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Low ICU Admission and Excellent Outcomes in MIS-C: A Swedish Study From an Open Society

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ABSTRACT

Aim: During the COVID-19 pandemic, Sweden chose a more open public health approach. A general concern was that this approach would affect the population negatively. We describe the Swedish national MIS-C cohort and risk factors for severe disease defined as admission to the intensive care unit and cardiogenic shock.

Methods: Nationwide population-based cross-sectional study. All children and adolescents from 0 to 19 years of age with MIS-C from March 2020 to August 2022 were included. Multivariable logistic regression with ICU admission and cardiogenic shock as outcomes was used to evaluate risk factors for severe disease.

Results: A total of 338 MIS-C cases were identified; 69 patients (20%) required intensive care and 38 patients (11%) developed cardiogenic shock. Clinical findings associated with ICU admission were cardiac involvement: OR 14.00 (6.28–34.70), airway involvement: OR 6.75 (3.23–14.80), hyperinflammation: OR 3.25 (1.34–7.97), oedema: OR 2.40 (1.07–5.44) and diarrhoea: OR 2.23 (1.07–4.80). Clinical findings associated with cardiogenic shock were hyperinflammation: OR 5.10 (2.16–12.00), airway involvement: OR 4.87 (2.12–12.00), higher age (13–19 vs. 0–5 years): OR 3.85 (1.17–15.60), obesity: OR 3.55 (1.14–10.5) and diarrhoea: OR 2.48 (1.09–5.92).

Conclusion: In Swedish national MIS-C cohort, the rate of ICU admission was low and outcome excellent. Identifying risk factors for ICU admission and cardiogenic shock may facilitate early detection of risk patients.

Abbreviations: CRP, C-reactive protein; ECMO, extracorporeal membrane oxygenation; ICD10, International Classification of Diseases; ICU, intensive care unit; LMWH, low-molecular-weight heparin; MAS, Macrophage Activation Syndrome; MIS-C, multisystem inflammatory syndrome in children; NT-proBNP, N-terminal pro-B-type natriuretic peptide; pedSRQ, Swedish National Quality Registry for Paediatric Rheumatology; SAR-CoV-2, severe acute respiratory syndrome coronavirus 2.

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Summary

- This nationwide Swedish cohort study identified clinical and laboratory predictors of severe MIS-C, defined as ICU admission and cardiogenic shock.
- Despite a non-restrictive public health approach during the pandemic, Sweden had low ICU admission rates and excellent outcomes among children with MIS-C, without having investigated whether the strategy affected these outcomes.
- Early identification of high-risk patients may support timely and aggressive treatment strategies to prevent critical illness.

1 | Introduction

Multisystem Inflammatory Syndrome in Children (MIS-C) is a severe hyperinflammatory complication of COVID-19 [1]. Though relatively rare, MIS-C can lead to severe morbidity and even mortality [1]. Between 32% and 68% of MIS-C cases were reported in various studies to require intensive care unit (ICU) admission [2–5], with cardiogenic shock described to affect between 50% and 80% of cases [6]. The mortality rate for MIS-C has been estimated to 1%–2% [1, 7, 8], although higher mortality rates have been reported [9–11]. The risk factors associated with admission to ICU for patients with MIS-C have been the subject of various studies [5, 9, 11–13].

The reported incidence of MIS-C has varied by country and over time [12, 13]. In Sweden, Rhedin et al. reported an incidence of 6.8 per 100,000 children from March 2020 to December 2021 [14]. In a recent publication, Eleftheriou et al. found a decreasing MIS-C incidence over the three pandemic waves, possibly due to increased immunity, vaccination and milder SARS-CoV-2 variants [15].

Sweden provides a unique setting for studies of COVID and especially MIS-C because of the country's open public strategy during the pandemic, its specific health care system properties, as well as the aggressive treatment strategy for MIS-C that was generally adopted all over Sweden. Numerous studies have explored MIS-C, but to our knowledge there is only one prior national prospective cohort study, conducted by Nygaard et al. [16] Here we present our nationwide population-based Swedish study with a focus on patient characteristics, acute disease presentation, and risk factors associated with ICU admission and cardiogenic shock.

