Multisystem inflammatory syndrome in children (MIS-C): A cohort study of 28 patients and comparison with Kawasaki disease and macrophage activation syndrome

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Supplementary materials

Supplemental Table 1. CDC and WHO Case Definitions for MIS-C

A. Centers for Disease Control and Preventions (CDC) Case Definition for MIS-C

An individual aged <21 years presenting with fever[i], laboratory evidence of inflammation[ii], and evidence of clinically severe illness requiring hospitalization, with multisystem (≥2) organ involvement (cardiac, renal, respiratory, hematologic, gastrointestinal, dermatologic or neurological);

AND

No alternative plausible diagnoses;

AND

Positive for current or recent SARS-CoV-2 infection by RT-PCR, serology, or antigen test; or COVID-19 exposure within the 4 weeks prior to the onset of symptoms

[I] Fever >38.0°C for ≥24 hours, or report of subjective fever lasting ≥24 hours

[ii] Including, but not limited to, one or more of the following: an elevated C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), fibrinogen, procalcitonin, d-dimer, ferritin, lactic acid dehydrogenase (LDH), or interleukin 6 (IL-6), elevated neutrophils, reduced lymphocytes and low albumin

B. World Health Organization (WHO) Preliminary Case Definition for MIS-C

Children and adolescents 0–19 years of age with fever > 3 days

AND two of the following:

1. Rash or bilateral non-purulent conjunctivitis or muco-cutaneous inflammation signs (oral, hands or feet).

2. Hypotension or shock.

3. Features of myocardial dysfunction, pericarditis, valvulitis, or coronary abnormalities (including ECHO findings or elevated Troponin/NT-proBNP),

4. Evidence of coagulopathy (by PT, PTT, elevated d-Dimers).

5. Acute gastrointestinal problems (diarrhea, vomiting, or abdominal pain).

AND

Elevated markers of inflammation such as ESR, C-reactive protein, or procalcitonin.

AND

No other obvious microbial cause of inflammation, including bacterial sepsis, staphylococcal or streptococcal shock syndromes.

AND

Evidence of COVID-19 (RT-PCR, antigen test or serology positive), or likely contact with patients with COVID-19.

