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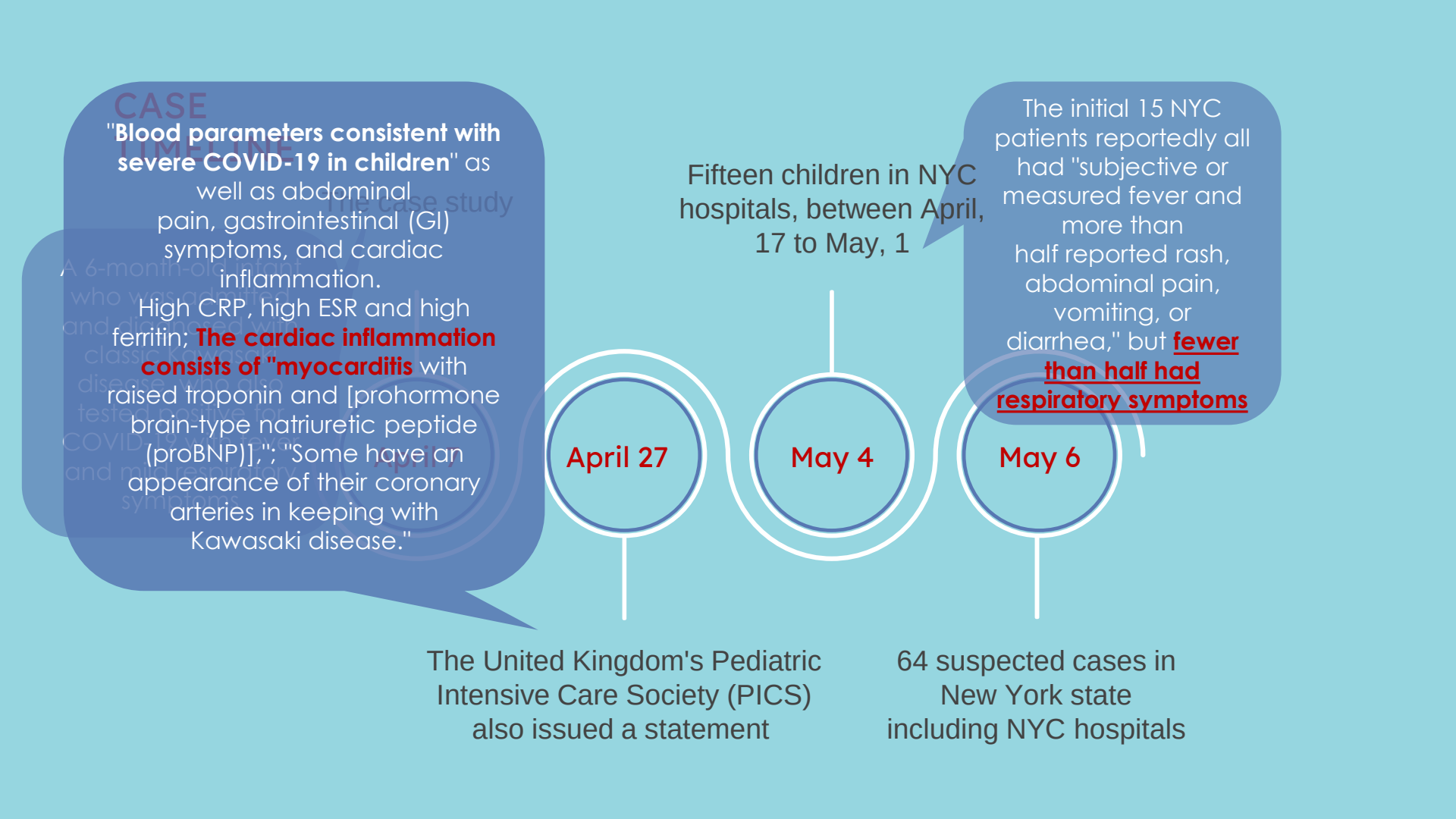
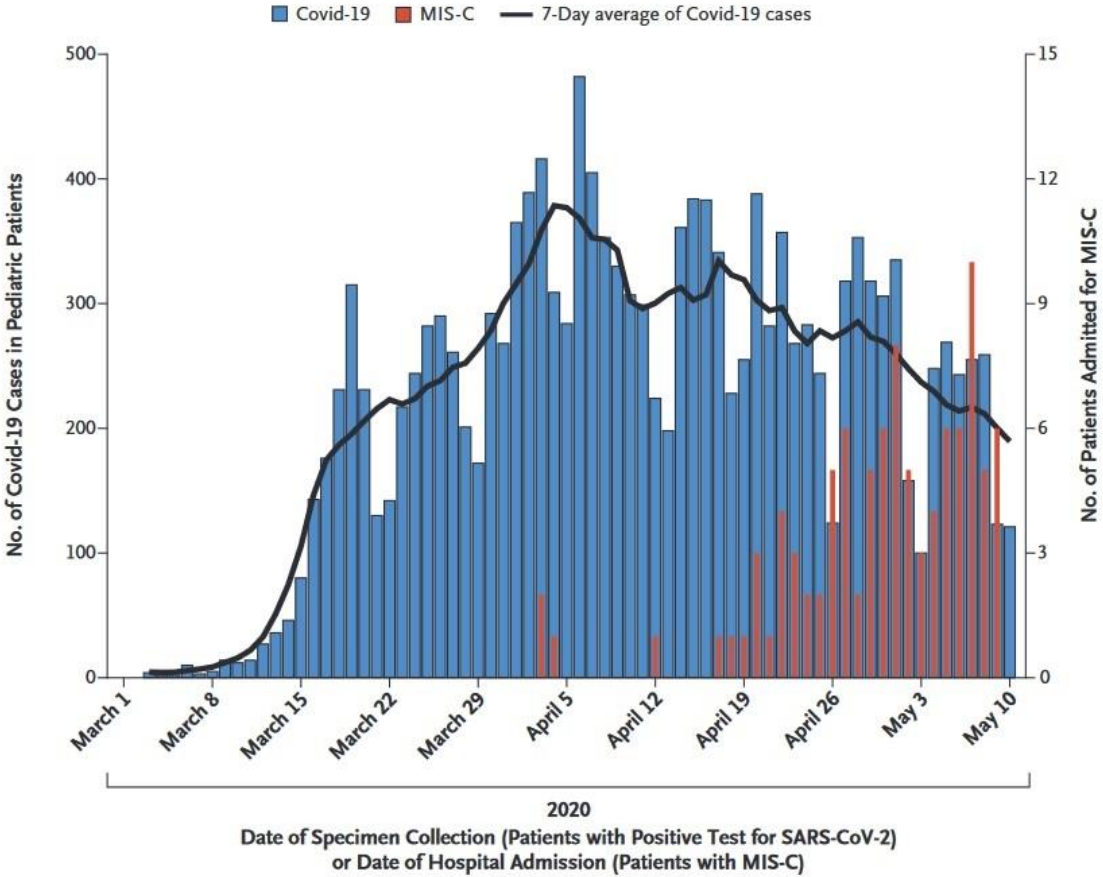
Multi-System Inflammatory Syndrome in Children(MIS-C) Following SARS-CoV-2 Infection


"Blood parameters consistent with severe COVID-19 in children" as well as abdominal pain, gastrointestinal (GI) symptoms, and cardiac inflammation.
High CRP, high ESR and high ferritin; The cardiac inflammation consists of "myocarditis with raised troponin and [prohormone brain-type natriuretic peptide (proBNP)],"; "Some have an appearance of their coronary arteries in keeping with Kawasaki disease."
April 27
The United Kingdom's Pediatric Intensive Care Society (PICS) also issued a statement
Fifteen children in NYC hospitals, between April, 17 to May, 1
May 4
64 suspected cases in New York state including NYC hospitals
The initial 15 NYC patients reportedly all had "subjective or measured fever and more than half reported rash, abdominal pain, vomiting, or diarrhea," but fewer than half had respiratory symptoms
May 6

MIS-C is a postinfectious condition

published on June 29, 2020, at: NEJM.org. N Engl J Med 2020;383:347-58.DOI: 10.1056/NEJMoa2021756