2 | Patients and Methods

2.1 | Study Design and Setting

This study employed a prospective, population-based cohort design, including all Swedish children aged 0–19 years diagnosed with MIS-C who were enrolled in the Swedish National Quality Registry for Paediatric Rheumatology (pedSRQ) (<https://barnrhumaregistret.se/>) from March 1, 2020 to August 31, 2022. Patients who fulfilled World Health Organization (WHO) criteria for MIS-C were classified according to International

Classification of Diseases (ICD10) code U10.9 [17]. The study was approved by the Swedish Ethical Review Authority (DNR 2020–06175).

2.2 | Study Population

A total of 366 patients were registered in pedSRQ. Patients were included in the study if they were admitted to a paediatric ward and registered as having MIS-C in pedSRQ, were under 20 years old at diagnosis, and gave patient or parental consent for sharing pseudonymized patient data for research purposes ($n = 356$). Patients not meeting World Health Organization (WHO) diagnostic criteria [17] or who were later diagnosed with alternate conditions were excluded ($n = 18$). Most cases were discussed and re-evaluated in our bi-weekly national web-based meetings to improve our expertise and to minimise risks of bias in the register.

2.3 | Data Sources and Variables

The pedSRQ is an electronic registry that collects prospective data on children with paediatric rheumatic diseases in Sweden since 2009. In 2020, a custom interface was designed to make it possible to enter MIS-C cases into the registry. Data extracted from the registry included demographic information, date of MIS-C diagnosis, patient characteristics, clinical symptoms during the course of MIS-C, complications/classification of MIS-C, level and length of care, therapies and outcome.

Weight categories were calculated via the ISO BMI, which considers age and gender and categorises weight status as: underweight (ISO BMI < 18.5), normal weight (ISO BMI 18.5–24.9), overweight (ISO BMI 25–29.9), or obese (ISO BMI > 30) [18, 19]. We did not separate underweight from normal weight, thus defining normal weight as ISO BMI < 25.

Mucocutaneous involvement was identified by at least one sign such as changes in mucous membranes, non-purulent conjunctivitis, redness of the lips, or a skin rash. *Cardiac involvement* was assessed by ECG and echocardiogram and characterized by conditions such as arrhythmia, pericarditis, myocarditis, and/or reduced ejection fraction. Manifestations of *airway involvement* included a sore throat, cough, and/or breathing difficulties. *CNS involvement* was defined by neurological symptoms including irritability, seizures, and/or encephalopathy. Lastly, we created the co-variable *hyperinflammation* by modifying the 2016 Classification Criteria for Macrophage Activation Syndrome (MAS) associated with Systemic Juvenile Idiopathic Arthritis, by Ravelli et al. [20] Our definition included the triad of serum C-reactive protein (CRP) > 200 mg/L, platelet count < 110×10^9 /L and raised liver transaminases. Serum ferritin levels were not included in the definition, as the threshold in our dataset (2000 mg/L) was significantly higher than the 684 mg/L included in the Ravelli criteria.

Outcome variables included ICU admission confirmed by either the documented date of admission to the ICU or the initiation of ECMO therapy. Cardiogenic shock was defined by the requirement for inotropic support. Our study divided the MIS-C cases

according to COVID-19 variants (Alpha, Delta and Omicron) and also whether patients were admitted to a general paediatric ward or to an ICU.

2.4 | Statistical Analysis

Continuous variables were presented using median and range while categorical variables were described using count and percentages. Univariable analyses were conducted using Wilcoxon signed rank test for continuous variables and Chi-square or Fisher's exact tests for categorical variables. For analysis of ICU admission rates over time, we used Pearson's chi squared test to describe differences in distribution. Multivariable logistic regression models were employed to assess the adjusted impact of baseline variables and patients' characteristics on ICU admission and shock. Variables included in the models were sex, age groups, weight groups, diarrhoea, oedema, hyperinflammation, airway affection, cardiac affection and mucocutaneous involvement. Sex, age, weight and symptom profile were considered possible risk factors based on clinical experience. Results were presented as Odds Ratios (ORs) with 95% confidence intervals (95% CI). The proportion of MIS-C patient admitted to ICU/PICU during different time-period was analysed with Chi-square test. All analyses were performed using R statistical software version 4.2.2 [21].

