

Supplementary Table 1 – Study definitions

Clinical manifestation	Definition
Intensive care unit admission	Admission to a pediatric or neonatal intensive care unit
Critical disease	Admission to an intensive care unit with use of vasopressors or non-invasive or mechanical ventilation
Viral co-infection ¹	Laboratory detection of any virus concurrent with SARS-CoV-2 infection
Bacterial co-infection ¹	Laboratory detection of one or more bacteria concurrent with SARS-CoV-2 infection and treated with antibiotics by the attending physician
Mucocutaneous involvement	Rash, conjunctivitis, strawberry tongue, red cracked lips or redness or swelling of extremities.
Gastrointestinal involvement	Vomiting, diarrhea or abdominal pain
Cardiac involvement	Echocardiographic evidence of pericarditis, valvulitis, coronary vessel abnormalities, or biochemical evidence with troponin >0.5 pg/ml or NT-proB-type Natriuretic Peptide (BNP) >100 pg/ml (11).
Acute kidney injury	Serum creatinine above 140 umol/L for children up to 7 days of age, 55 umol/L for children 7 to 364 days of age, 100 umol/L for children 1 to 12 years of age and 140 umol/L for those 13 to 17 years of age (excluding children with chronic renal disease) (14).
Hepatitis	Alanine aminotransferase (ALT) >40 IU/L and/or aspartate aminotransferase (AST) > 50 IU/L (15).
Neurological complications	Worsening or new onset of seizure, encephalopathy, dystonia, chorea, athetosis, hemiparesis and/or abnormal cerebrospinal fluid cell count for age (>15 X 10 ⁹ /L if less than 30 days of age and >5 X 10 ⁹ /L if older)
Clinical hematological complications	Disseminated intravascular coagulation, thrombosis or bleeding.

¹ Investigations were at the discretion of the treating clinician.

Supplementary Table 2 – Characteristics of 232 cases of MIS-C, according to country of admission

	Canada (N=190)	Costa Rica (N=30)	Iran (N=12)
Median age (IQR)	6.23 (2.80-9.82)	6.08 (3.93-8.34)	3.43 (2.03-4.81)
Sex - Male	108 (57%)	17 (57%)	5 (42%)
Median days of fever prior to admission (IQR)	5 (3-6)	4 (3-6)	3.5 (3-5)
Median total duration of fever in days (IQR)	6 (5-8)	5 (4-8)	8.5 (7-10)
Mucocutaneous signs	159 (84%)	29 (97%)	8 (67%)
Gastrointestinal involvement	165 (87%)	30 (100%)	12 (100%)
Median length of stay in days (IQR)	5 (4-8)	7 (5-9)	9.5 (8-11)

Appendix 2, as submitted by the authors. Appendix to: Merckx J, Cooke S, El Tal T, et al. Predictors of severe illness in children with multisystem inflammatory syndrome after SARS-CoV-2 infection: a multicentre cohort study. *CMAJ* 2022. doi: 10.1503/cmaj.210873.

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Highest level of care required			
Ward admission:	128 (67%)	26 (87%)	5 (42%)
No supplemental oxygen	118 (62%)	21 (70%)	4 (33%)
Supplemental oxygen	10 (5%)	5 (17%)	1 (8%)
ICU admission:	62 (33%)	4 (13%)	7 (58%)
Observation +/- supplemental oxygen	17 (9%)	1 (3%)	4 (33%)
Required vasopressors	33 (17%)	0 (0%)	2 (17%)
Required non-invasive ventilation	4 (2%)	0 (0%)	0 (0%)
Required mechanical ventilation	4 (2%)	3 (10%)	1 (8%)
Admitted for indications other than MIS-C	4 (2%)	0 (0%)	0 (0%)
Cardiac involvement	105 (55%)	26 (87%)	5 (42%)
Treatment ¹			
IVIG	153 (81%)	29 (97%)	12 (100%)
Corticosteroids	104 (55%) ²	14 (47%) ³	8 (75%) ⁴
Anakinra	10 (5%)	0 (0%)	0 (0%)
None of the above	23 (12%)	1 (3%)	0 (0%)

Legend: IQR – interquartile range; IVIG – intravenous immunoglobulin

¹ Many patients received a combination of these treatments.