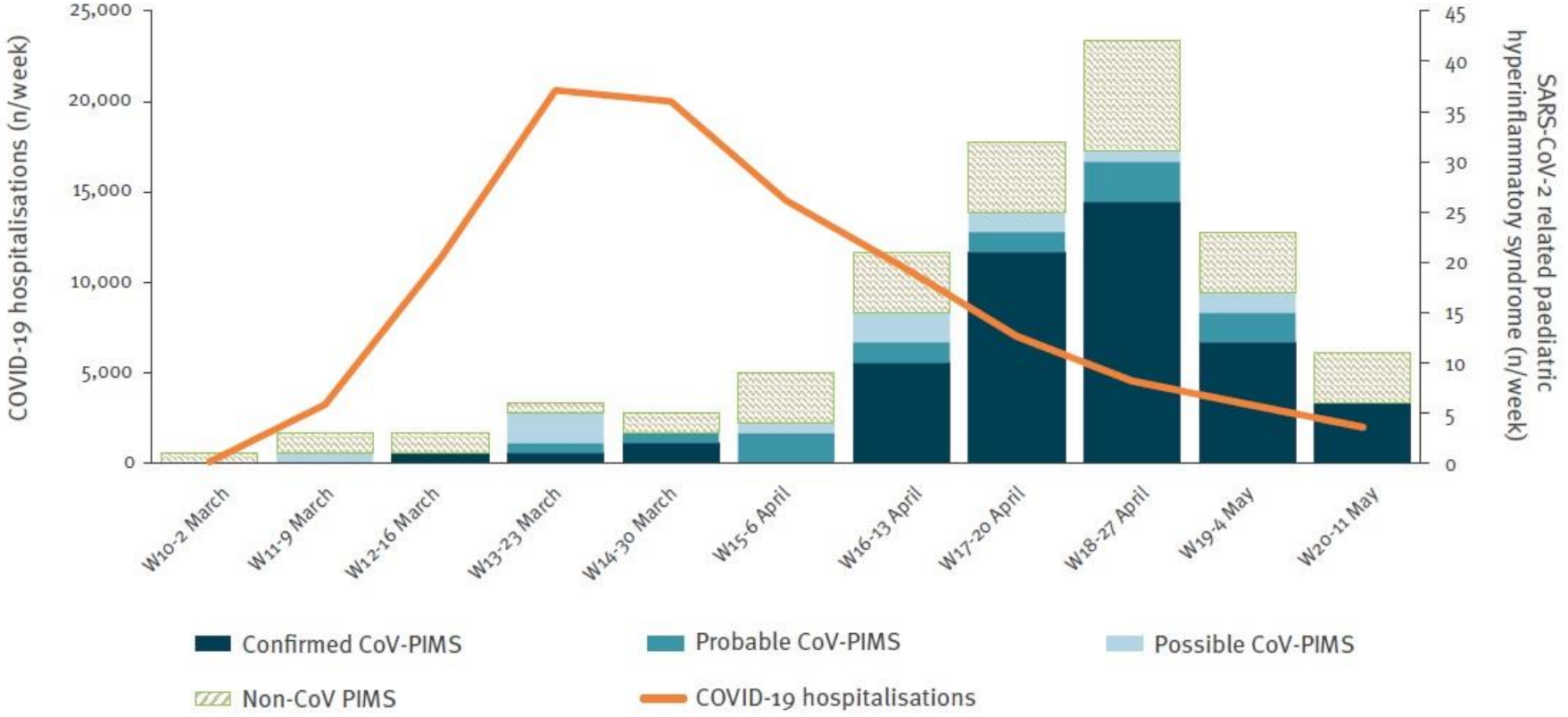


Pediatric Cases of Coronavirus Disease 2019 (Covid-19) and of MIS-C

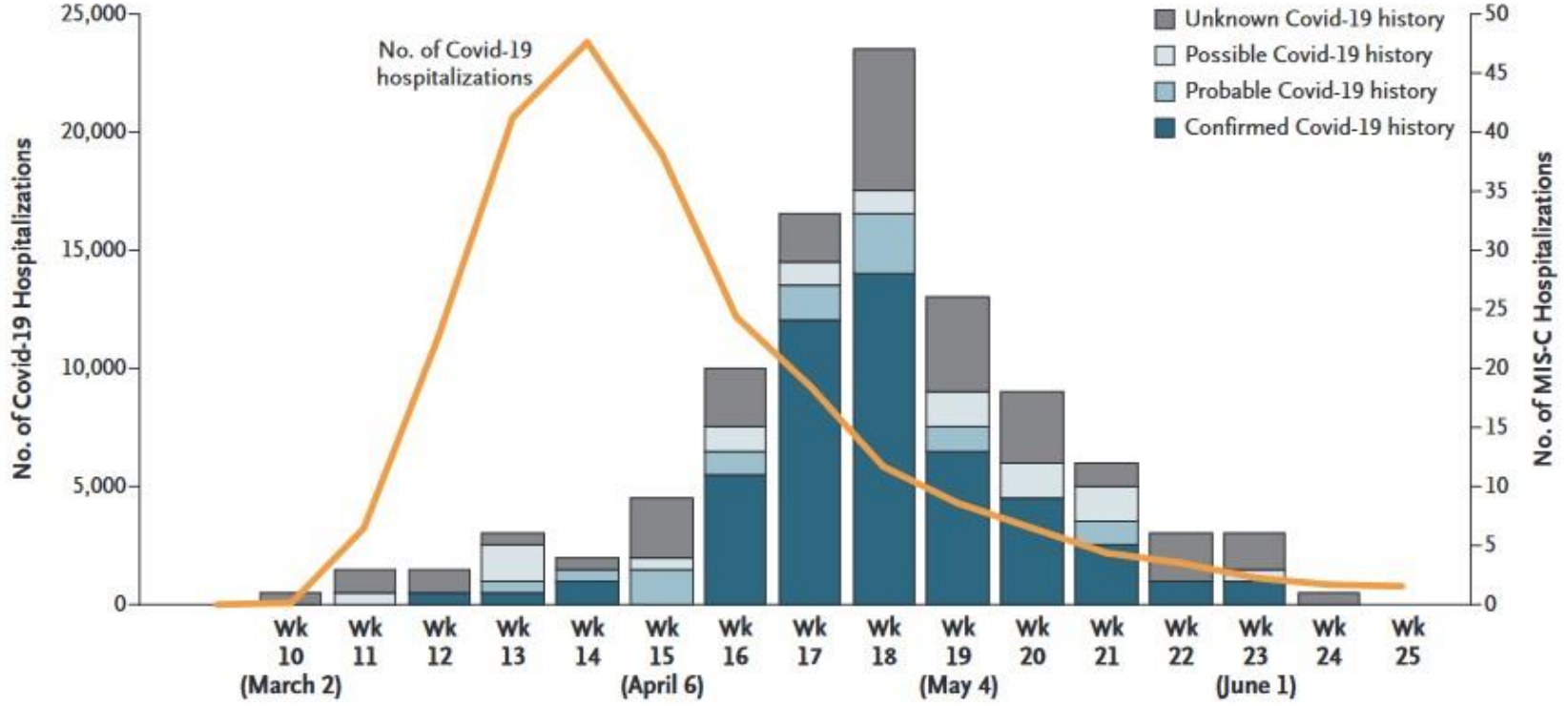
All data are for patients younger than 21 years of age in New York State from March through May, 2020. Covid-19 was defined by a positive test for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).

Temporal distribution of COVID-19 hospitalisations and SARS-CoV2 hyperinflammatory paediatric cases, France, 2 March–17 May (n = 108)

https://doi.org/10.2807/1560-7917.ES.2020.25.22.2001010/ published on 04 Jun 2020



CoV-PIMS: SARS-CoV-2-related paediatric inflammatory multisystem syndrome;COVID-19: coronavirus disease; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2.

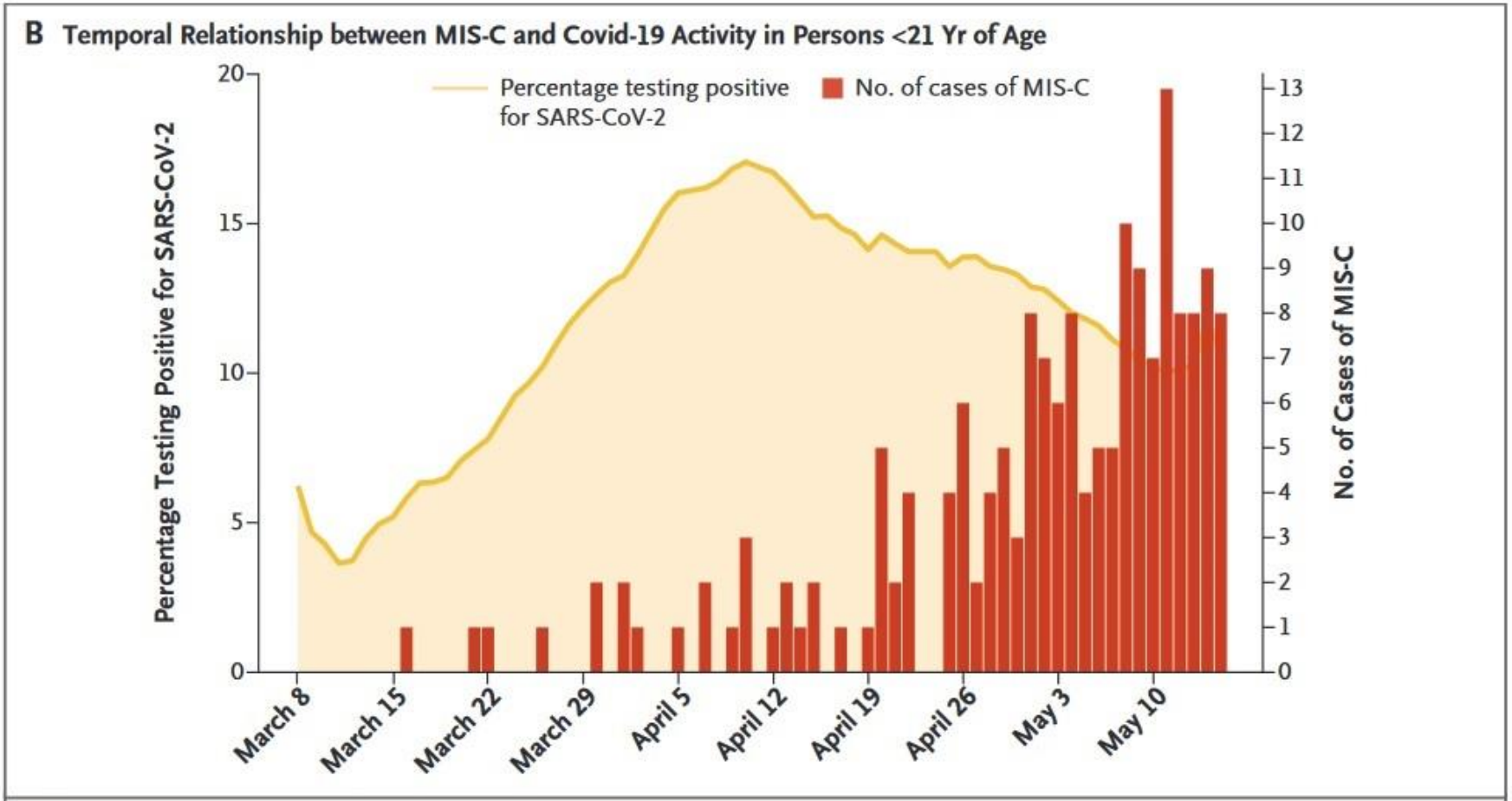


Temporal Distribution of Hospitalizations for Covid-19 and MIS-C in France

Between March 2 and June 21, 2020, a total of 195 hospitalizations for the multisystem inflammatory syndrome in children (MIS-C) were reported in France, of which 138 cases were classified as being associated (possible, probable, or confirmed history) with SARS-CoV-2, the virus that causes coronavirus disease 2019 (Covid-19). Also shown is the number of hospitalizations for Covid-19 in the general population in France.

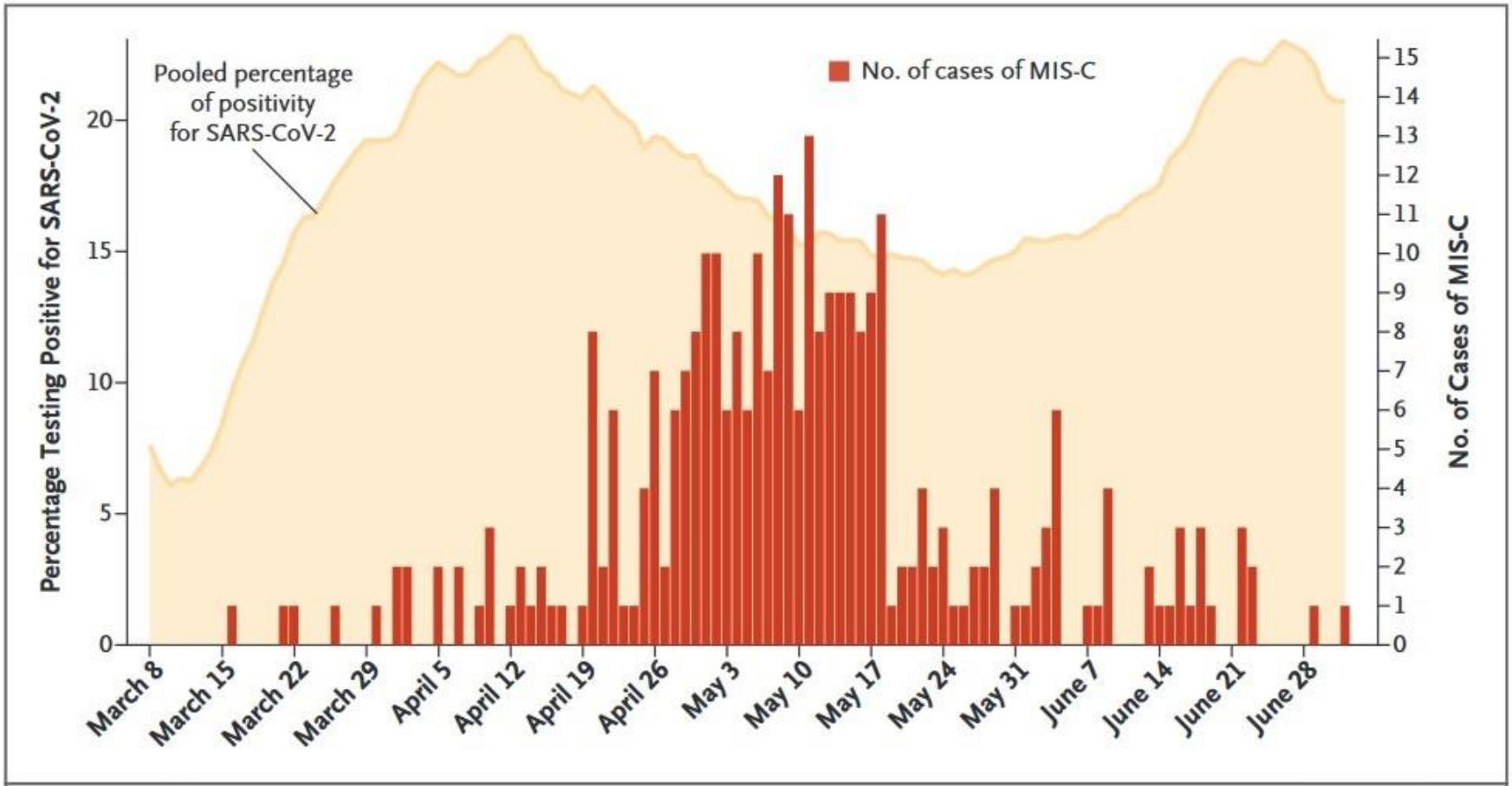
- Similar to other reports, France report showed a median patient age of 8 years
- A sharp decrease in the incidence of cases occurred 3 to 4 weeks after the decrease in the Covid-19 outbreak in France

N Engl J Med 2020;383:334-46.DOI:10.1056/NEJMoa2021680



Geographic and Temporal Representation of Cases of Multisystem Inflammatory Syndrome in Children (MIS-C).

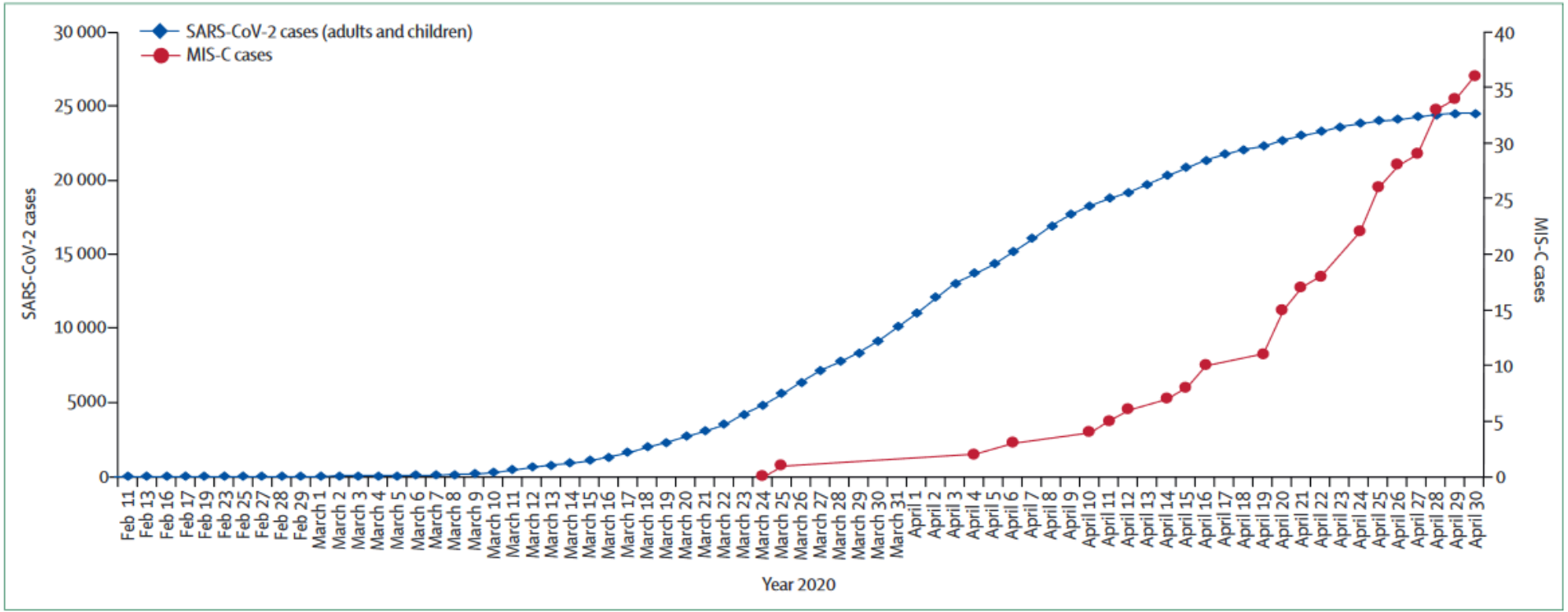
Published on June 29, 2020, and updated on July 2, 2020, at NEJM.org



Temporal Representation of Cases of MIS-C, as Compared with U.S. Statewide Pooled Percentages of Positivity for SARS-CoV-2 Testing of Respiratory Specimens Obtained from Persons Younger Than 21 Years of Age.