3 | Results

3.1 | Most Patients Were Treated on General Paediatric Ward

In total, 338 patients diagnosed with MIS-C fulfilled the inclusion criteria. Patient characteristics are presented in Table 1. There was a dominance of boys versus girls (63% vs. 37%). The median age at diagnosis was 9.3 years (range 0.3–19). The age distribution was 0–6 years ($n=92$; 27%), 7–12 years ($n=138$; 41%) and 13–19 years ($n=108$; 32%). The median duration from first symptom(s) until diagnosis was 5 days. Fourteen percent of the children were overweight, and 8% were obese.

For the majority of patients ($n=263$, 78%), the paediatric ward was the highest level of care, whereas 6 patients fulfilled the inclusion criteria but did not require any inpatient care. The median hospital stay was 9 days (range 1–48 days). Of the 338 patients, 20% were admitted to ICU; the majority of these were admitted to the ICU within the first or following day of hospital admission. Three patients required ECMO care. No mortality was observed. The median stay in ICU was 3 days in addition to the number of days at the general paediatric ward (range 0–18 days in ICU; 0 days refers to patients who were in ICU <24 h), and 6 days for patients on ECMO (range 5–8 days). All patients could be discharged home (Table 1).

3.2 | Differences in Symptoms Between ICU and Non-ICU Group

Changes in mucous membranes represented 12% in non-ICU versus 3% in the ICU group ($p=0.023$) (Table 2). The

following findings were statistically more common among patients treated in the ICU versus those not in the ICU: arrhythmia, pericarditis, myocarditis, reduced ejection fraction, sore throat, cough, shortness of breath, irritability, lethargy, diarrhoea, oedema (Table 2).

3.3 | Increased Inflammatory Response in Patients Admitted to ICU

Patients admitted to ICU had higher CRP, lower albumin, and higher levels of NT-Pro-BNP and troponin, as well as more frequent anaemia, thrombocytopenia, bicytopenia, increased IL-6, and increased liver enzymes than patients treated at general paediatric wards. NT-pro-BNP and troponin were often elevated and sometimes to very high levels (NT-pro-BNP median 4169, range 45–84 027 ng/L and troponin median 21, range 2–25 000 ng/L). Thrombocytopenia or bicytopenia was seen in almost half of the patients at presentation. The majority of patients were lymphopenic (80%). Approximately one third of cases had high serum ferritin ($>2000 \mu\text{g/L}$). In those analyzed, sIL2R levels were increased in almost all patients, and IL-6 was increased in almost half of the patients. Increased liver enzymes were present in around half of the cases (Table 2).

3.4 | Majority of Patients Were Treated With Combination Therapy

The combination of intravenous immunoglobulin and glucocorticosteroids was given to the vast majority (88%). Intravenous administration of short-acting IL-1 blockade (anakinra) was given to 41% and anti-IL-6 (tocilizumab) was given to 1% of patients. The anakinra dosage was 5–10 mg/kg intravenously divided into four daily doses. The ICU group had a higher usage of anakinra and IVIG + corticosteroids + anakinra in comparison to the non-ICU group. Both patients given anti-IL-6 therapy were admitted to the ICU and had failed therapy with IVIG + corticosteroids + anakinra. The six out-patients did not receive any treatment and resolved their symptoms spontaneously.

Inotropic support for treatment of cardiogenic shock was used in 11% of patients. Five patients needed dialysis. Three patients were treated in ECMO.

Supportive therapy with intravenous albumin was given to a third of patients. Albumin supplementation and low-molecular-weight heparin (LMWH) in treatment doses were more common among ICU patients than in patients treated at general paediatric wards (Table 3).

3.5 | Risk Factors for Admission to the ICU

There was no statistically significant variation in the rate of ICU admissions for patients with MIS-C over time during different COVID-19 variants ($p=0.90$) (Figure S1).

Risk factors for admission to ICU and/or ECMO were evaluated in logistic regression models. In crude analyses, overweight

TABLE 1 | Baseline characteristics of 338 MIS-C patients, stratified by ICU admission.