Supplemental Table 2. Comparison of ICU and non-ICU patients with MIS-C*

	All (n = 28)*	ICU (n = 17)	Non-ICU (n = 9)	p value
Demographics				
Age, median [IQR]	9.0 yr [0.1 - 17]	9.0 yr [3 - 14]	11.0 yr [5.5 – 14.5]	0.74
Pre-existing condition	14/28 (50%)	8/17 (47%)	6/11 (55%)	0.99
Duration of symptoms (days)	5 d [4 – 6]	4 d [2 - 7]	5 d [4 - 6]	0.78
SARS-CoV2 diagnostics				
SARS-CoV2 PCR +	17/28 (61%)	13/17 (76%)	4/11(36%)	0.052
SARS-CoV2 antibody +	18/19 (95%)	9/9 (100%)	9/10 (90%)	0.99
Clinical manifestations (%)				
Skin rash	10/28 (36%)	6/17 (35%)	4/11 (36%)	0.99
Conjunctivitis	16/28 (57%)	10/17 (59%)	6/11 (55%)	0.99
Gastrointestinal symptoms	15/28 (54%)	10/17 (59%)	5/11 (45%)	0.70
Supplemental O2 requirement	12/28 (43%)	9/17 (53%)	3/11 (27%)	0.25
Hypotension / shock	15/28 (54%)	13/17 (76%)	2/11 (18%)	**0.005**
Coronary abnormalities	6/28 (21%)	3/17 (18%)	3/11 (27%)	0.65
Ejection fraction < 55%	11 (39%)	7/17 (41%)	4/11 (36%)	0.99
Laboratory studies, median [IQR]				
CRP (mg/dL)	13.3 [5.3 – 21.6]	17.4 [5.5 - 22.1]	9.5 [5.6 - 16.4]	0.38
Procalcitonin (ng/mL)	1.1 [0.4 – 7.9]	5.4 [0.9 - 9.6]	0.4 [0.2 - 1.0]	**0.009**
ESR (mm/hr)	43 [13 – 62]	31 [11 - 81]	55 [27 - 59]	0.74
Ferritin (ng/mL)	537 [238 – 1473]	958 [265 - 1500]	240 [206 - 947]	0.20
WBC (x 10^3/mL)	8.1 [5.1 – 13.0]	9.0 [6.4 - 18]	6.4 [4.8 - 10.2]	0.20
ALC (x 10^3/mL)	1.3 [07 – 1.7]	1.3 [0.6 - 2.0]	1.2 [0.8 - 1.6]	0.85
Platelets (x 10^3/mL)	155 [117 – 230]	157 [107 - 250]	132 [123 - 211]	0.68
D-dimer (mg/mL)	2.6 [1.2 – 4.3]	3.1 [1.5 - 4.9]	1.5 [0.9 – 3.2]	0.17
Fibrinogen (mg/dL)	528 [365 – 579]	528 [355 - 565]	529 [449 - 671]	0.34
BNP (pg/mL)	145 [19 – 681]	453 [125 - 904]	15 [10 - 65]	**0.008**
Troponin (ng/mL)	0.01 [0 – 0.1]	0.05 [0 - 0.2]	0 [0 – 0.01]	0.062
AST (U/L)	46 [30 – 65]	51 [43 - 62]	41 [26 - 67]	0.44
LDH (U/L)	320 [248 – 393]	366 [311 - 481]	243 [220 - 317]	0.11
Creatinine (mg/dL)	0.4 [0.3 – 0.7]	0.5 [0.3 - 0.6]	0.4 [0.3 - 0.7]	0.99
BUN (mg/dL)	10 [8 – 15]	12 [9 - 23]	10 [6 -12]	0.13

ALC, absolute lymphocyte count; AST, Aspartate Aminotransferase; BNP, B-type natriuretic peptide; CRP, C reactive protein; ESR, erythrocyte sedimentation rate; IQR, interquartile range; LDH, lactic acid dehydrogenase; WBC, white blood cell;

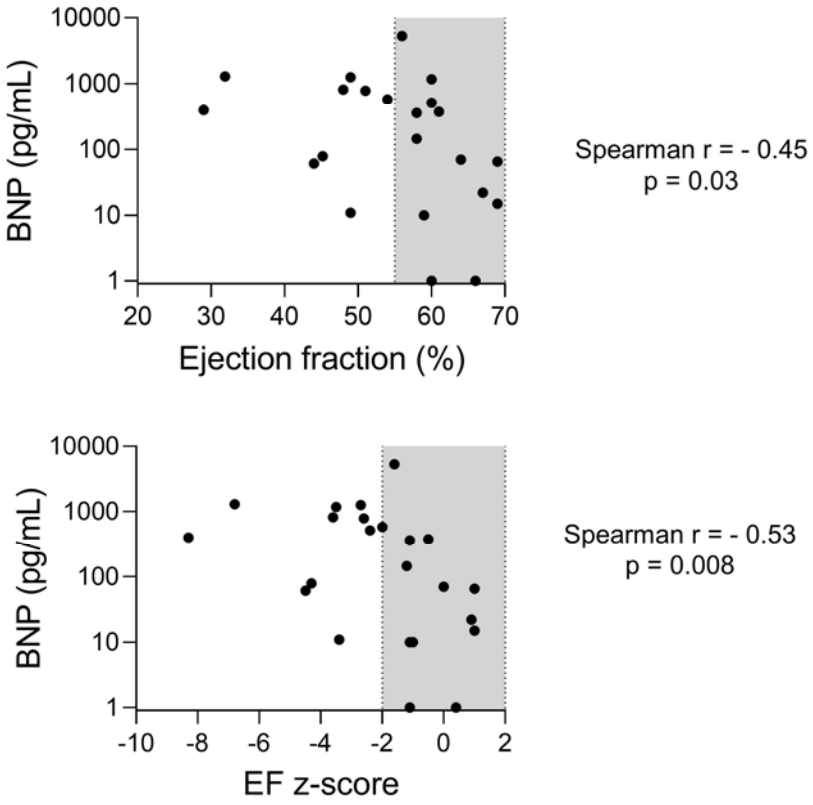
Supplemental Table 3. Coronary artery abnormalities in patients with MIS-C