- Unlike France, the United States has had sustained high transmission of SARS-CoV-2 since the end of June 2020

Only incudes PCR-positive cases in London, UK. Data taken from Public Health England



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MIS-C
Definition

- The clinical presentation of MIS-C includes fever, severe illness, and the involvement of two or more organ systems, in combination with laboratory evidence of inflammation and laboratory or epidemiologic evidence of SARS-CoV-2infection

- MISC can lead to shock and multiple organ failure requiring intensive care

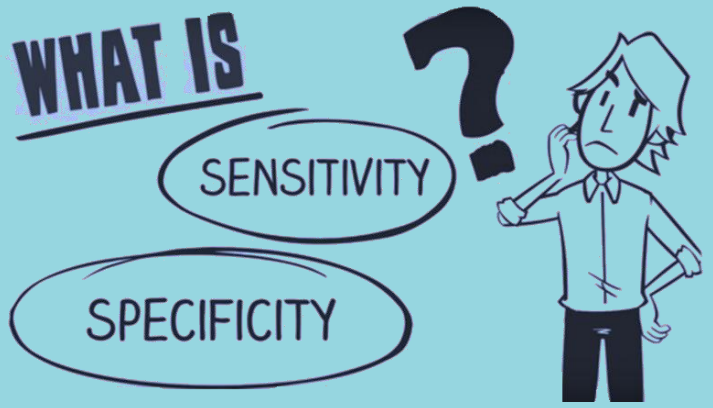
Pediatric Inflammatory Multisystem Syndrome: Temporally Associated with SARS-CoV-2 (PIMS-TS)

	MIS-C associated with COVID-19
Organisation or publication	WHO[6]
Age	0–19 years
Inflammation	Fever and elevated

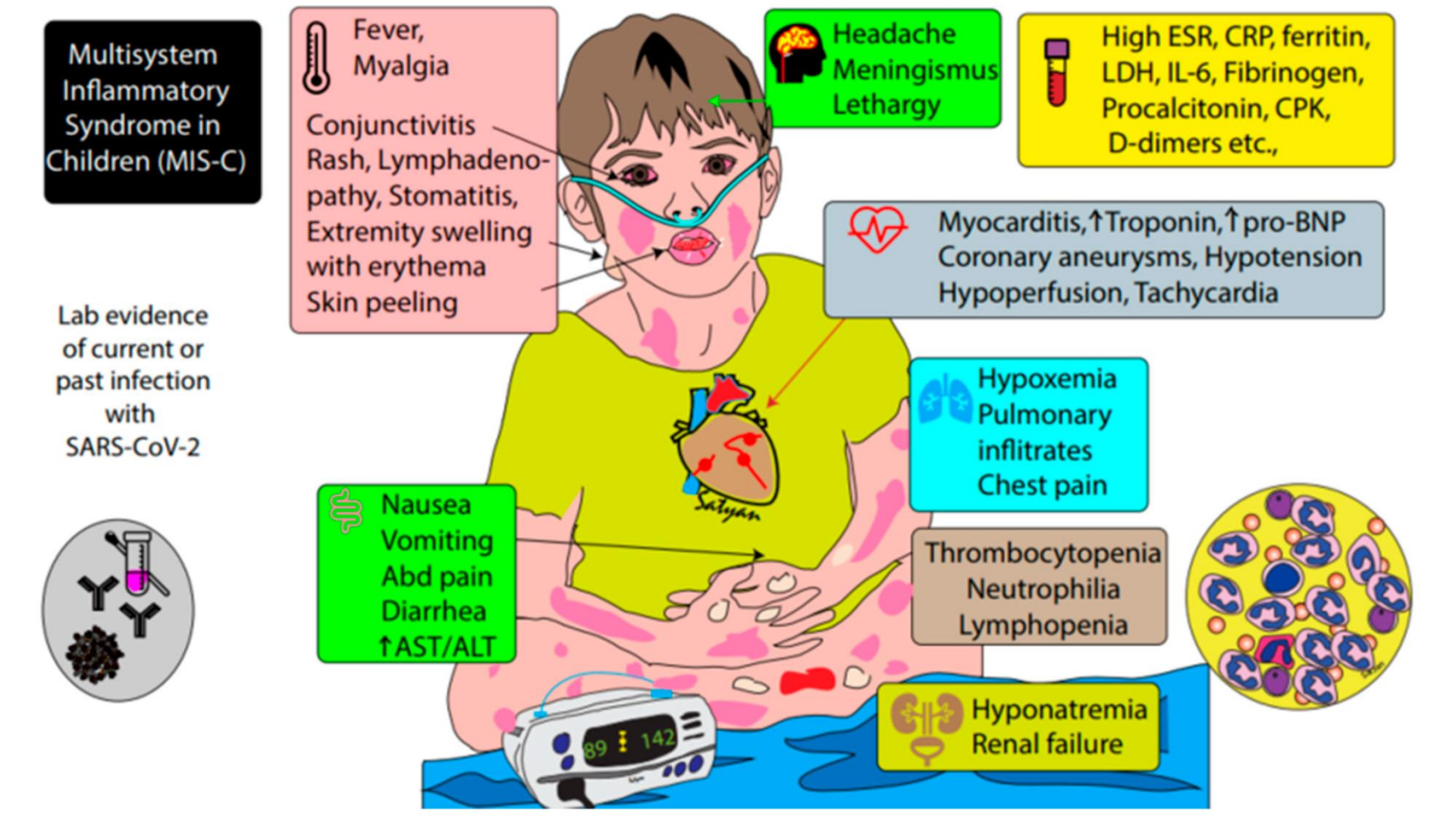
	MIS-C associated with COVID-19	PIMS-TS	MIS-C associated with COVID-19
Organisation or publication	WHO	Royal College of Pediatrics and Child Health	US Centers for Disease Control and Prevention
Exclusion	Other microbial cause of inflammation	Any other microbial cause	Other plausible alternative diagnoses
SARS-CoV-2 status	Positive RT-PCR, antigen test, or serology; or any contact with patients with COVID-19	RT-PCR positive or negative	Positive RT-PCR, serology, or antigen test; or COVID-19 exposure within the past 4 weeks before symptom onset

natriuretic peptide); (D) evidence of coagulopathy (elevated prothrombin time, partial thromboplastin time, and elevated D-dimers); and (E) acute gastrointestinal problems (diarrhoea, vomiting, or abdominal pain)

- A broader UK definition of MISC describes this illness as a spectrum ranging from persistent fever and inflammation, to characteristic features of Kawasaki disease in children, and to children who are severely ill with shock and multiple organ failure

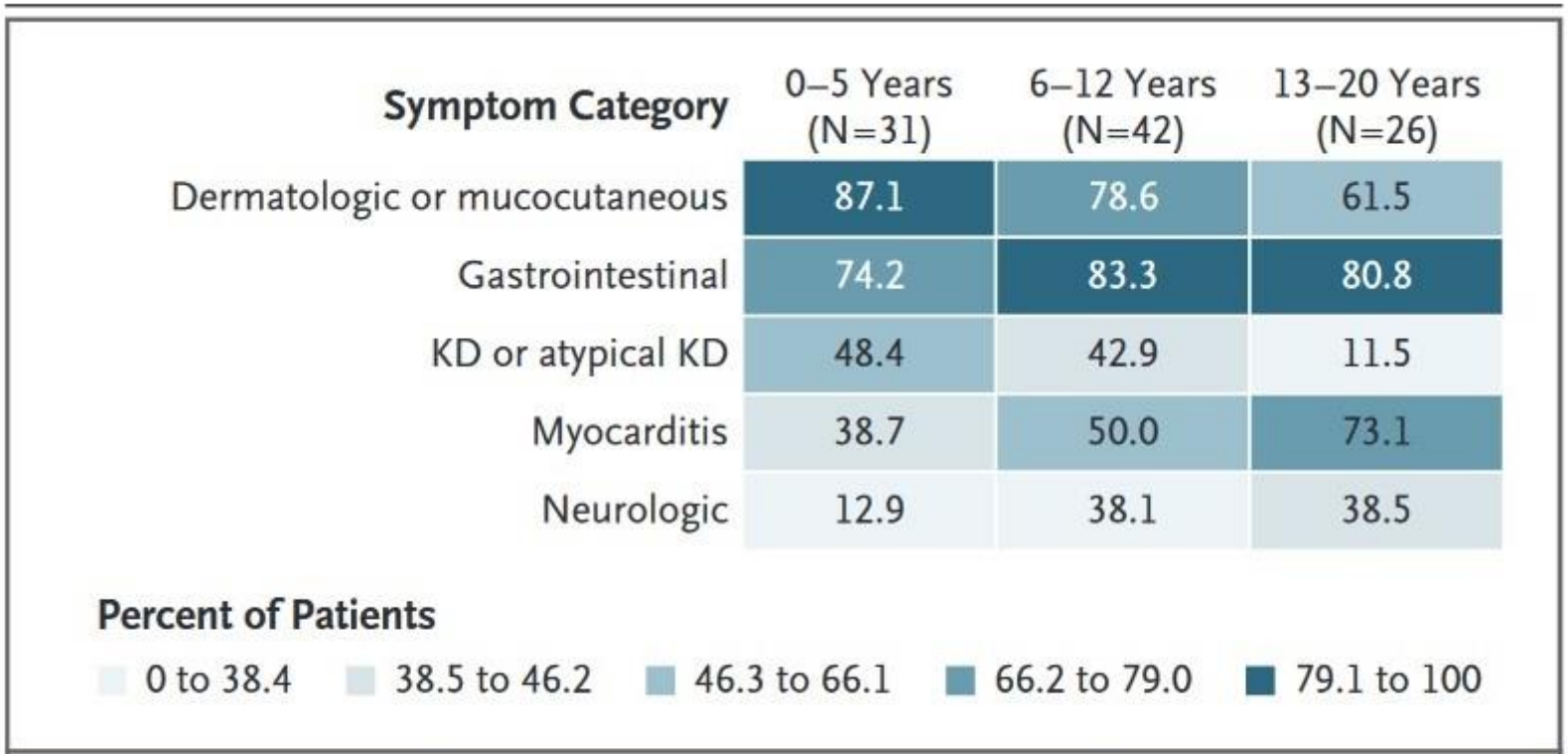


- In the study by Dufort and colleagues, 1/3 of the reported cases did not meet the US CDC case definition for MISC but presented with similar clinical and laboratory features to those seen in confirmed cases


Multisystem Inflammatory Syndrome in Children (MIS-C)
Fever, Myalgia
Conjunctivitis
Rash, Lymphadeno-pathy, Stomatitis,
Extremity swelling with erythema
Skin peeling
Headache
Meningismus
Lethargy
High ESR, CRP, ferritin, LDH, IL-6, Fibrinogen, Procalcitonin, CPK, D-dimers etc.,
Myocarditis, ↑Troponin, ↑pro-BNP
Coronary aneurysms, Hypotension
Hypoperfusion, Tachycardia
Hypoxemia
Pulmonary inflitrates
Chest pain
Lab evidence of current or past infection with SARS-CoV-2
Nausea
Vomiting
Abd pain
Diarrhea
↑AST/ALT
Thrombocytopenia
Neutrophilia
Lymphopenia
Hyponatremia
Renal failure
89
142

Investigations as part of PIMS-TS screen

Blood tests	Microbiology
FBC and Film	Blood culture
U + E	Urine and stool culture
LFT	Throat swab culture
CRP	NPA or throat swab for respiratory panel
ESR	Mycoplasma titres
Glucose	Pneumococcal, Meningococcal, Group A strep, Staph aureus Blood PCR
Blood gas with lactate	
Coagulation + Fibrinogen	
D-Dimer	Anti-Streptolysin O Titre
LDH	EBV, CMV, Adenovirus, Parvovirus, Enterovirus PCR on Blood
Triglycerides	
Ferritin	HIV
Troponin I	Blood for enterotoxin/staph toxins
Pro-BNP	Stool for virology
CK	
Vitamin D	
Amylase	
Save EDTA and serum for PCR and serological studies (pre IVIG)	
Cardiac investigations	**SARS-CoV-2 Investigations**
ECG	SARS-CoV-2 Respiratory PCR
Echocardiogram	Consider PCR on stool and blood
	SARS-CoV-2 serology



Syndrome Clusters According to Age Group among Patients with Multisystem Inflammatory Syndrome in Children (MIS-C)

Comparison of possible, probable and confirmed CoV-PIMS with non-CoV PIMS following our classification criteria, France, 1 March–17 May (n = 156)

	CoV-PIMS (n = 108)		Unrelated CoV-PIMS (n = 48)		p value
Age in years (median; IQR)	8 (5–11)		3 (1–7)		<0.0005
Sex ratio male/female	0.96		1		0.99
Clinical presentation	n	%	n	%	
Kawasaki-like disease	66	61	39	81	<0.01
Myocarditis	76	70	5	10	<0.0001
MAS	25	23	1	2	<0.001
Seritis	24	22	5	10	0.11
Intensive care unit	72	67	4	8	<0,0001

IQR: interquartile range; MAS: macrophage activation syndrome; NA: not applicable.

p values were calculated using the Mann-Whitney test for quantitative values and Fisher's exact test for qualitative ones.