	All patients; <i>n</i> (%)	ICU; <i>n</i> (%)	Non-ICU; <i>n</i> (%)	<i>p</i>
Patients; <i>n</i> (%)	338	69 (20)	269 (80)	
Sex; <i>n</i> (%)				
Male	212 (63)	39 (56)	173 (64)	0.233
Female	126 (37)	30 (44)	96 (36)	
Age at diagnosis; median years (range)	9.3 (0.3–19)	10.9 (0.3–19)	8.90 (0.6–18)	0.062
Age groups; <i>n</i> (%)				
0–6 years	92 (27)	17 (25)	75 (28)	0.360
7–12 years	138 (41)	25 (36)	113 (42)	
13–19 years	108 (32)	27 (39)	81 (30)	
Days from symptom onset to diagnosis				
> 6 days	79 (23)	15 (22)	64 (24)	0.870
Comorbidities; <i>n</i> (%)				
Any (except obesity and overweight) ^a	57 (17)	13 (19)	44 (16)	0.623
Overweight	46 (14)	15 (22)	31 (11.5)	
Obesity	28/337 (8)	9/68 (13)	19/268 (7)	0.110
Overweight/Obese	74/337 (22)	24/68 (35)	50/268 (19)	0.003
SARS-CoV-2; <i>n</i> (%)				
PCR	119 (35)	22 (32)	97 (36)	0.279
Serology	290 (86)	62 (90)	228 (85)	0.279
PCR and/or serology	303 (90)	66 (96)	237 (88)	0.066
Outcome				
Outpatients	6 (1.8)	0	6 (2.2)	
Days at ward (patients) ^b ; median (IQR)	(332); 9 (1–48)	10 (2–48)	263/269, (6 outpatients); 9 (1–38)	
Days in ICU; median (range)	NA	3 (0–18) ^c	NA	
Days in ECMO; median (range)	NA	6 (5–8)	NA	
Case-fatalities; number (%)	0 (0)	0 (0)	0 (0)	

Abbreviations: ECMO, extracorporeal membrane oxygenation; ICU, intensive care unit.

^aAny comorbidity (Attention-Deficit/Hyperactivity Disorder (ADHD), asthma bronchiale, eczema, type 1 diabetes, congenital heart disease).

^bDays at ward exclude outpatients.

^cZero days refers to patients who were in ICU <24 h.

as well as obesity compared to normal weight was associated with a more than doubled risk of admission to ICU/ECMO. Diarrhoea or oedema as presenting symptoms were associated with an almost threefold increased risk for ICU admission. Hyperinflammation and airway symptoms were associated with a sevenfold increase, and cardiac affection with a 16-fold increased risk for ICU admission as compared to patients without these symptoms. CNS and mucocutaneous symptoms were not statistically associated with admission to ICU/ECMO and were omitted from the multivariate analysis. In the adjusted model, the association of overweight and obesity with admission to ICU/ECMO was no longer statistically significant whereas the associations of the other risk factors were not significantly changed (Table 4).

3.6 | Risk Factors for Cardiogenic Shock

Risk factors for cardiogenic shock were evaluated in logistic regression models. In crude analyses, being 13–19 years old as compared to 0–6 years old was associated with an almost fivefold increased risk of cardiogenic shock. Being obese as compared to normal weight was associated with a threefold increased risk of cardiogenic shock. Among the symptoms, diarrhoea was associated with an almost threefold increased risk, hyperinflammation with an almost eightfold increased risk, and airway affection with an almost sixfold increased risk of cardiogenic shock as compared to the absence of these respective symptoms. Cardiac affection was associated with a 23-fold increased risk for cardiogenic shock. Cardiac affection was considered to be a precursor to cardiogenic

TABLE 2 | Clinical characteristics and laboratory findings of 338 MIS-C patients, by ICU admission.