² 66 children were given 1 to 3 days of pulse methylprednisolone (>10 mg/kg/day)

³ No children were given pulse methylprednisolone (>10 mg/kg/day)

⁴ One child was given pulse methylprednisolone (>10 mg/kg/day)

Supplementary Table 3: Risk factors for hospital length of stay in 232 children with MIS-C - adjusted model coefficients from multivariable linear regression

	Difference in length of stay* - days (95% CI)	
Age		
Age 6-12 years	2.0 (-0.1 to 4.1)	
Age 13-18 years	3.0 (-0.3 to 6.4)	
Sex		
Female	0.7 (-1.2 to 2.7)	
Country		
Costa-Rica	0.1 (-2.8 to 3.0)	
Iran	7.7 (3.2 to 12.2)	
Initial WBC count†		
Initial WBC < 5000 X 10 ⁹ /L	0.6 (-2.7 to 3.9)	
WBC > 15,000 X 10 ⁹ /L	0.3 (-2.2 to 2.8)	
Initial platelets < 150,000 X 10 ⁹ /L†	-0.04 (-2.4 to 2.3)	
Initial ferritin > 500 mcg/L†	2.8 (0.5 to 5.1)	
Gastrointestinal involvement	0.1 (-3.1 to 3.4)	
Mucocutaneous involvement	-0.9 (-3.7 to 1.9)	
Admission Nov 1, 2020-Mar 7, 2021	1.2 (-0.8 to 3.2)	

Models are adjusted for sex, age, country, presence of comorbidity, coinfection, treatment and admission time.

*Values represent difference in length of stay in days by covariate, compared to the reference group.

†Number of observations differing from complete dataset of 232, WBC: 4 missing; platelets: 2 missing; ferritin: 7 missing

Supplementary Table 4 – Risk factors for intensive care unit admission stratified by confirmed (N=106) and probable (N=126) cases with MIS-C - adjusted model estimates

	Confirmed cases (N=106)*			Probable cases (N=126)*		
	Absolute risk (%) 95% CI	Risk difference (%) (95% CI)	Relative risk 95%CI	Absolute risk (%) 95% CI	Risk difference (%) (95% CI)	Relative risk 95%CI
ICU admission						
Age 0-5 years	33.8 (19.6-48.0)	-	-	7.5 (2.6-12.5)	-	-
Age 6-12 years	55.2 (42.3-68.2)	21.4 (1.4-41.5)	1.63 (0.82-2.45)	34.6 (22.0-47.3)	27.1 (13.5-40.7)	4.60 (1.14-8.06)
Age 13-18 years	54.5 (29.5-79.5)	20.7 (-9.1-50.5)	1.61 (0.57-2.66)	39.7 (13.1-66.2)	32.1 (5.0-59.2)	5.16 (0.29-10.24)
Male	43.7 (32.5-55.0)	-	-	16.7 (8.3-25.2)	-	-
Female	49.6 (36.4-62.8)	5.9 (-11.7-23.4)	1.13 (0.71-1.56)	21.6 (12.6-30.5)	4.8 (-8.0-17.6)	1.29 (0.41-2.16)
Canada	58.2 (46.2-70.3)	-	-	17.1 (11.3-22.9)	-	-
Costa-Rica	14.4 (0.9-27.8)	-43.9; -62.8, -25.0	0.25 (0.01-0.49)	NA	NA	NA
Iran	57.7 (21.2-94.2)	-0.6 (-40.4-39.3)	0.99 (0.31-1.67)	75.3 (38.2-112.4)	58.2 (20.6-95.8)	4.40 (1.75-7.05)
Initial WBC<5000 X 10 ⁹ /L	34.5 (7.3-61.7)	-10.5 (-40.0-19.0)	0.77 (0.13-1.40)	22.3 (5.8-38.9)	3.0 (-15.2-21.3)	1.15 (0.18-2.13)
WBC 500-15,000 X 10 ⁹ /L	45.0 (35.0-55.0)	-	-	19.3 (11.2-27.4)	-	-
WBC >15,000 X 10 ⁹ /L	55.4 (31.4-79.3)	10.4 (-15.6-36.3)	1.23 (0.63-1.83)	16.8 (3.9-29.8)	-2.5 (-18.5-13.5)	0.87 (0.07-1.67)