- Confirmed/proven cases of SARS-CoV-2-related PIMS (CoV-PIMS) were children presenting with one or more of the following symptoms: seritis, characteristics of MAS, myocarditis and/or KLD and a positive SARS-CoV-2 RT-PCR or serology;

- Probable CoV-PIMS cases were children presenting with any of the above clinical features and either a direct epidemiological link with a confirmed COVID-19 case or a chest computed tomography scan favouring the diagnosis of COVID-19;

- Possible CoV-PIMS cases were children presenting with at least two of the above clinical features with pending or not performed PCR and serology;

- Non-CoV PIMS cases were children with both negative PCR and serology or with pending or not performed PCR and serology and presenting with only one of the above clinical features.

We compared the characteristics of the non-CoV PIMS and CoV-PIMS populations using Mann and Whitney test.

Circulation. 2020;142:429–436.
DOI:10.1161/CIRCULATIONAHA.120.048360

Cardiac Signs

Characteristic	Value
Clinical signs, n (%)	
Chest pain	6 (17)
Cardiogenic shock with collapse	28 (80)
Ventricular arrhythmia	1 (3)
Systolic blood pressure at admission, percentile (interquartile range)	1 (1–10)
Coronary artery dilatation *z* score >2	6 (17)
Aneurysms at day 10 (echocardiography only), n (%)	0 (0)
Left ventricular ejection fraction at baseline, n (%)	
<30%	10 (28)
30%–50%	25 (72)
Evolution of left ventricular ejection fraction, median±SD, %	
Baseline (35 patients)	32±9
Day 3 (23 patients)	52±10
Day 7 (34 patients)	60±6
Recovery left ventricular ejection fraction	
>60% at day 7, n (%)	25 (71)
Time to full recovery, median (range), d	2 (2–5)

Data are median (interquartile range) or n (%), where number is the total number of patients with available data.

Over a 2-month period, contemporary with the SARS-CoV-2 pandemic in **France and Switzerland**, we retrospectively collected clinical, biological, therapeutic, and early outcomes data in children who were admitted to pediatric intensive care units in **14 centers** for cardiogenic shock, left ventricular dysfunction, and severe inflammatory state (35 patients fulfilling the inclusion criteria)

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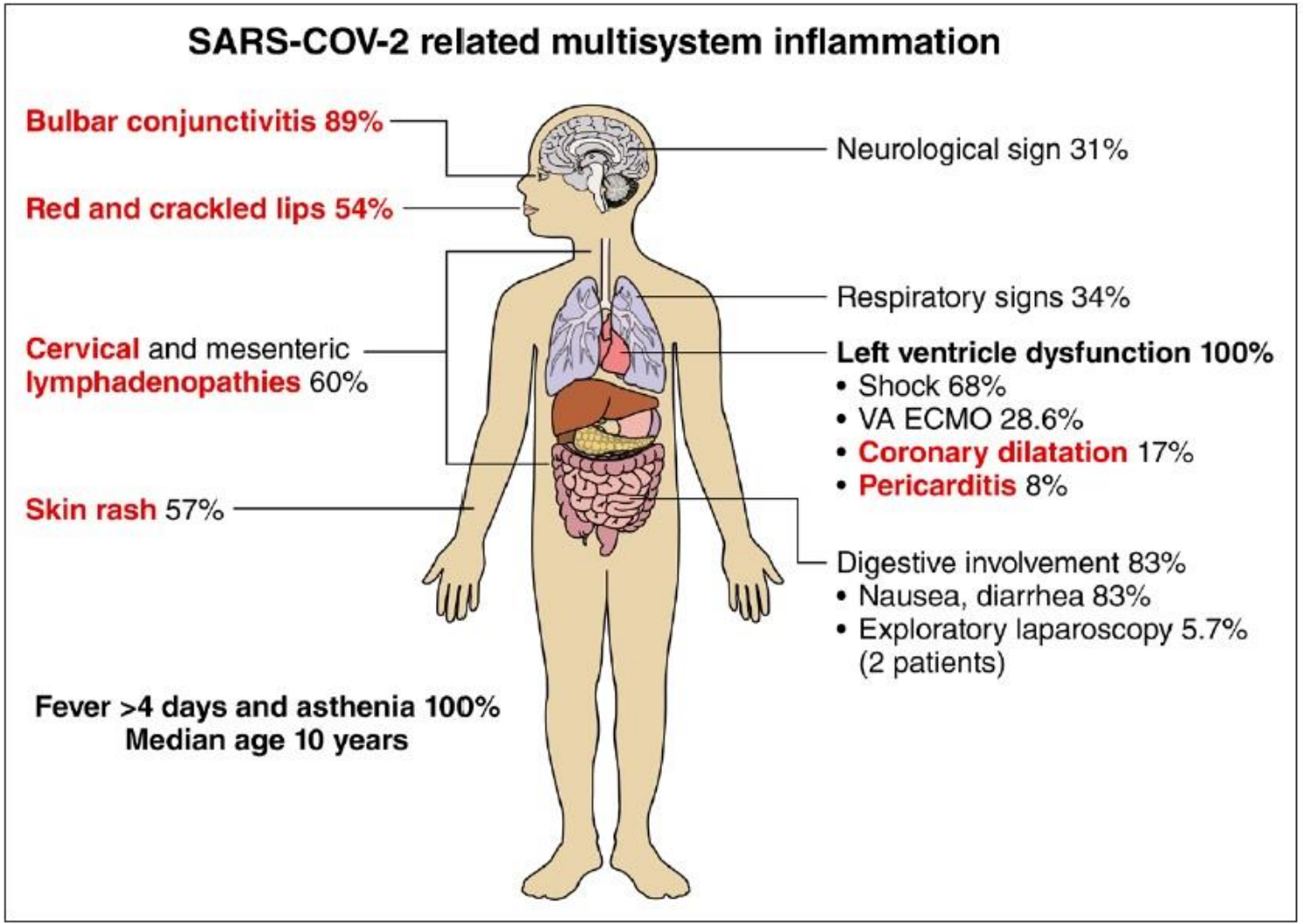
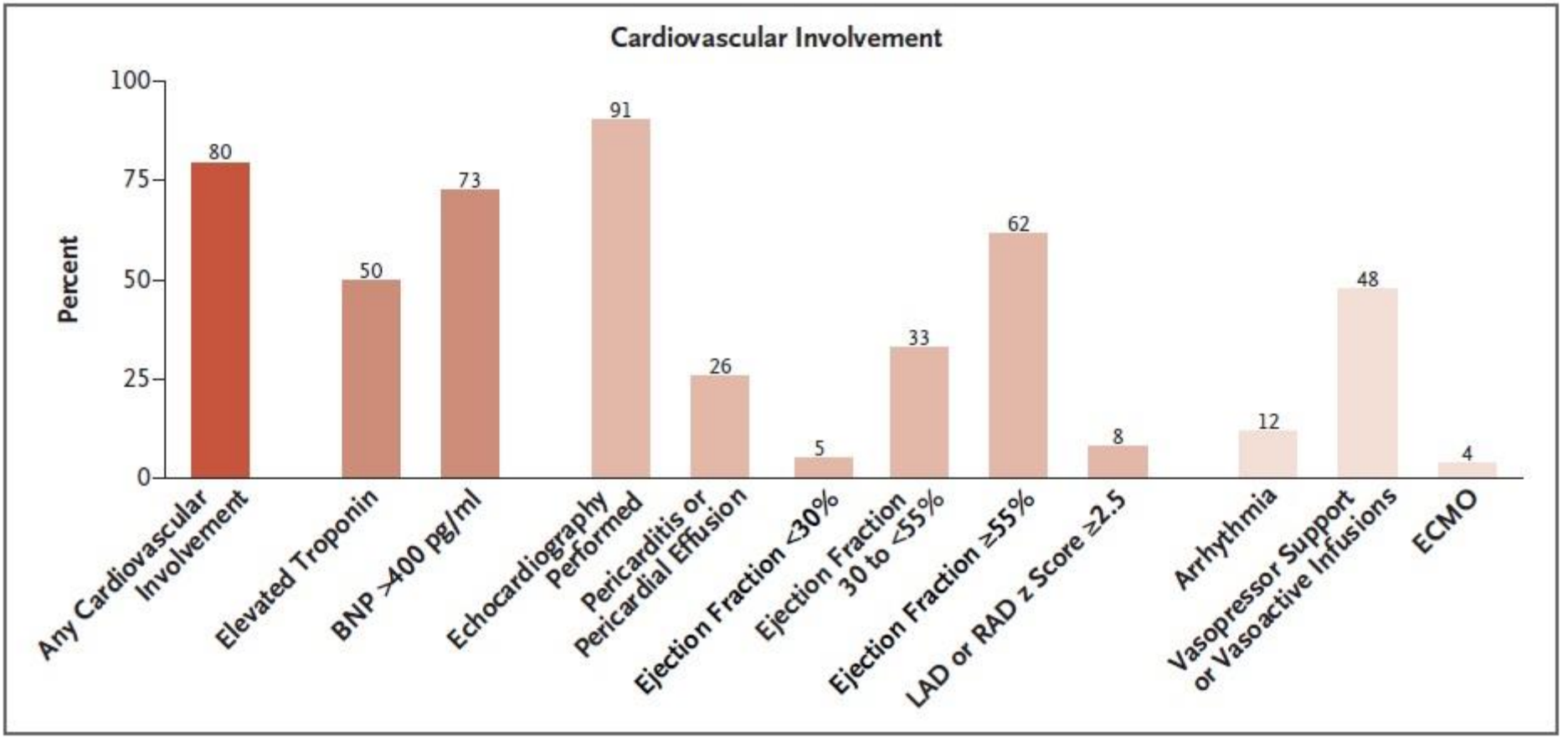


Left ventricular ejection fraction at baseline <60%



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Overlap syndrome?