Case ID	Age	COVID testing	Care level	KD criteria	Coronary findings	EF
C1*	11	PCR - serology +	Non-ICU	rash, conjunctivitis, mucositis	RCA z = 2.1	61%
C2	1	PCR + serology +	ICU	none	LMCA z = 3.0	69%
C3	9	PCR - serology +	ICU	Conjunctivitis, extremity erythema	LAD z = 2.6	51%
C4	7	PCR + serology +	ICU	rash, conjunctivitis	RCA z = 2.2	54%
C5	17	PCR + serology +	Non-ICU	conjunctivitis, mucositis	RCA z = 3.6	45%
C6	7	PCR + serology +	Non-ICU	mucositis	RCA z = 3.1	69%
C7**	4	PCR - serology +	Non-ICU	none	Prior aneurysm unchanged (LAD z = 2.7)	64%

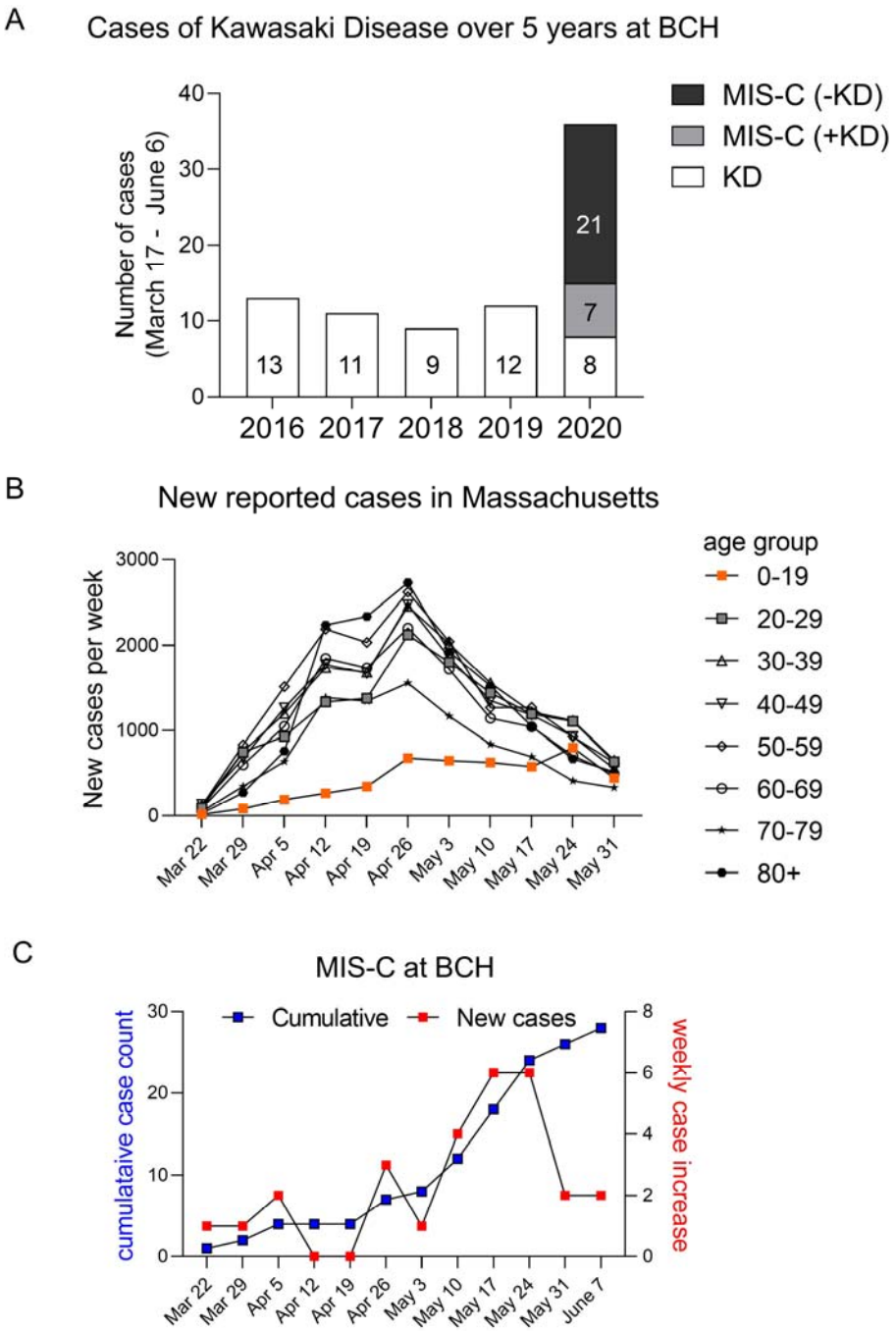
* Diagnosed with KD at 4 years of age, without a history of coronary aneurysm.