Initial platelets <150,000 X 10 ⁹ /L	46.1 (30.1-62.1)	-1.4 (-21.2-18.3)	0.97 (0.56-1.38)	22.7 (10.0-35.5)	4.8 (-10.0-19.6)	1.27 (0.39-2.15)
Initial platelets ≥150,000 X 10 ⁹ /L	47.6 (37.1-58.1)	-	-	17.9 (11.1-24.8)	-	-
Initial ferritin >500 mcg/L	61.1 (47.5-74.6)	21.2 (4.1-38.3)	1.53 (1.01-2.05)	31.8 (16.2-47.5)	16.8 (-0.3-34.0)	2.12 (0.72-3.52)
Gastrointestinal involvement	45.1 (36.3-53.9)	-16.3 (-51.2-18.6)	0.73 (0.31-1.16)	18.2 (12.2-24.1)	-10.3 (-31.2-10.7)	0.64 (0.14-1.14)
Mucocutaneous involvement	48.1 (38.8-57.4)	11.1 (-13.2-35.5)	1.30 (0.48-2.13)	18.8 (12.6-25.0)	-3.0 (-22.5-16.5)	0.86 (0.07-1.64)
Admission prior to Nov 1, 2020	45.6 (27.4-63.9)	-	-	14.5 (8.0-21.0)	-	-
Admission Nov 1, 2020-Mar 7, 2021	46.4 (27.4-63.9)	0.8 (-20.4-22.0)	1.02 (0.55-1.49)	32.4 (18.6-46.3)	17.9 (22.7-33.6)	2.24 (0.81-3.66)

Models are adjusted for sex, age, country, presence of comorbidity, coinfection, confirmed case status, treatment and admission time.

Average marginal effects are presented with adjusted RDs from multivariable logistic regressions.

NA: not applicable, empty cell for Costa-Rico probable cases

*: Number of observations differing from complete dataset of 106 for confirmed cases:

WBC: 4 missing, platelets: 2 missing, ferritin: 3 missing; of 126 for probable cases: 1 missing for all models, ferritin: 5 missing.

Supplementary Table 5 – Risk of severe MIS-C (defined as intensive care unit admission) in 190 children in Canada by quarter of the year

	Absolute risk (%) 95% CI	Risk difference (%) (95% CI)	Relative risk 95%CI
ICU admission			
Admission March-May 2020 (Q1)	17.8 (3.8-31.8)	-	-
Admission June-August (Q2)	32.4 (16.4-48.3)	14.6 (-5.9-35.1)	1.82 (0.18-3.47)
Admission September-November (Q3)	24.2 (13.1-35.2)	6.4 (-11.2-24.1)	1.36 (0.13-2.59)
Admission Dec 2020-March 2021 (Q4)	43.1 (31.8-54.3)	25.3 (6.5-44.0)	2.42 (0.36-4.50)

Model is adjusted for sex, age, presence of comorbidity, coinfection, confirmed case status and treatment.

Average marginal effects are presented with adjusted RDs from multivariable logistic regression.

Supplementary Table 6 - Risk of critical disease (defined as intensive care unit admission with need for vasopressors or ventilation) in 232 children with MIS-C – adjusted model estimates

	Absolute risk (%) 95% CI	Risk difference (%) (95% CI)	Relative risk 95%CI
Age 0-5 years	8.1 (3.2-12.9)	-	-
Age 6-12 years	33.7 (24.6-42.8)	25.7 (15.0-36.3)	4.19 (1.33-7.05)
Age 13-18 years	27.8 (11.4-44.2)	19.7 (2.3-37.1)	3.45 (0.44-6.46)
Male	18.9 (12.7-25.0)	-	-
Female	22.0 (14.8-29.1)	3.1 (-6.5-12.7)	1.16 (0.62-1.71)
Canada	22.6 (17.1-28.2)	-	-
Costa-Rica	7.1 (-0.1-14.6)	-15.6 (-25.2-59.8)	0.31 (-0.04-0.66) #
Iran	30.2 (55.2-55.0)	7.6 (-18.0-33.2)	1.34 (0.18-2.49)
Initial WBC<5000 X 10 ⁹ /L	21.7 (8.0-35.4)	3.5 (-11.4-18.4)	1.19 (0.35-2.03)
WBC 500-15,000 X 10 ⁹ /L	18.2 (12.8-23.6)	-	-
WBC >15,000 X 10 ⁹ /L	27.0 (14.4-39.6)	8.8 (-5.2-22.7)	1.48 (0.64-2.32)
Initial platelets <150,000 X 10 ⁹ /L	24.1 (14.5-33.6)	5.2 (-6.2-16.5)	1.27 (0.63-1.92)
Initial platelets ≥150,000 X 10 ⁹ /L	18.9 (13.3-24.4)	-	-
Initial ferritin >500 mcg/L	39.6 (28.3-50.9)	25.7 (13.3-38.2)	2.86 (1.53-4.19)
Gastrointestinal involvement	19.8 (15.0-24.5)	-6.4 (-25.3-12.4)	0.75 (0.20-1.31)
Mucocutaneous involvement	22.7 (17.6-27.9)	14.0 (4.6-23.3)	2.59 (0.24-4.95)
Admission prior to Nov 1, 2020	13.1 (6.4-19.7)	-	-
Admission Nov 1, 2020-Mar 7, 2021	26.5 (18.5-34.5)	13.4 (2.1-24.7)	2.03 (0.73-3.32)

Models are adjusted for sex, age, country, presence of comorbidity, coinfection, confirmed case status, treatment and admission time.

