (0.59–2.07)
Mental illness	8 (15.4)	15 (16.7)	0.52 (0.13–2.07)	66 (13.2)	0.77 (0.26–2.31)	5,204 (24.1)	0.59 (0.27–1.27)
Substance use disorder	11 (21.2)	13 (14.4)	1.05 (0.25–4.37)	73 (14.6)	0.51 (0.21–1.27)	4,643 (21.5)	0.81 (0.41–1.60)

[a] Odds ratio for a prior medical risk factor vs. no risk factor, adjusted for sex, age at first admission, location prior to admission, rural residence, and socioeconomic deprivation. Results are for three separate models comparing the outcome MIS-A with Kawasaki disease, MIS-A with toxic shock syndrome, and MIS-A with other Covid-19 complications.

[b] Allergic conjunctivitis, rhinitis, urticaria, dermatitis.

[c] Anaphylaxis, allergic purpura, allergic otitis media, alveolitis, pulmonary eosinophilia, allergic gastroenteritis and colitis, allergic arthritis.

[d] Excludes pneumonia and Covid-19 infection.

However, an American study of nationwide hospital data reported that MIS-A patients had a median age of 62 years [6]. Most studies noted that MIS-A was more frequent among men [2,6–8]. In our study, over 70% of MIS-A patients were men and most were 65 years and older. Earlier studies reported that MIS-A rarely led to death or the need for invasive treatment [2,5,7,8], but a recent investigation found that 43% of patients died in hospital and 57% needed mechanical ventilation [6]. In our data, half of MIS-A patients died and 42% required intubation. Life threatening outcomes were also more frequent for MIS-A than toxic shock syndrome, Kawasaki disease, and other Covid-19 complications.

MIS-A is considered a severe complication of Covid-19 [1,2], yet comparisons with other inflammatory disorders are lacking. The only study that contrasted MIS-A against other disorders assessed demographic characteristics of acute Covid-19 infection [7]. The study found that patients with MIS-A were younger than patients with other acute Covid-19 complications (median age 45.1 vs. 56.5 years) [7]. There was no difference in race, ethnicity, underlying health conditions, or length of stay [7]. In our data, patients with MIS-A also tended to be younger, but we were unable to study race or ethnicity. However, patients with MIS-A had greater odds of death, admission to an intensive care unit, intubation, carditis, myocardial infarction, shock, and renal and respiratory failure than patients with other Covid-19 complications.

Studies have yet to contrast MIS-A with Kawasaki disease. Kawasaki is more frequent in males [20], but is less prevalent in adults than children [21]. At the beginning of the pandemic, children with MIS-C were found to have a Kawasaki-like syndrome due to an elevated prevalence of mucocutaneous and cardiac manifestations [9,10]. In our study, men with MIS-A had a greater frequency of cardiogenic shock, pulmonary embolism, respiratory and renal failure, and admission to an intensive care unit than men with Kawasaki disease. However, men with MIS-A were not at risk of coronary aneurysm. Vasculitis leading to coronary aneurysm is a central hallmark of Kawasaki disease, resulting from interleukin-1 mediated coronary endothelial cell inflammation [10,22]. In multisystem inflammatory syndrome, cardiac dysfunction instead appears to be caused by interleukin-6, which acts as a myocardial depressor in the context of a cytokine storm [22,23].

Some have proposed that MIS-A has clinical features closer to toxic shock syndrome [9]. Toxic shock syndrome is a systemic inflammatory reaction caused by superantigenic toxins released by certain strains of *Staphylococcus aureus* and *Streptococcus pyogenes* [12,24]. Superantigens trigger cytokine production through widespread activation of T cells [25]. Toxic shock syndrome is more prevalent in females, likely due to extraneous sources of infection [24]. Compared with toxic shock syndrome, women with MIS-A in our study had a greater risk of respiratory complications, intubation, and death, but had a similar risk of shock, renal failure, and heart failure. Because MIS-A and toxic shock syndrome both generate a cytokine storm, it has been suggested that the SARS-CoV-2 spike protein possesses superantigen properties [12,25,26]. The common presence of a cytokine storm could explain why MIS-A and toxic shock syndrome are both associated with shock and multiorgan failure [9,24], although our data suggest that MIS-A is more life-threatening.