Clinical characteristics, <i>n</i> (%)	All patients	ICU	Non-ICU	<i>p</i>
	<i>n</i> = 338	<i>n</i> = 69 (20)	<i>n</i> = 269 (80)	
Clinical symptoms				
Mucocutaneous involvement	257 (76.0)	49 (69.6)	209 (77.7)	
<u>Changes in mucous membranes</u>	35 (10)	2 (3)	33 (12)	0.023
<u>Non-purulent conjunctivitis</u>	182 (54)	38 (55)	144 (54)	0.819
<u>Redness of the lips</u>	62 (18)	13 (19)	49 (18)	0.905
<u>Skin rash</u>	202 (60)	36 (51)	166 (62)	0.150
Peeling skin	22 (6)	5 (7)	17 (6)	0.781
Cardiac involvement	132 (39.1)	58 (84.1)	74 (27.5)	
(UCG perf)	332/335 (99)	69 (99)	264/266 (99)	0.584
<u>Arrythmia</u>	25/331 (8)	13/68 (19)	12/263 (5)	<0.001
<u>Pericarditis</u>	38/327 (12)	19/65 (29)	19/262 (7)	<0.001
<u>Myocarditis</u>	71/322 (22)	38/64 (59)	33/258 (13)	<0.001
<u>Reduced EF</u>	83/330 (25)	51/67 (76)	32/263 (12)	<0.001
Coronary involvement	48/328 (15)	11/65 (17)	37/262 (14)	0.568
Airway involvement	126 (37.3)	51 (73.9)	75 (27.9)	
<u>Sore throat</u>	82 (24)	30 (43)	52 (19)	<0.001
<u>Cough</u>	48 (14)	18 (26)	29 (11)	0.001
Shortness of breath	39 (12)	23 (34)	16 (6)	0.001
CNS involvement	18 (5.3)	5 (7.2)	13 (4.8)	
<u>Irritability</u>	57 (17)	21 (30)	36 (13)	<0.001
<u>Seizures</u>	3 (1)	1 (1)	1 (1)	0.497
<u>Encephalopathy</u>	18 (5)	4 (6)	13 (5)	0.744
Headache	128 (38)	28 (41)	100 (37)	0.603
Lethargy	102 (30)	36 (52)	66 (24)	<0.001
Other				
Vomiting	153 (45)	34 (49)	119 (44)	0.453
Abdominal pain	219 (65)	49 (71)	170 (63)	0.225
Diarrhoea	171 (51)	49 (71)	122 (45)	<0.001
Splenomegaly and/or hepatomegaly	81/263 (31)	24/59 (41)	57/204 (28)	0.062
Lymphadenopathy	80 (24)	16 (23)	64 (24)	0.916
Edema	73 (22)	27 (39)	46 (17)	<0.001
Arthralgia	26 (8)	2 (3)	24 (9)	0.094
Laboratory; median (range)				
CRP (mg/L)	(28–600) <i>n</i> = 338	(55–600) <i>n</i> = 69	(28–520) <i>n</i> = 269	<0.001
ESR (mm)	52 (2–129) <i>n</i> = 299	61 (6–115) <i>n</i> = 57	51 (2–129) <i>n</i> = 242	0.170
Albumin (g/L)	23 (13–42) <i>n</i> = 334	20 (13–38) <i>n</i> = 68	24 (14–42) <i>n</i> = 266	<0.001
NT-pro-BNP (ng/L)	4169 (45–84027) <i>n</i> = 333	13676 (713–84027) <i>n</i> = 68	3385 (45–35500) <i>n</i> = 265	<0.001
Troponin T (ng/L)	21 (2–25500) <i>n</i> = 308	81 (4–25500) <i>n</i> = 66	17 (2–2500) <i>n</i> = 242	<0.001

(Continues)

TABLE 2 | (Continued)