** Diagnosed with KD at 1 year of age with known coronary aneurysm of the LAD.

EF, ejection fraction; KD, Kawasaki disease; LAD, left anterior descending coronary artery; LMCA, left main coronary artery; RCA, right coronary artery.



Supplemental Figure 1. Correlations between serum BNP levels and ventricular function in MIS-C patients (n = 23). Ventricular function is quantified by ejection fraction % (left panel) or ejection fraction z score (right panel). Shaded region indicates the normal range.



Supplemental Figure 2. A) Number of KD cases diagnosed during the period of March 17 – June 6 from 2016 to 2020. MIS-C cases are divided based on whether they meet criteria for KD. MIS-C +KD, cases that met complete or incomplete KD criteria. MIS-C -KD, cases that did not meet KD criteria. B) Trajectory curve of new confirmed cases per week between March and May 2020 in the state of Massachusetts. Data are sorted by age group based on information provided by the Massachusetts Department of Public Health. C) Weekly tally of new cases and cumulative count of confirmed MIS-C patients at Boston Children's Hospital based on the CDC case definition.

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	✓
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	✓
Objectives	3	State specific objectives, including any prespecified hypotheses	✓
Methods			
Study design	4	Present key elements of study design early in the paper	✓
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	✓
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	✓
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	N/A
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	✓
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	✓
Bias	9	Describe any efforts to address potential sources of bias	✓
Study size	10	Explain how the study size was arrived at	✓
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	✓
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	✓
		(*b*) Describe any methods used to examine subgroups and interactions	N/A
		(*c*) Explain how missing data were addressed	N/A
		(*d*) If applicable, explain how loss to follow-up was addressed	N/A
		(*e*) Describe any sensitivity analyses	N/A
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	✓
		(b) Give reasons for non-participation at each stage	N/A
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	✓
		(b) Indicate number of participants with missing data for each variable of interest	✓
		(c) Summarise follow-up time (eg, average and total amount)	N/A
Outcome data	15*	Report numbers of outcome events or summary measures over time	✓
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	N/A
		(*b*) Report category boundaries when continuous variables were categorized	✓
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A

Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	N/A
Discussion			
Key results	18	Summarise key results with reference to study objectives	✓
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	✓
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	✓
Generalisability	21	Discuss the generalisability (external validity) of the study results	✓
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	✓

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.