Average marginal effects are presented with adjusted RDs from multivariable logistic regressions.

*: Number of observations differing from complete dataset of 232, WBC: 4 missing; platelets: 2 missing; ferritin: 7 missing

#: The margins package calculates the confidence interval using the delta method assuming a sampling distribution that is normal and therefore rarely provides a theoretical implausible lower bound smaller than zero.

Supplementary Table 7 – Risk factors for cardiac involvement in 232 children with MIS-C - adjusted model estimates

	Absolute risk (%) 95% CI	Risk difference (%) (95% CI)	Relative risk 95%CI
Cardiac involvement¹			
Age 0-5 years	56.8 (48.9-64.7)	-	-
Age 6-12 years	62.4 (52.9-71.9)	5.6 (-7.0-18.2)	1.10 (0.87-1.33)
Age 13-18 years	54.9 (37.1-72.8)	-1.9 (-21.7-17.9)	0.97 (0.62-1.31)
Male	61.5 (54.0-68.9)	-	-
Female	55.1 (46.6-63.6)	-6.4 (-17.8-5.0)	0.90 (0.72-1.07)
Canada	57.4 (51.0-63.9)	-	-
Costa-Rica	78.1 (60.3-95.9)	20.7 (12.0-40.1)	1.36 (1.00-1.72)
Iran	38.2 (13.3-63.1)	-19.2 (-45.1-6.7)	0.67 (0.22-1.11)
Initial WBC<5000 X 10 ⁹ /L	55.8 (37.0-74.5)	-3.8 (-23.8-16.3)	0.94 (0.60-1.27)
WBC 500-15,000 X 10 ⁹ /L	60.0 (52.6-66.5)	-	-
WBC >15,000 X 10 ⁹ /L	55.7 (42.7-68.7)	-3.8 (-18.7-11.1)	0.94 (0.69-1.18)
Initial platelets <150,000 X 10 ⁹ /L	64.6 (53.1-76.0)	7.9 (-5.7-21.5)	1.14 (0.89-1.39)
Initial platelets ≥150,000 X 10 ⁹ /L	56.7 (50.0-63.3)	-	-
Initial ferritin >500 mcg/L	64.6 (51.8-77.3)	6.3 (-8.2-20.9)	1.11 (0.85-1.36)
Gastrointestinal involvement	57.2 (51.2-63.2)	-11.9 (-28.8-5.1)	0.83 (0.62-1.03)
Mucocutaneous involvement	58.8 (52.6-64.9)	0.8 (-14.6-16.3)	1.01 (0.74-1.28)
Admission prior to Nov 1, 2020	44.1 (34.9-53.3)	-	-
Admission Nov 1, 2020-Mar 7, 2021	75.0 (66.4-83.6)	30.9 (17.3-44.4)	1.70 (1.27-2.13)

¹ Defined as features of myocardial dysfunction, pericarditis, valvulitis, or coronary abnormalities (including echocardiographic findings or elevated Troponin/NT-proBNP) Models are adjusted for sex, age, country, presence of comorbidity, coinfection, confirmed case status and admission time.

Average marginal effects are presented with adjusted RDs from multivariable logistic regressions.

*: Number of observations differing from complete dataset of 232, WBC: 4 missing; platelets: 2 missing; ferritin: 7 missing

Supplementary Table 8 – Risk factors for cardiac involvement stratified by confirmed (N=106) and probable (N=126) cases with MIS-C - adjusted model estimates