Clinical characteristics, <i>n</i> (%)	All patients	ICU	Non-ICU	<i>p</i>
	<i>n</i> = 338	<i>n</i> = 69 (20)	<i>n</i> = 269 (80)	
Laboratory; <i>n</i> abnormal (%)				
Hyperinflammation^a	230 (68.0)	60 (87.0)	170 (63.2)	
Hb (<92 g/L)	105/336 (31)	28/68 (41)	77/268 (29)	0.048
Leukopenia (WBC < 5 × 10 ⁹ /L)	166/334 (50)	31 (45)	135/265 (51)	0.373
Lymphocytes < 1.5 × 10 ⁹ /L	269/335 (80)	60 (87)	209/266 (79)	0.119
Platelets (< 110 × 10 ⁹ /L)	143/333 (43)	41 (59)	102/264 (39)	0.002
Bi-cytopenia ^b	145/333 (43)	38 (55)	107/264 (41)	0.030
Ferritin (> 2000 µg/L)	98/329 (30)	24 (35)	74/260 (29)	0.307
IL-6 increased ^c	75/180 (42)	27/45 (60)	48/135 (36)	0.004
sIL2R increased ^d	69/78 (89)	24/26 (92)	45/52 (86)	0.710
Liver transferases (AST, ALT) increased ^e	161/333 (48)	43 (62)	118/264 (45)	0.009

Note: Underlined symptoms are described in definition of Mucocutaneous, Cardiac, Airway and CNS involvement. / Number of patients with symptom versus (/) total number of patients registered with symptom.

^aHyperinflammation defined as a triad of serum C-reactive protein (CRP) > 200 mg/L, platelet count < 110 × 10⁹/L and raised liver transaminases.

^bBi-cytopenia defined as leukopenia (WBC < 5 × 10⁹/L) and thrombocytopenia (< 110 × 10⁹/L).

^cIL-6 increased (interleukin-6 increased over normal value).

^dsIL2R increased (soluble interleukin-2 receptor increased over normal value).

^eAST (age 6–12 months girls/boys, 0.55–1.1 µkat/L; 1–4 years girls/boys, 0.41–0.93; 5–8 years girls/boys 0.40–0.80; 9–18 years girls/boys, 0.28–0.72), ALAT (6 months–8 years, girls 0.13–0.39 µkat/L; 6 months–8 years, boys 0.12–0.29; 9–18 years girls/boys 0.17–0.51).

TABLE 3 | Immunomodulatory and supportive treatments in 338 MIS-C patients, by ICU admission.

Characteristic; <i>n</i> (%)	All patients	ICU	Non-ICU	<i>p</i>
	<i>n</i> = 338	<i>n</i> = 69 (21)	<i>n</i> = 269 (89)	
Immunomodulatory treatment, <i>n</i> (%)				
None	16 (5)	2 (3)	14 (5)	0.541
IVIG	310 (92)	65 (94)	245 (91)	0.401
Steroids	308 (91)	66 (96)	242 (90)	0.138
IL1 Inhibition (anakinra)	137 (41)	50 (73)	87 (32)	<0.001
IL6 inhibition (tocilizumab)	2 (1)	2 (3)	0 (0)	0.005
IVIG + steroids	296 (88)	64 (93)	232 (86)	0.144
IVIG + steroids + IL1 inhibition	135 (40)	49 (71)	86 (32)	<0.001
IVIG + steroids + IL1-IL 6 inhibitions	2 (1)	2 (3)	0 (0)	0.005
ICU procedures, <i>n</i> (%)				
Inotropic agents	38 (11)	38 (55)	0 (0)	<0.001
Dialysis	5 (1)	1 (1)	4 (1)	1.000
ECMO	3 (1)	3 (4)	0 (0)	NA
Supportive treatments, <i>n</i> (%)				
Albumin infusion	99 (29)	29 (42)	70 (26)	0.009
Acetylsalicylic acid, low dose	266 (79)	50 (73)	216 (80)	0.156
LMWH, prophylactic dose	158 (47)	36 (52)	122 (45)	0.311
LMWH, therapeutic dose	95 (28)	29 (42)	66 (25)	0.004

Note: Combination therapy: IVIG + steroids; IVIG + steroids + IL 1 inhibition; IVIG + steroids + IL1-IL 6 inhibitions. Abbreviations: IL, interleukin; IVIG, intravenous immunoglobulin; LMWH, low molecular weight heparin.

TABLE 4 | Crude and adjusted odds ratios for ICU admission or ECMO among 326 MIS-C patients.