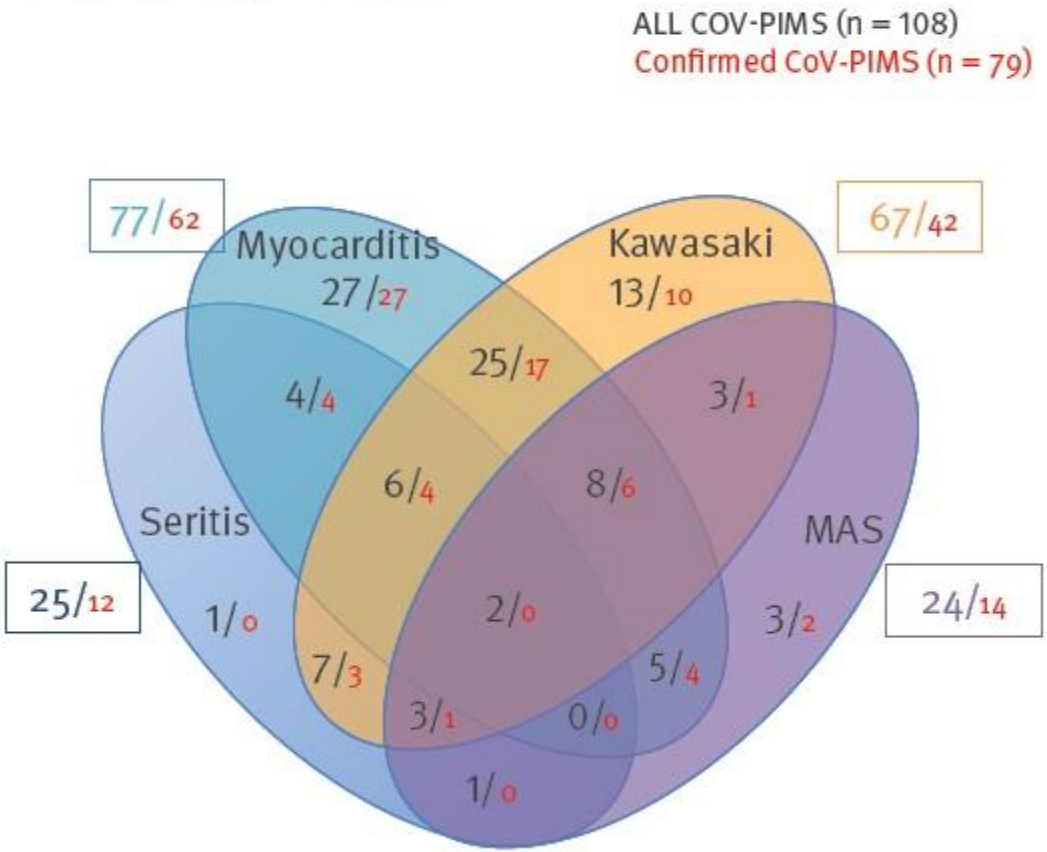
- Toxic shock syndrome
  - Seems implausible because most MISC cases had negative blood cultures
- Kawasaki disease
- Kawasaki disease shock syndrome (KDSS)
- MAS

Similarities between MIS-C and toxic shock syndrome

- SARS-CoV-2 spike (S) protein contains a *superantigen-like region* similar to that of staphylococcal enterotoxin B (SEB), with predicted binding to T-cell receptors and MHC class II molecules
- ***Superantigen-mediated mechanism*** *versus* acquired immunity to SARS-CoV-2 develop??

Similarities between MIS-C and Kawasaki disease

Venn diagram of clinical features of SARS-CoV-2-related paediatric inflammatory multisystem syndrome, France, 1 March–17 May (n = 108)



Overlap syndrome?

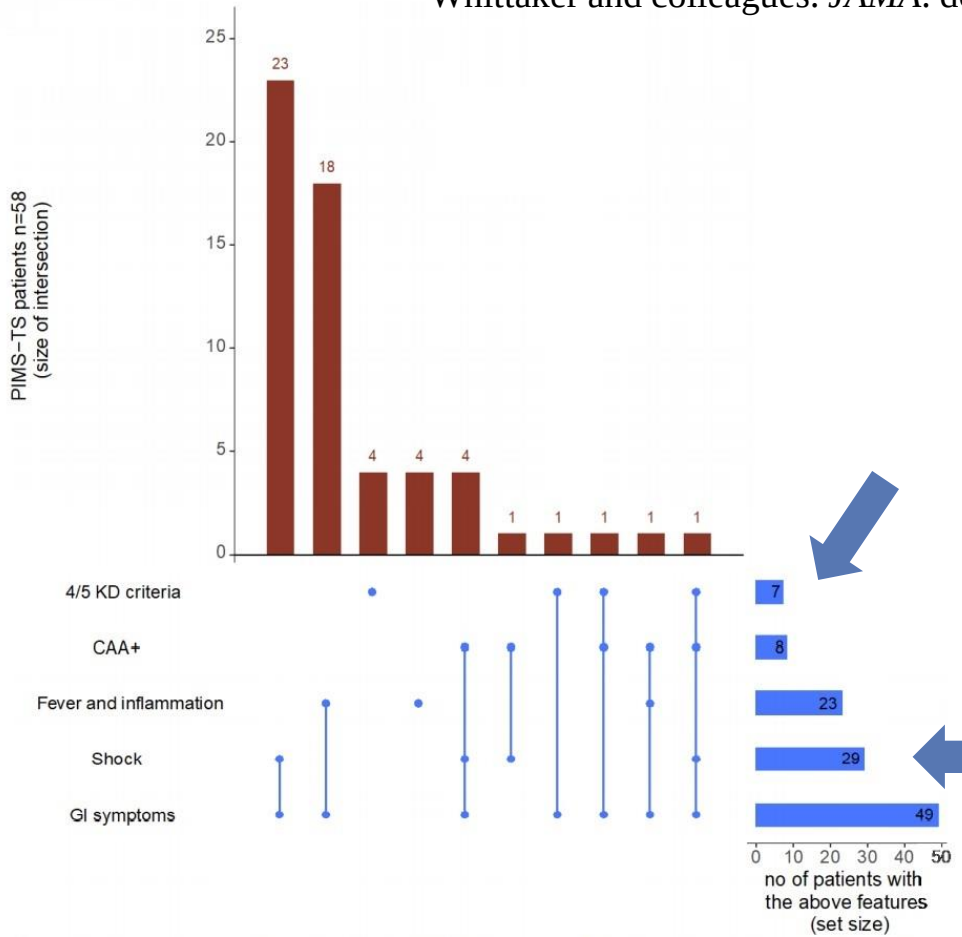
- A large number of MISC cases present with Kawasaki like clinical symptoms, and cardiac impairment and shock similar to Kawasaki disease shock syndrome

- Gastrointestinal symptoms, *hyponatremia*, *hypoalbuminemia*, and *intravenous immunoglobulin resistance* are also common in KDSS and MISC

Whittaker and colleagues. *JAMA*. doi:10.1001/jama.2020.10369

Characteristic	No. (%)[a] All PIMS-TS cases (n = 58)[b]	Febrile and inflammatory (n = 23)[c]	Stratification by shock[d] Shock present (n = 29)	Shock absent (n = 29)	Stratification by Kawasaki disease[e] Kawasaki disease (n = 13)	Not Kawasaki disease (n = 45)	Stratification by Kawasaki clinical criteria[e] Criteria met (n = 7)	Criteria not met (n	Stratification by coronary artery aneurysm[f] Present (n = 8)	Absent (n = 50)	Stratification by evidence of SARS-CoV-2 infection[g] Positive (n = 45)	Negative (n = 13)
Clinical features at presentation[l]												
Abdominal pain	31 (53)	13 (57)	18 (62)	13 (45)	2 (15)	29 (64)	1 (14)	30 (59)	2 (33)	29 (58)	24 (55)	7 (50)
Diarrhea	30 (52)	10 (44)	19 (66)	11 (38)	7 (54)	23 (51)	2 (29)	28 (55)	6 (75)	24	25 (75)	5 (36)
Rash	30 (52)	9 (39)	15 (50)	15 (50)	10 (77)	20 (44)	7 (100)	23 (45)	4 (63)	25 (50)	21 (48)	9 (64)
Shock[d]	29 (50)	0	29 (100)	0	6 (46)	23 (51)	1 (14)	28 (55)	6 (75)	2	25 (56)	4 (31)
Vomiting	26 (45)	10 (44)	15 (52)	11 (38)	5 (38)	21 (47)	2 (29)	23 (45)	5 (63)	21 (42)	20 (45)	6 (43)
Conjunctival injection	26 (45)	9 (39)	11 (38)	15 (52)	11 (85)	15 (33)	7 (100)	19 (37)	5 (63)	21 (42)	20 (45)	6 (43)
Mucous membrane changes	17 (29)	5 (22)	6 (21)	11 (38)	6 (46)	11 (24)	6 (86)	11 (22)	1 (17)	11 (22)	11 (25)	6 (43)
Headache	15 (26)	4 (17)	11 (38)	4 (14)	4 (31)	11 (24)	1 (14)	14 (27)	4 (50)	11 (22)	13 (30)	2 (14)
Respiratory symptoms	12 (21)	2 (13)	9 (31)	3 (10)	3 (23)	9 (20)	1 (14)	11 (22)	3 (38)	9 (18)	9 (20)	3 (21)
Lymphadenopathy	9 (16)	3 (13)	2 (7)	7 (24)	5 (38)	4 (9)	4 (57)	5 (10)	2 (33)	7 (14)	8 (18)	1 (7)
Swollen hands and feet	9 (16)	2 (13)	4 (14)	5 (17)	4 (31)	5 (11)	4 (57)	5 (10)	1 (17)	7 (14)	7 (16)	2 (14)
Sore throat	6 (10)	1 (4)	5 (17)	1 (3)	0	6 (13)	0	6 (12)	1 (17)	5 (10)	6 (14)	0
Confusion	5 (9)	0	5 (17)	0	1 (8)	4 (9)	0	5 (10)	1 (17)	4 (8)	5 (11)	0

Whittaker and colleagues. *JAMA*. doi:10.1001/jama.2020.10369



eFigure 2 Characteristics of the patients in the PIMS-TS group (n=58). The red bars indicate the size of the intersection of the features/clinical symptoms, and the blue bars the number of patients with the features/clinical symptoms. ;KD: Kawasaki Disease, CAA+ :Coronary Artery Aneurysm; GI: Gastrointestinal.

Some KD patients presenting without CAAs

2-cases wi
CAAs+K

Shock may be better predictor for CAA invol.

6-cases with CAAs+Shock

Overlap syndrome?

- Despite differences in severity, coronary aneurysms have occurred in all three groups of patients, including those with shock, those who meet the criteria for Kawasaki disease, and those with fever and inflammation but who do not have shock or meet the criteria for Kawasaki disease

Whittaker and colleagues. *JAMA*. doi:10.1001/jama.2020.10369

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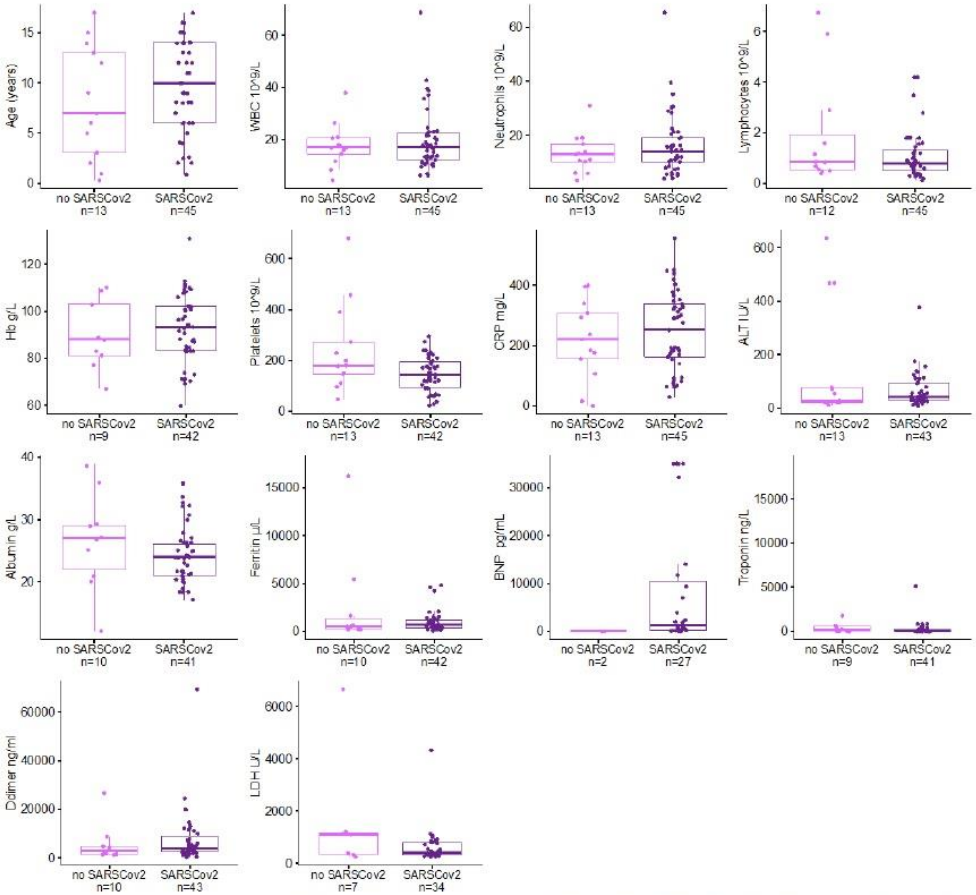
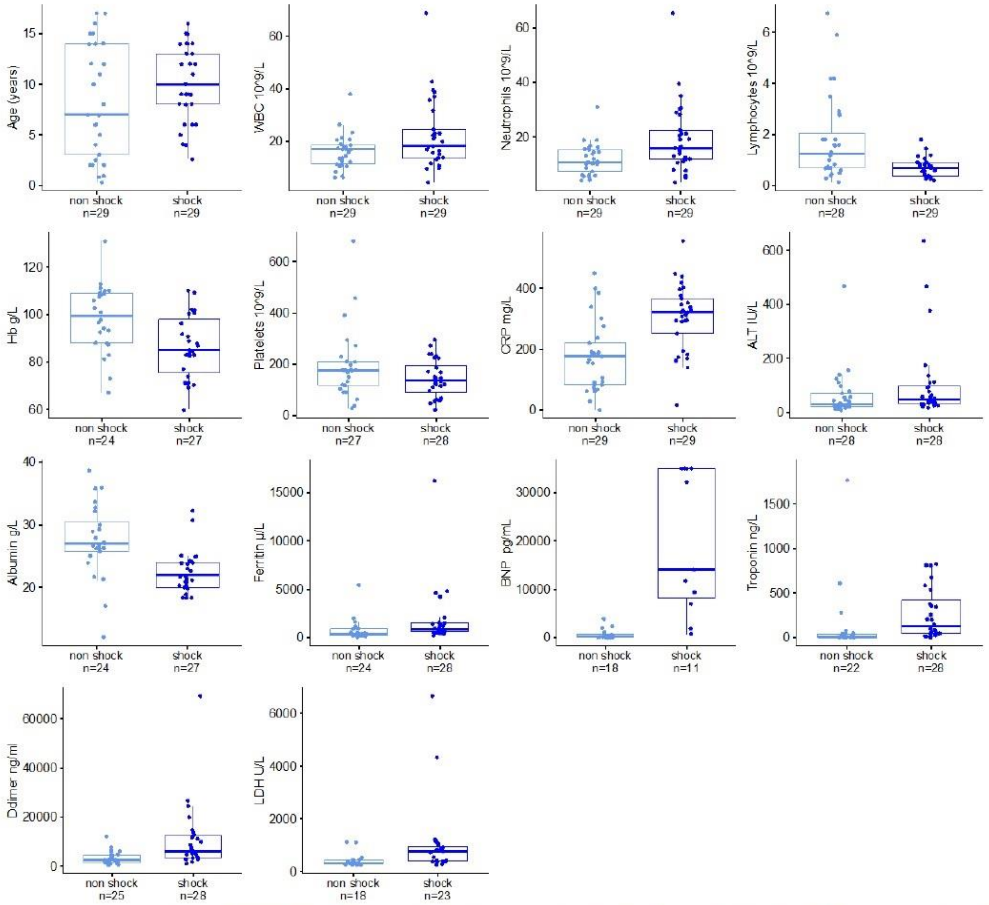