	Confirmed cases (N=106)*			Probable cases (N=126)*		
	Absolute risk (%) 95% CI	Risk difference (%) (95% CI)	Relative risk 95%CI	Absolute risk (%) 95% CI	Risk difference (%) (95% CI)	Relative risk 95%CI
Cardiac involvement¹						
Age 0-5 years	66.6 (53.4-79.7)	-	-	45.4 (34.8-56.0)	-	-
Age 6-12 years	85.5 (75.5-95.5)	18.9 (1.8-36.0)	1.28 (0.98-1.59)	42.0 (27.8-56.2)	-3.4 (-21.2-14.4)	0.93 (0.54-1.31)
Age 13-18 years	78.9 (58.3-99.6)	12.4 (-12.9-37.6)	1.19 (0.78-1.59)	32.5 (5.8-59.2)	-12.9 (-41.8-15.9)	0.72 (0.10-1.33)
Male	80.3 (71.2-89.4)	-	-	46.8 (35.8-57.8)	-	-
Female	71.1 (58.9-83.2)	-9.2 (-24.6-6.2)	0.89 (0.70-1.07)	38.9 (27.2-50.6)	-7.9 (-24.3-8.4)	0.83 (0.51-1.15)
Canada	73.8 (63.5-84.1)	-	-	43.6 (35.6-51.7)	-	-
Costa-Rica	86.8 (75.2-98.5)	13.0 (-3.0-29.0)	1.18 (0.94-1.41)	NA	NA	NA
Iran	60.6 (24.7-96.5)	-13.2 (-51.6-25.2)	0.82 (0.31-1.33)	30.6 (-8.0-69.3)	-13.0 (-52.6-26.6)	0.70 (0.00-1.60)
Initial WBC<5000 X 10 ⁹ /L	89.5 (74.8-104.3)	14.5 (-2.9-31.9)	1.19 (0.95-1.44)	31.1 (5.0-57.3)	-15.5 (-43.8-12.8)	0.66 (0.09-1.25)
WBC 500-15,000 X 10 ⁹ /L	75.0 (66.4-83.7)	-	-	46.7 (35.7-57.6)	-	-
WBC >15,000 X 10 ⁹ /L	72.8 (53.5-92.1)	-2.2 (-23.6-19.2)	0.97 (0.69-1.25)	39.6 (21.7-57.5)	-7.1 (-28.4-14.2)	0.85 (0.41-1.29)

Initial platelets <150,000 X 10 ⁹ /L	77.4 (63.3-91.6)	6.9 (-16.6-17.9)	1.01 (0.78-1.23)	53.4 (35.3-71.6)	13.2 (-7.7-34.1)	1.33 (0.77-1.89)
Initial platelets ≥150,000 X 10 ⁹ /L	76.7 (67.8-85.6)	-	-	40.2 (31.2-49.3)	-	-
Initial ferritin >500 mcg/L	81.8 (69.3-94.4)	4.6 (-11.0-20.1)	1.06 (0.85-1.26)	50.6 (27.9 -73.4)	8.9 (-15.7-33.6)	1.21 (0.61-1.82)
Gastrointestinal involvement	76.2 (68.6-83.8)	-3.4 (-34.6-27.7)	0.96 (0.58-1.33)	41.0 (32.3-49.7)	-14.1 (-37.3-9.1)	0.74 (0.41-1.07)
Mucocutaneous involvement	76.6 (68.3-84.9)	1.0 (-21.2-23.3)	1.01 (0.72-1.31)	43.8 (35.1-52.5)	3.7 (-18.4-25.7)	1.09 (0.50-1.68)
Admission prior to Nov 1, 2020	67.9 (50.4-85.5)	-	-	31.8 (22.5-41.2)	-	-
Admission Nov 1, 2020-Mar 7, 2021	79.0 (70.7-87.3)	11.1 (-8.6-30.8)	1.16 (0.83-1.49)	74.7 (60.1-89.3)	42.8 (25.3-60.3)	2.34 (1.51-3.18)

¹ Defined as features of myocardial dysfunction, pericarditis, valvulitis, or coronary abnormalities (including echocardiographic findings or elevated Troponin/NT-proBNP) Models are adjusted for sex, age, country, presence of comorbidity, coinfection, confirmed case status and admission time.

Average marginal effects are presented with adjusted RDs from multivariable logistic regressions.

Methodological note: Differences between the groups (confirmed versus probable) are not estimated and their difference cannot be purely inferred by comparison of the stratum specific estimates to the null (cf Gelman A, Stern H. The difference between “significant” and “not significant” is not itself statistically significant. *Am Stat* 2006; 60:328–331.) It also needs to be recognized that uncertainty is high (cf. wide confidence intervals), due to small sample sizes of the stratified groups.

*: Number of observations differing from complete dataset of 106 for confirmed cases: WBC: 4 missing, platelets: 2 missing, ferritin: 3 missing; of 126 for probable cases: 1 missing for all models, ferritin: 5 missing.