Risk factor	N (%)	Crude		Adjusted model ^a	
		OR	95% CI	OR	95% CI
Sex					
Male	122 (37.4)	1.00	Ref	1.00	Ref
Female	204 (62.6)	0.79	0.46–1.38	0.91	0.43–1.96
Age group					
0–6	90 (27.6)	1.00	Ref	1.00	Ref
7–12	136 (41.7)	1.04	0.52–2.12	0.84	0.33–2.19
13–19	100 (30.7)	1.63	0.81–3.33	0.93	0.35–2.48
Weight group					
Normal	254 (77.9)	1.00	Ref	1.00	Ref
Overweight	45 (13.8)	2.45	1.19–4.90	1.05	0.39–2.73
Obese	27 (8.3)	2.45	0.99–5.71	1.64	0.51–5.18
Symptom ^b					
Diarrhoea	163 (50.0)	2.90	1.65–5.26	2.23	1.07–4.80
Edema	72 (22.1)	2.94	1.63–5.27	2.40	1.07–5.44
Hyperinflammation	223 (68.4)	7.00	3.51–14.2	3.25	1.34–7.97
Airway affection	121 (37.1)	7.07	3.93–13.2	6.75	3.23–14.8
Cardiac affection	131 (40.2)	16.4	8.10–37.1	14.0	6.28–34.7
CNS	16 (4.9)	1.82	0.56–5.20	Omitted	
Mucocutaneous	247 (75.8)	0.63	0.35–1.16	Omitted	

^aModel adjusted for sex, age group, weight group, diarrhoea, edema, hyperinflammation, airway affection and cardiac affection.

^bIn the symptom variables, the reference is absence of specific symptom.

shock instead of a confounder and was therefore omitted from the multivariate model. Mucocutaneous symptoms were associated with a reduced risk of cardiogenic shock. Oedema and CNS affection were not statistically associated with cardiogenic shock and were omitted from the multivariate model. In the adjusted model, the association of the highest age group was reduced to almost a fourfold risk ($p=0.038$), and the association of obesity to cardiogenic shock was similar ($p=0.023$), but overweight was no longer statistically significant. The associations of the other risk factors were not significantly changed in the adjusted model except for mucocutaneous symptoms, which were no longer statistically significant (Table 5).

4 | Discussion

This nationwide prospective study describes the clinical characteristics, treatment and short-term outcome of 338 Swedish children diagnosed with MIS-C between March 2020 and August 2022. Despite Sweden's relatively open public health strategy during the COVID-19 pandemic and limited ICU capacity, we observed low ICU admission rates (20%) and no mortality, without exploring if the Swedish health-care strategy possibly influenced our results. The findings suggest that consistent national guidelines, early treatment strategies and

centralised specialist collaboration may have contributed to favourable outcomes.

Several symptoms were more prevalent among children requiring intensive care, including cardiac dysfunction, respiratory symptoms, diarrhoea and oedema. These findings are consistent with previously published data from other cohorts [1, 2, 22]. Many ICU patients showed signs of capillary leak, including hypoalbuminemia and oedema, which may contribute to clinical deterioration [23]. Neurological symptoms were reported in 30% with irritability and headache being more common in 41% ICU patients, which is in line with reports of CNS involvement in severe MIS-C [24].

The inflammatory response was pronounced in patients admitted to ICU, with elevated CRP, NT-pro-BNP and troponin levels, as well as lymphopenia and cytopenias. Elevated NT-pro-BNP levels, even in patients with preserved cardiac function, may reflect systemic inflammation rather than isolated myocardial injury [25]. These hematologic and biochemical findings are consistent with those reported in other cohorts describing severe MIS-C [7, 26].

The Swedish MIS-C treatment strategy was characterised by early and widespread use of IVIG and corticosteroids. Anakinra was used in 41% of cases, predominantly in ICU patients, in contrast to stepwise approaches used in many other

TABLE 5 | Crude and adjusted odds ratios for cardiogenic shock among 335 MIS-C patients.