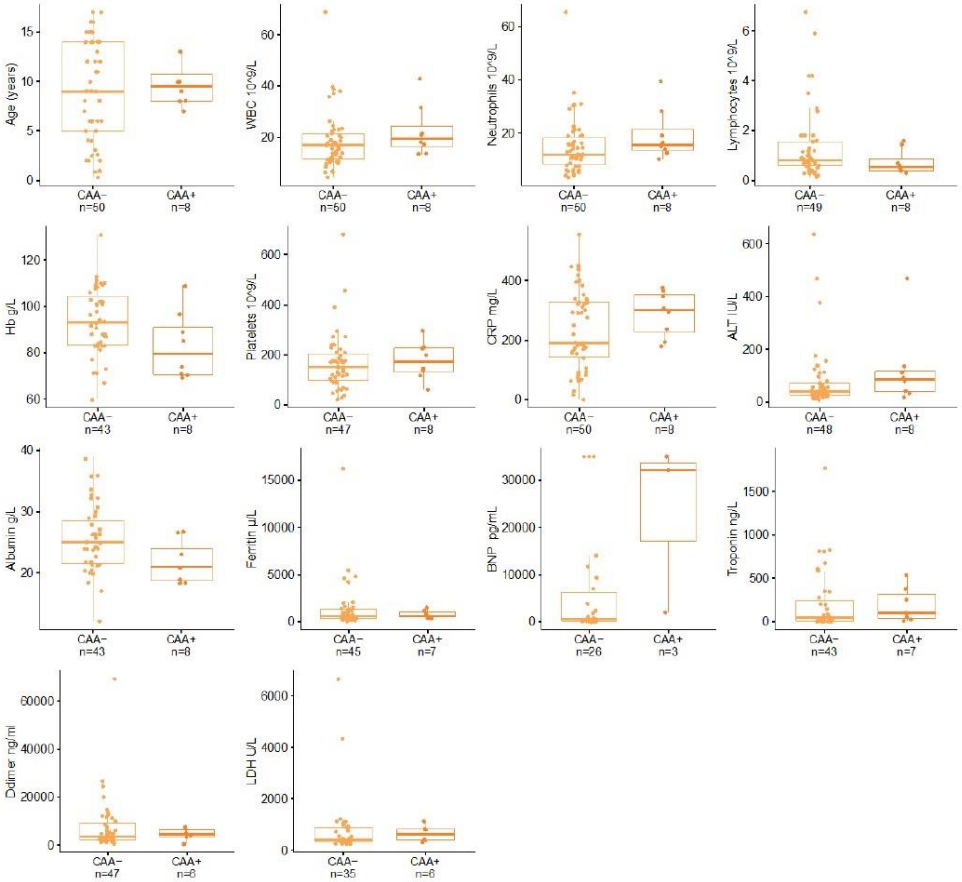
Comparison of age and laboratory features in 58 children with PIMS-TS and either no evidence of SARS-CoV-2 infection (no SARSCov2; n=13) or evidence of SARS-CoV-2 (PCR and/or IgG antibody) (SARSCov2; n=45). Horizontal lines in boxes indicate medians; lower and upper edges of boxes interquartile range and the bars extent to the highest and lowest value within 1.5 times the interquartile ranges. For clarity of visualisation a patient with a ferritin value of 63,626; and a patient with troponin value of 5,113 are not shown on the plot.

Whittaker and colleagues. *JAMA*. doi:10.1001/jama.2020.10369



Comparison of PIMS-TS children with shock vs non shock Shock was defined as fluid resuscitation of greater than 20ml/kg or use of inotropic agents. Horizontal lines in boxes indicate medians; lower and upper edges of boxes indicate interquartile range and the bars extend to the highest and lowest value within 1.5 times the interquartile ranges. For clarity of visualisation a patient in the shock group with a ferritin value of 63,626; and a patient in the shock group with troponin value of 5,113 are not shown on the plot. Details available in Table 4 and eTable 2

Whittaker and colleagues. *JAMA*. doi:10.1001/jama.2020.10369



Comparison of age and laboratory features in 58 children with PIMS-TS and either no coronary artery aneurysms (CAA-; n=50) or coronary artery aneurysms (CAA+; n=8). Horizontal lines in boxes indicate medians; lower and upper edges of boxes interquartile range and the bars extent to the highest and lowest value within 1.5 times the interquartile ranges. For clarity of visualisation a patient with a ferritin value of 63,626; and a patient with troponin value of 5,113 are not shown on the plot. Further detail available in Table 4 and eTable 2.

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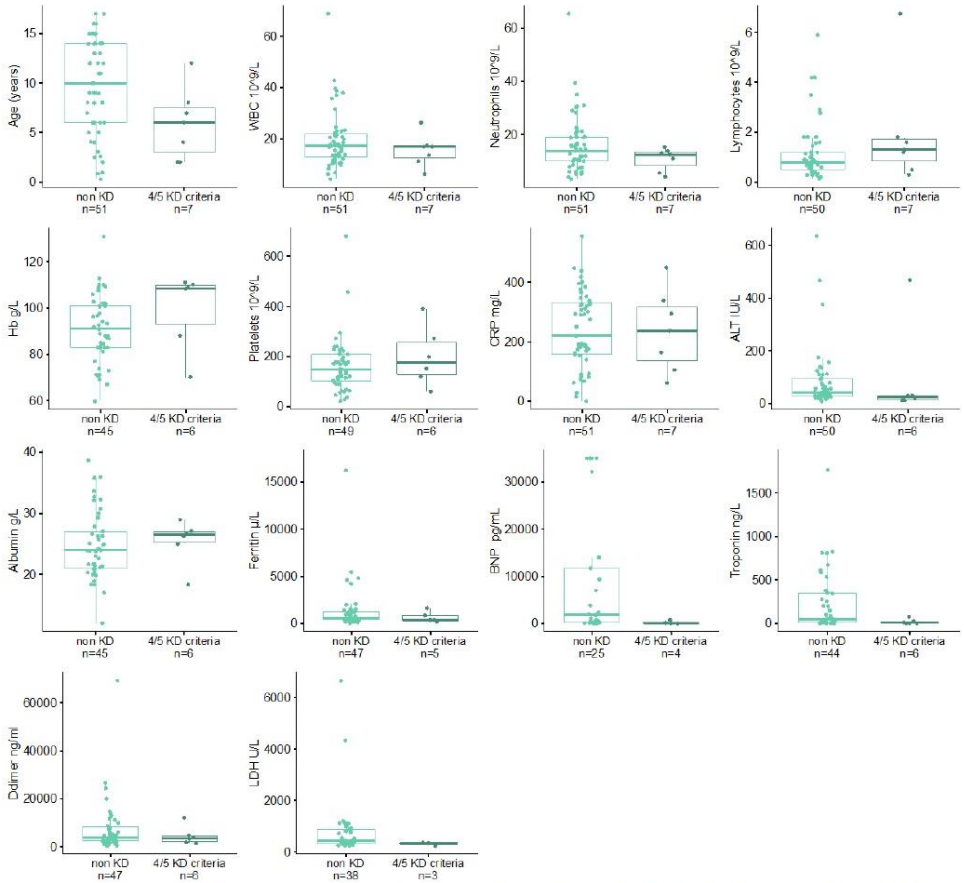

Comparison of age and laboratory features in 58 children with PIMS-TS who either didn't fulfil the clinical diagnostic criteria for Kawasaki disease (4/5 features of mucocutaneous involvement) (non-KD; n=51) or did fulfil the clinical diagnostic criteria (4/5 KD criteria; n=7). Horizontal lines in boxes indicate medians; lower and upper edges of boxes interquartile range and the bars extent to the highest and lowest value within 1.5 times the interquartile ranges. Bars indicate median and interquartile range. For clarity of visualisation a patients with a ferritin values of 63,626 is not shown on the plot. Further detail available in Table 4 and eTable 2.

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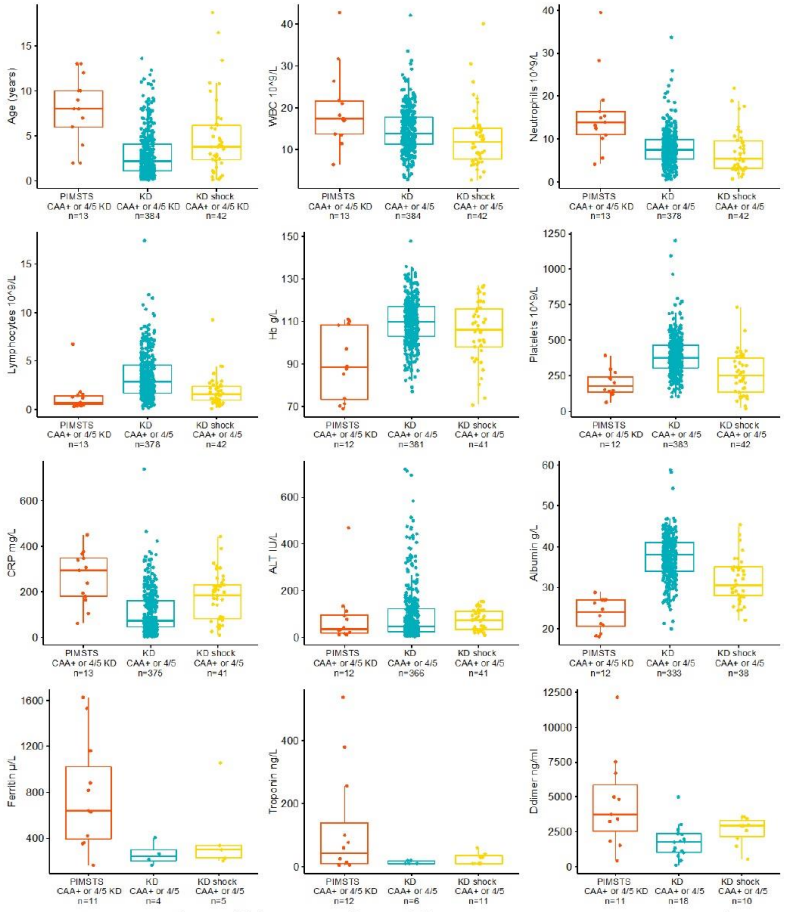


Comparison of age and laboratory results in 3 different patient groups. PIMS-TS CAA+ or 4/5 KD – children with PIMS-TS with coronary artery aneurysms and/or meeting 4/5 clinical diagnostic criteria for Kawasaki disease, n=13; KD CAA+ or 4/5 – cohort of 384 children with Kawasaki Disease who have coronary artery aneurysms and/or meet 4/5 clinical diagnostic criteria for Kawasaki disease, KD-shock CAA+ or 4/5 – cohort of 42 children with Kawasaki Disease shock syndrome and coronary artery aneurysms and/or meet 4/5 clinical diagnostic criteria for Kawasaki disease.. Horizontal lines in boxes indicate medians; lower and upper edges of boxes indicate interquartile range and the bars extend to the highest and lowest value within 1.5 times the interquartile ranges. Details available in eTable 1 and eTable 2.