Less is known about prior medical risk factors for MIS-A compared with other inflammatory conditions. One study found that MIS-A and acute Covid-19 infection did not differ significantly in the prevalence of comorbidities at admission, including cancer, hypertension, diabetes mellitus, obesity, chronic obstructive pulmonary disease, chronic kidney disease, and heart failure [7]. In our data, prior medical history was not more strongly associated with MIS-A than Kawasaki disease, toxic shock syndrome, or other Covid-19 complications, suggesting that risk factors for these conditions may be similar. Nevertheless, patients with a history of asthma, allergic disorders, and cancer had a slightly higher risk of MIS-A than other inflammatory disorders. Patients with allergies have a tendency for inadequate immune regulation [27]. Allergic disorders such as asthma are usually associated with a T-helper 2 response, but can be exacerbated by interleukin-6 [28]. In cancer, tumor cells often express interleukin-6, and patients with elevated concentrations of this cytokine typically have a poorer prognosis [29]. Interleukin-6 levels are frequently elevated in patients with multisystem inflammatory syndrome [22].

This study has a number of limitations. Medical administrative data are subject to coding errors. A working definition for MIS-A was not published until later in the pandemic [5], thus misclassification may have been greater early on. Nevertheless, validation data suggested that sensitivity and specificity for MIS-C was high even at the start of the pandemic [3]. The dataset does not include covariates such as ethnicity, hence there may be residual confounding. Data on previous history of Covid-19 infection were not available, but reinfections were rare. We were able to identify prior medical hospitalizations, not underlying medical conditions that never resulted in hospitalization. We could not account for individuals treated in outpatient settings. We did not examine the long-term outcomes of MIS-A, Kawasaki disease, toxic shock syndrome, and other Covid-19 complications. MIS-A is a heterogeneous condition that shares inflammatory features with other conditions in this study. How MIS-A compared with infectious disorders such as sepsis or other acute respiratory distress syndrome remains to be investigated. As the sample size was small, we were limited by low statistical power for some comparisons. We did not have access to laboratory data, and could not examine biomarker profiles or confirm that patients with MIS-A had a positive Covid-19 test prior to diagnosis. Generalizability of our findings requires further investigation, although the data encompassed a culturally diverse population that was covered by universal health insurance. The elderly were eligible for vaccination towards the end of the study.

5. Conclusions

In this observational study, adult patients hospitalized with MIS-A had a greater likelihood of mortality compared with Kawasaki disease, toxic shock syndrome, and other Covid-19 complications. Women with MIS-A were more likely to experience respiratory complications, while men had a greater prevalence of cardiovascular complications. Prior medical history was not disproportionately associated with the development of MIS-A compared with other inflammatory diseases, although patients with MIS-A had a slightly higher prevalence of allergy and cancer. More research will be needed to confirm if there are sex-based differences in presentation and identify biomarker profiles that can accurately detect MIS-A. Overall, this preliminary study suggests that MIS-A has a different clinical presentation than Kawasaki disease, toxic shock syndrome, and other Covid-19 complications, but a better understanding of risk factors for MIS-A is needed.

Author contributions

Nathalie Auger: Conceptualization, Methodology, Writing - Original Draft, Writing - Review & Editing, Visualization, Supervision, Funding acquisition. **Philippe Bégin**: Conceptualization, Writing - Review & Editing. **Harb Kang**: Conceptualization, Writing - Review & Editing. **Ernest Lo**: Conceptualization, Methodology, Writing - Review & Editing. **Émilie Brousseau**: Conceptualization, Formal analysis, Visualization, Writing - Original Draft. **Jessica Healy-Profitós**: Conceptualization, Writing - Review & Editing. **Brian J. Potter**: Conceptualization, Writing - Review & Editing.

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Declaration of competing interest

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Appendix A. Supplementary data

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