Risk factor	N (%)	Crude		Adjusted model ^a	
		OR	95% CI	OR	95% CI
Sex					
Male	125 (37.3)	1.00	Ref	1.00	Ref
Female	210 (62.7)	1.16	0.58–2.43	1.35	0.59–3.26
Age group					
0–6	92 (27.5)	1.00	Ref	1.00	Ref
7–12	137 (40.9)	2.70	0.94–9.74	2.64	0.82–10.4
13–19	106 (31.6)	4.80	1.72–17.1	3.85	1.17–15.6
Weight group					
Normal	261 (77.9)	1.00	Ref	1.00	Ref
Overweight	46 (13.7)	1.42	0.50–3.47	0.88	0.27–2.49
Obese	28 (8.4)	3.15	1.15–7.86	3.55	1.14–10.5
Symptom ^b					
Diarrhoea	168 (50.1)	2.72	1.33–5.90	2.48	1.09–5.92
Edema	73 (21.8)	1.79	0.83–3.68	Omitted	
Hyperinflammation	228 (68.1)	7.58	3.53–16.2	5.10	2.16–12.0
Airway affection	123 (36.7)	5.95	2.86–13.4	4.87	2.12–12.0
Cardiac affection	131 (39.1)	23.3	8.14–98.5	Omitted	
CNS	18 (5.4)	1.61	0.36–5.19	Omitted	
Mucocutaneous	254 (75.8)	0.44	0.22–0.90	0.53	0.23–1.26

^aModel adjusted for sex, age group, weight group, diarrhoea, hyperinflammation, airway affection and mucocutaneous symptoms. Cardiac affection variable was excluded due to collinearity with cardiogenic shock.

^bIn the symptom variables, the reference is absence of specific symptom.

countries. The high use of biologics likely reflects early national consensus and frequent multidisciplinary discussions. Although our study was not designed to evaluate treatment efficacy, our outcomes compare favourably to international reports and align with data from the RECOVERY trial supporting early corticosteroids and biologics in selected cases [27].

Cardiac involvement was the strongest independent risk factor for ICU admission (OR 14.0), followed by airway symptoms (OR 6.8), hyperinflammation, diarrhoea and oedema. These results confirm observations from other cohorts [4, 5]. Risk factors for cardiogenic shock included older age, obesity, airway involvement and hyperinflammation. The association between obesity and shock has been described previously and may be related to pre-existing subclinical inflammation [26, 28]. Mucocutaneous involvement appeared to be associated with a reduced risk of shock in univariable analyses but not in the adjusted model.

Despite a relatively low ICU bed density (5.8 per 100000) compared to countries such as the United States (29.4 per 100000) [29], outcomes were excellent, with no deaths and all patients discharged home. The centralised case management model,

with frequent national case discussions and uniform treatment protocols, likely contributed to this.

The main strength of this study is its population-based design and use of a national quality register, which enabled inclusion of nearly all diagnosed MIS-C cases during the study period. Centralised review and consensus-based management likely improved data consistency and care quality. This study provides one of the few national descriptions of MIS-C in a setting with a non-restrictive pandemic response.

Clinical features and laboratory parameters were not uniformly available for all patients, which may have introduced selection bias. Additionally, although data collection was prospective, clinical data were entered by different clinicians across multiple centres, which could introduce variability in reporting. At the very beginning of the inclusion period, a few cases may have been missed, potentially introducing bias due to the novelty of the condition. Also, we did not specifically ask for the individual reason for admission to ICU, and due to the multiple centres involved, some clinical variable definitions, such as cardiogenic shock, had to be pragmatically determined. Furthermore, the capacity to manage severely ill patients outside the ICU may

have varied between hospitals, which could have influenced ICU admission thresholds and introduced site-dependent bias.

5 | Conclusion

This Swedish population-based study of MIS-C highlights low ICU admission and excellent outcomes in a healthcare setting with limited ICU capacity but strong coordination by the Swedish paediatric MIS-C consortium bi-weekly meetings and early treatment strategies with consensus-based management. We identified clear clinical and laboratory predictors of severe disease. These findings emphasise the importance of early recognition, aggressive immunomodulatory therapy and national coordination. The opportunity to identify risk factors for ICU admission and cardiogenic shock might become a valuable tool for early detection and treatment of high-risk patients.

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Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section. **Appendix S1:** apa70329-sup-0001-AppendixS1.docx.