Differences in medians	Age (years)	Total white cell count *10⁹/L	Neutrophil count *10⁹/L	Lymphocyte count *10⁹/L	Haemoglobin g/L	Platelet number (*10⁹/L)	CRP (mg/L)	ALT (IU/L)	Albumin (g/L)	FerritiN (mg/L)	NT-Pro-BNP (pg/ml)	Troponin (ng/L)	D-dimer (ng/ml)	LDH (U/L)
SARS-CoV-2 — no SARS-CoV-2	3.00	0.00	1.04	-0.04	5.00	-38.50	31.00	14.00	-3.00	172.50	-211.00	1013.50	1129.00	-690.50
shock — no shock	3.00	1.20	5.20	-0.55	-14.50	-40.50	145.00	15.50	-5.00	508.50	115.50	3515.00	13804.50	437.00
CAA positive — CAA negative	0.50	2.61	3.70	-0.28	-13.50	22.00	110.00	45.50	-4.00	68.00	55.00	797.00	31540.00	206.50
at least 4/5 KD criteria — no 4/5 criteria	-4.00	-0.40	-1.50	0.52	17.50	26.00	17.90	-17.50	2.50	-270.00	-37.25	-416.00	-1715.00	-75.00
PIMS-TS CAA+ or 4/5 KD criteria — KD 4/5 CAA+ or 4/5 criteria	5.80	3.55	6.47	-2.17	-21.50	-198.00	221.00	-11.50	-14.00	402.00	32.50	1985.00	682.00	NA
PIMS-TS CAA+ or 4/5 KD criteria — KD shock CAA+ or 4/5 criteria	4.21	5.60	8.45	-0.86	-17.50	-74.00	109.00	-37.50	-6.50	341.00	32.50	820.00	442.50	NA

eTable 1. Differences in median values for all categories on the x-axis in Figure 1 and eFigures 1,3,4,5,6,7. Red indicates an increase in median value between comparisons and blue indicates a decrease in median value. Colour coding by each column, in a 3-color scale with red indicating the highest value for the column, blue indicating the lowest value for the column and grey for 0 values. WBC = white blood cell count Hb= haemoglobin, PLT = platelet number, CRP = C reactive protein, ALT = alanine aminotransferase, BNP = N terminal pro B-type natriuretic peptide, LDH Lactate dehydrogenase KD = Kawasaki disease TSS =toxic shock syndrome CAA = coronary artery aneurysm

Whittaker and colleagues. *JAMA*. doi:10.1001/jama.2020.10369

MMWR

- Latent class analysis (LCA), a statistical modeling technique that can divide cases into groups by underlying similarities, was used to identify and describe differing manifestations in patients who met the MIS-C case definition

- The indicator variables used in the LCA were the presence or absence of SARS-CoV-2–positive test results by (RT-PCR) or serology, shock, pneumonia, and involvement of organ systems

https://www.cdc.gov/mmwr/volumes/69/wr/pdfs/mm6932e2-H.pdf

Class 1

- 203 (35.6%) patients who had the highest number of involved organ systems
- 99 (48.8%) had involvement of ≥6 organ systems
- The most commonly affected systems were cardiovascular (100.0%) and gastrointestinal (97.5%)

https://www.cdc.gov/mmwr/volumes/69/wr/pdfs/mm6932e2-H.pdf

Class 1

- Compared with the other classes, patients in class 1 had significantly higher prevalence of abdominal pain, shock, myocarditis, lymphopenia, markedly elevated CRP, ferritin, troponin (indicative of cardiac damage), brain natriuretic peptide (BNP), or proBNP (indicative of heart failure) ($p<0.01$)

- Almost all class 1 patients (98.0%) had positive SARS-CoV-2 serology test
- These cases closely resembled MIS-C without overlap with acute COVID-19 or Kawasaki disease

https://www.cdc.gov/mmwr/volumes/69/wr/pdfs/mm6932e2-H.pdf

Class 2

- 169 (29.6%) patients
- These patients were significantly more likely to have cough, shortness of breath, pneumonia, and acute respiratory distress syndrome (ARDS)
- 129 (76.3%) had respiratory system involvement
- These cases closely resembled acute COVID-19 or a combination of acute COVID-19 and MIS-C

https://www.cdc.gov/mmwr/volumes/69/wr/pdfs/mm6932e2-H.pdf

Class 2

- The rate of SARS-CoV-2 RT-PCR positivity (without seropositivity) in this group (84.0%) was significantly higher than that for class 1 (0.5%) or class 3 (2.0%) patients ($p<0.01$)
- The case fatality rate among class 2 patients was the highest (5.3%) among all three classes ($p<0.01$)

https://www.cdc.gov/mmwr/volumes/69/wr/pdfs/mm6932e2-H.pdf

Class 3

- Class 3 patients more commonly met criteria for complete Kawasaki disease (6.6%) compared with class 1 (4.9%) and class 2 (3.0%) patients (p = 0.30), and had the lowest prevalence of underlying medical conditions, organ system involvement, complications (e.g., shock, myocarditis), and markers of inflammation and cardiac damage

https://www.cdc.gov/mmwr/volumes/69/wr/pdfs/mm6932e2-H.pdf

Class 3

- 198 (34.7%) patients
- The median age (6 years) was younger than that of the class 1 patients (9 years) or class 2 patients (10 years) ($p<0.01$)
- The highest prevalence of rash (62.6%), and mucocutaneous lesions (44.9%)
- Although not statistically significant ($p = 0.49$), the prevalence of CAD (18.2%) was higher than that in class 2 patients (15.8%), but lower than that in class 1 patients (21.1%)

https://www.cdc.gov/mmwr/volumes/69/wr/pdfs/mm6932e2-H.pdf

- Among class 3 patients, 63.1% had positive SARS-CoV-2 serology only and 33.8% had both serologic confirmation and positive RT-PCR results

https://www.cdc.gov/mmwr/volumes/69/wr/pdfs/mm6932e2-H.pdf

Different Multisystem inflammatory syndrome phenotypes

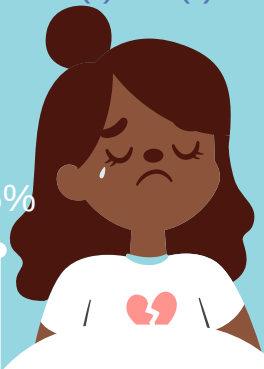
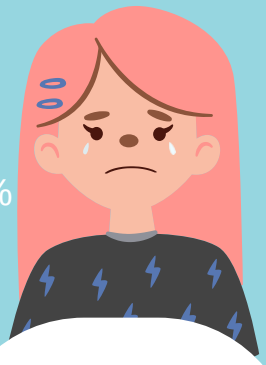
Median age

Symptoms

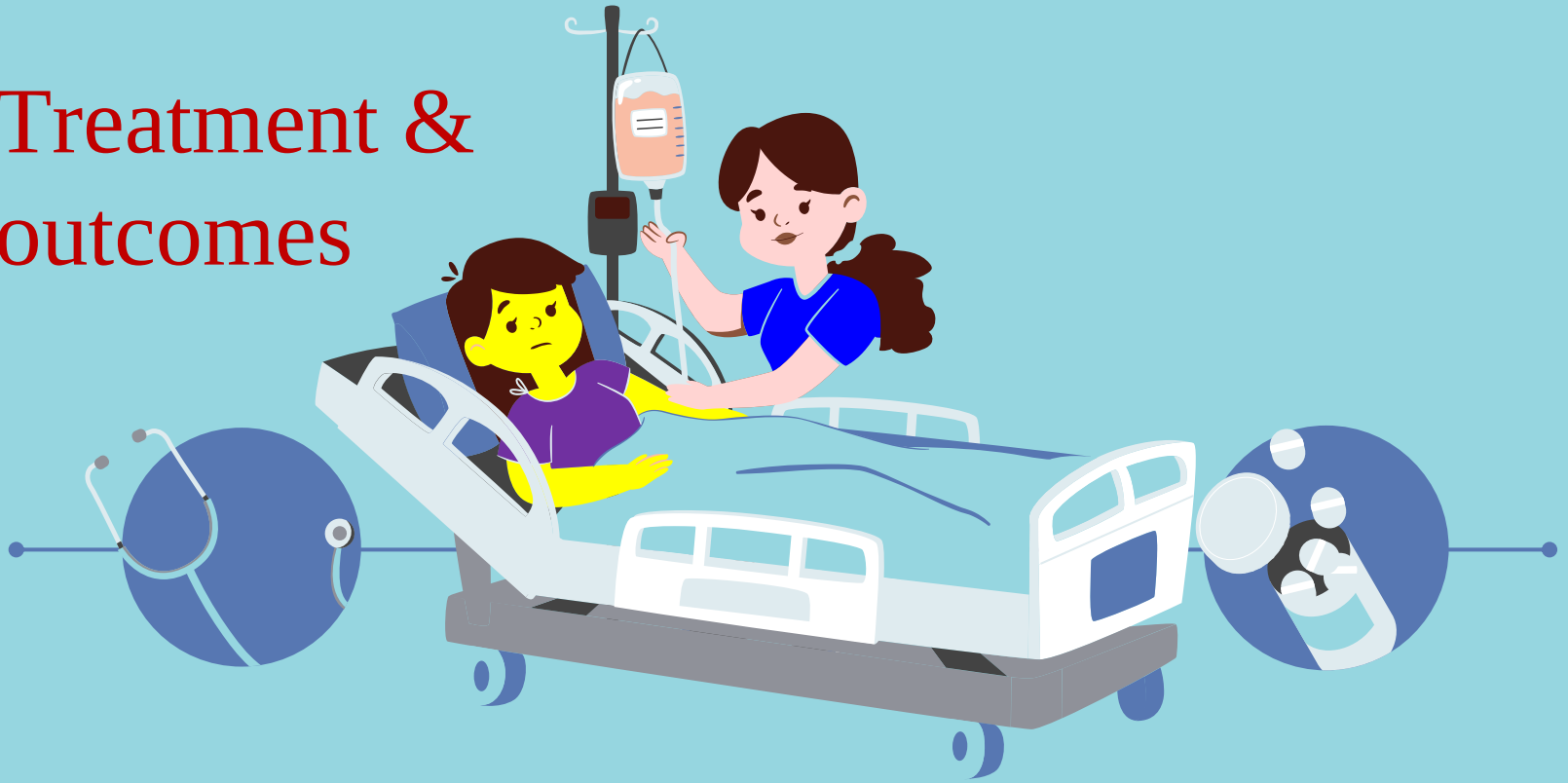
Acute phase reactants

COVID-PCR/-Serology

Mortality

MIS-C acute COVID-19 (-)/KD(-)	MIS-C with severe acute COVID-19	MIS-C with Kawasaki dis.
35%	30%	35%
		
9 yr	10 yr	6 yr
Cardiovascular (+), GI (+), ≥4 organ involvement, shock, cardiac dysfunction	Respiratory involvement (cough, dyspnea, pneumonia, ARDS)	Rash and mucocutaneous involvement, shock (±), cardiac dysfunction (±)
↑↑	20 mg/dl>	20 mg/dl>
±/≈100%	≈100%/≈(-)	++/+
0.5%	5.3%	0%

Treatment & outcomes



- There are currently insufficient data for the NIH-COVID-19 Treatment Guidelines Panel to recommend either for or against any therapeutic strategy for the management of MIS-C [*Last Updated: June 11, 2020*]
  - Intravenous immune globulin
  - Steroids
  - Immunomodulators (including interleukin-1 and interleukin-6 inhibitors)
  - Antiplatelet and anticoagulant therapy
  - The role of antiviral medications that specifically target SARS-CoV-2 is not clear at this time
- MIS-C management decisions should involve a multidisciplinary team of pediatric specialists in intensive care, infectious diseases, cardiology, hematology, and rheumatology

https://www.covid19treatmentguidelines.nih.gov/special-populations/children/

	Royal College of Paediatrics and Child Health[39]	US Centers for Disease Control and Prevention[37]
Supportive care	Only recommended for mild to moderate disease; discuss early with paediatric intensive care unit and paediatric infectious disease, immunology, and rheumatology team; if clinically deteriorating or in cases of severe disease, discuss transfer with paediatric intensive care unit retrieval teams	Fluid resuscitation, inotropic support, respiratory support, and in rare cases, extracorporeal membranous oxygenation
Directed care against underlying inflammatory process	Immunotherapy should be discussed with a paediatric infectious diseases unit and experienced clinicians on a case-by-case basis and used in the context of a trial if eligible and available	Intravenous immunoglobulin, steroids, aspirin, and anticoagulation treatment
Antiviral therapy	Should be given only in the context of a clinical trial and should be discussed at multidisciplinary team meetings with a clinician from an external trust	..
Antibiotics for sepsis	..	Given while waiting for bacterial cultures
Other	All children treated as if they have COVID-19 and all should be considered for recruitment in research studies	..

Published guidance on the management of multisystem inflammatory syndrome in children associated with COVID-19

Characteristic	No. (%)[a]											
	All PIMS-TS cases (n = 58)[b]	Febrile and inflammatory (n = 23)[c]	Stratification by shock[d]		Stratification by Kawasaki disease[e]		Stratification by Kawasaki clinical criteria[e]		Stratification by coronary artery aneurysm[f]		Stratification by evidence of SARS-CoV-2 infection[g]	
			Shock present (n = 29)	Shock absent (n = 29)	Kawasaki disease (n = 13)	Not Kawasaki disease (n = 45)	Criteria met (n = 7)	Criteria not met (n = 51)	Present (n = 8)	Absent (n = 50)	Positive (n = 45)	Negative (n = 13)
Respiratory												
Intubation	25 (43)	2 (9)	23 (79)	2 (7)	5 (38)	20 (44)	1 (14)	24 (47)	5 (63)	20 (40)	20 (45)	5 (36)
Pharmacotherapy												
Intravenous immunoglobulin	41 (71)	14 (61)	21 (72)	20 (69)	13 (100)	28 (62)	7 (100)	34 (68)	8 (100)	33 (66)	33 (75)	8 (57)
Corticosteroids	37 (64)	12 (52)	19 (66)	18 (62)	12 (92)	25 (56)	7 (100)	30 (59)	7 (88)	30 (60)	33 (75)	4 (29)
Anakinra (IL-1 receptor antagonist)	3 (5)	1 (4)	2 (7)	1 (3.4)	0	3 (7)	0	3 (6)	0	3 (6)	2 (5)	1 (8)
Infliximab (TNF-α antagonist)	8 (14)	4 (17)	2 (7)	6 (21)	4 (31)	4 (9)	3 (43)	5 (19)	3 (38)	5 (10)	7 (16)	1 (8)
No. of immunomodulatory agents												
2[i]	35 (60)	11 (48)	18 (62)	17 (59)	12 (92)	23 (51)	7 (100)	28 (55)	7 (88)	28 (56)	32 (71)	3 (23)
3[j]	11 (19)	4 (17)	3 (10)	6 (21)	4 (31)	5 (11)	3 (43)	6 (12)	3 (38)	6 (12)	8 (18)	1 (8)
Outcomes												
Coronary artery aneurysm (z score >2)	8 (14)	1 (4)	5 (17)	3 (10)	8 (62)	0	1 (14)	7 (14)	8 (100)	0	6 (13)	2 (15)
Death	1 (2)	0	1 (3)	0	0	1 (2)	0	1 (2)	0	1 (2)	1 (2)	0

Two/three agents of intravenous immunoglobulin, corticosteroids, anakinra, or infliximab were given to manage inflammation

Whittaker and colleagues. *JAMA*. doi:10.1001/jama.2020.10369

published on June 29, 2020, at: NEJM.org. N Engl J Med 2020;383:347-58.DOI: 10.1056/NEJMoa2021756

Clinical Course and Outcomes, According to Age Group

Variable	Overall (N=99)	0–5 Years (N=31)	6–12 Years (N=42)	13–20 Years (N=26)
Median time from symptom onset to hospital admission (IQR) — days	4 (3–6)	4 (3–6)	5 (4–5)	4 (3–6)
ICU admission — no. (%)	79 (80)	19 (61)	38 (90)	22 (85)
Median time to ICU entry (IQR) — days	0 (0–1)	0 (0–2)	0 (0–1)	0 (0–1)
Median length of stay (IQR) — days				
Overall	6.0 (4.0–9.0)	6.0 (3.0–8.0)	6.0 (4.0–10.0)	6.5 (6.0–10.0)
Among those discharged	6.0 (4.0–8.0)	5.0 (3.0–7.0)	4.0 (4.0–8.0)	6.0 (5.0–10.0)
Therapy — no. (%)				
BiPAP or CPAP†	7 (7)	1 (3)	3 (7)	3 (12)
High-flow nasal cannula†	16 (16)	1 (3)	10 (24)	5 (19)
Mechanical ventilation†	10 (10)	3 (10)	3 (7)	4 (15)
ECMO	4 (4)	1 (3)	2 (5)	1 (4)
Vasopressor support	61 (62)	15 (48)	29 (69)	17 (65)
Systemic glucocorticoids	63 (64)	16 (52)	30 (71)	17 (65)
IVIG	69 (70)	26 (84)	30 (71)	13 (50)
Systemic glucocorticoids and IVIG	48 (48)	15 (48)	25 (60)	8 (31)

	Patients with 4 or 5 Features (N = 38)	Patients with 2 or 3 Features plus Laboratory Findings (N = 36)	Other (N = 112)†	All Patients (N = 186)
Clinical Characteristics of the Patients According to the Number of Kawasaki's Disease–like Features Present				
Treatment				
Intravenous immune globulin — no. (%)	38 (100)	35 (97)	71 (63)	144 (77)
Median day of illness on which treatment was received (IQR)	6 (6–8)	7 (6–8)	6 (5–8)	6 (5–8)
Second dose received — no. (%)	16 (42)	9 (25)	14 (12)	39 (21)
Systemic glucocorticoid — no. (%)	20 (53)	18 (50)	53 (47)	91 (49)
Interleukin-6 inhibitor — no. (%)‖	1 (3)	1 (3)	12 (11)	14 (8)
Interleukin-1Ra inhibitor — no. (%)**	5 (13)	6 (17)	13 (12)	24 (13)
Anticoagulation therapy — no. (%)††	14 (37)	18 (50)	55 (49)	87 (47)

Published on June 29, 2020, and updated on July 2, 2020, at NEJM.org. N Engl J Med 2020;383:334-46. DOI: 10.1056/NEJMoa2021680

Characteristics of patients (N = 570) reported with multisystem inflammatory syndrome in children (MIS–C) United States, March–July 2020

Characteristic	No. (%)				p value
		Latent class analysis group*			
	Total (N = 570)	Class 1 (n = 203)	Class 2 (n = 169)	Class 3 (n = 198)	
Treatment					
IVIG	424 (80.5%)	174 (87.9%)	96 (62.7%)	154 (87.5%)	<0.01
Steroids	331 (62.8%)	145 (73.2%)	80 (52.3%)	106 (60.2%)	<0.01
Antiplatelet medication	309 (58.6%)	113 (57.1%)	69 (45.1%)	127 (72.2%)	<0.01
Anticoagulation medication	233 (44.2%)	92 (46.5%)	76 (49.7%)	65 (36.9%)	0.03
Vasoactive medications	221 (41.9%)	129 (65.2%)	64 (41.8%)	28 (15.9%)	<0.01
Respiratory support, any	201 (38.1%)	104 (52.5%)	79 (51.6%)	18 (10.2%)	<0.01
Intubation and mechanical ventilation	69 (13.1%)	37 (18.7%)	30 (19.6%)	2 (1.1%)	<0.01
Immune modulators	119 (22.6%)	52 (26.3%)	34 (22.2%)	33 (18.8%)	0.18
Dialysis	2 (0.4%)	0 (0.0%)	2 (1.3%)	0 (0.0%)	0.08

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https://www.cdc.gov/mmwr/volumes/69/wr/pdfs/mm6932e2-H.pdf

THE LANCET
Infectious Diseases

Characteristics	Events	Total No.	Pooled mean proportion % (95%CI)	Heterogeneity I^2 (%)
Pooled meta-analysis of demographic and clinical characteristics of MIS-C/PIMS-TS patients				
Treatment				
ICU admission	481	606	79.1 (70.8-85.5)	61.7
Mechanical ventilation	187	648	29.2 (19.9-40.5)	79.3
ECMO	32	525	7.6 (4.1-13.8)	57.1
Outcomes				
Recovered	530	619	91.1 (82.3-95.7)	76.8
Death	11	625	3.5 (2.2-5.5)	0

Supplement to: Jiang L, Tang K, Levin M, et al. COVID-19 and multisystem inflammatory syndrome in children and adolescents. Lancet Infect Dis 2020; published online August 17. https://doi.org/10.1016/S1473-3099(20)30651-4

PEDIATRIC INFECTIOUS DISEASES SOCIETY

The Pediatric Infectious Disease Journal

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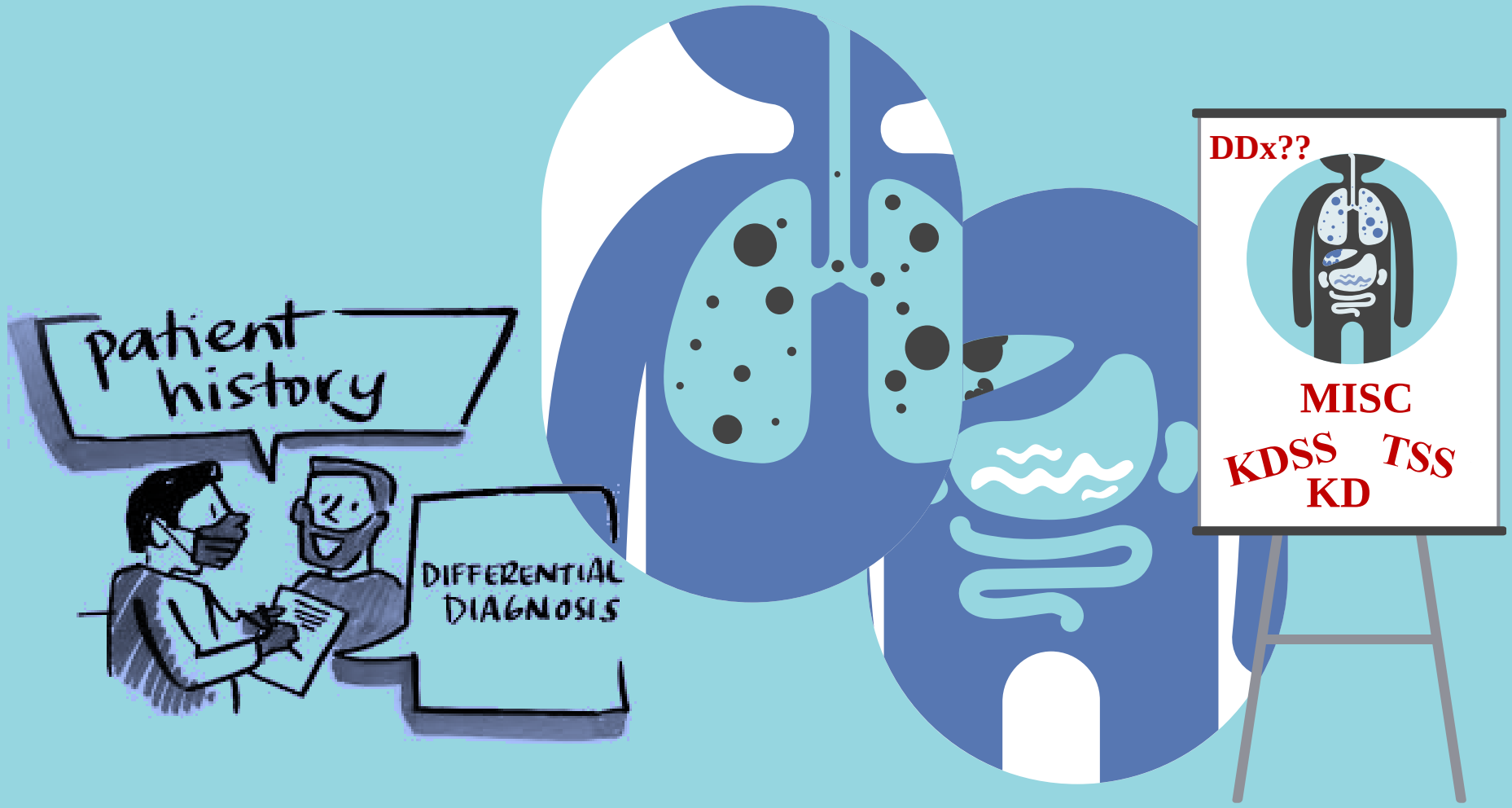
	IVIG	Aspirin	Methylprednisolone or prednisone	Anticoagulation	Infliximab	Anakinra	Tocilizumab	Vasoactive Agents	Mechanical Ventilation	ECMO
Pain, Lancet Rheum[4]	-	1	-	-	-	1	-	1	1	0
Balasubramanian, IndJPeds[15]	1	1	0	0	-	0	1	-	-	-
Belhadjer, Circulation[16]	25	-	12	23	-	3	0	28	22	10
Cabrero-Hernandez, PIDJ[17]	-	-	5	5	-	-	4	4	1	0
Deza-Leon, JPIDS[18]	1	1	-	1	-	-	-	1	1	1
Grimaud, An Crit Care[19]	20	-	2	-	-	1	1	19	8	0
Oberweis, PIDJ[20]	1	-	-	1	-	-	1	1	-	-
Rauf, Ind J Peds[21]	1	1	1	-	-	-	-	1	-	-
Verdoni, Lancet[5]	10	2	8	0	0	0	0	2	-	-
Toubiana, BMJ[22]	21	21	7	-	-	-	-	15	11	0
Jones, Hosp Pediatr[23]	1	1	-	-	-	-	-	-	-	-
Miller, Gastroenterology[8]	36	0	42	40	0	8	0	.	1	0
Dolinger, JPGN[24]	-	-	-	1	1	-	-	-	-	-
Feldstein, LR, NEJM[9]	144		91	87	-	24	14	90	37	8
DufortNEJM[12]	69		63					61	10	4
DaviesLancetChAdol[14]	59	45	57	39	7	8	3	65	36	3

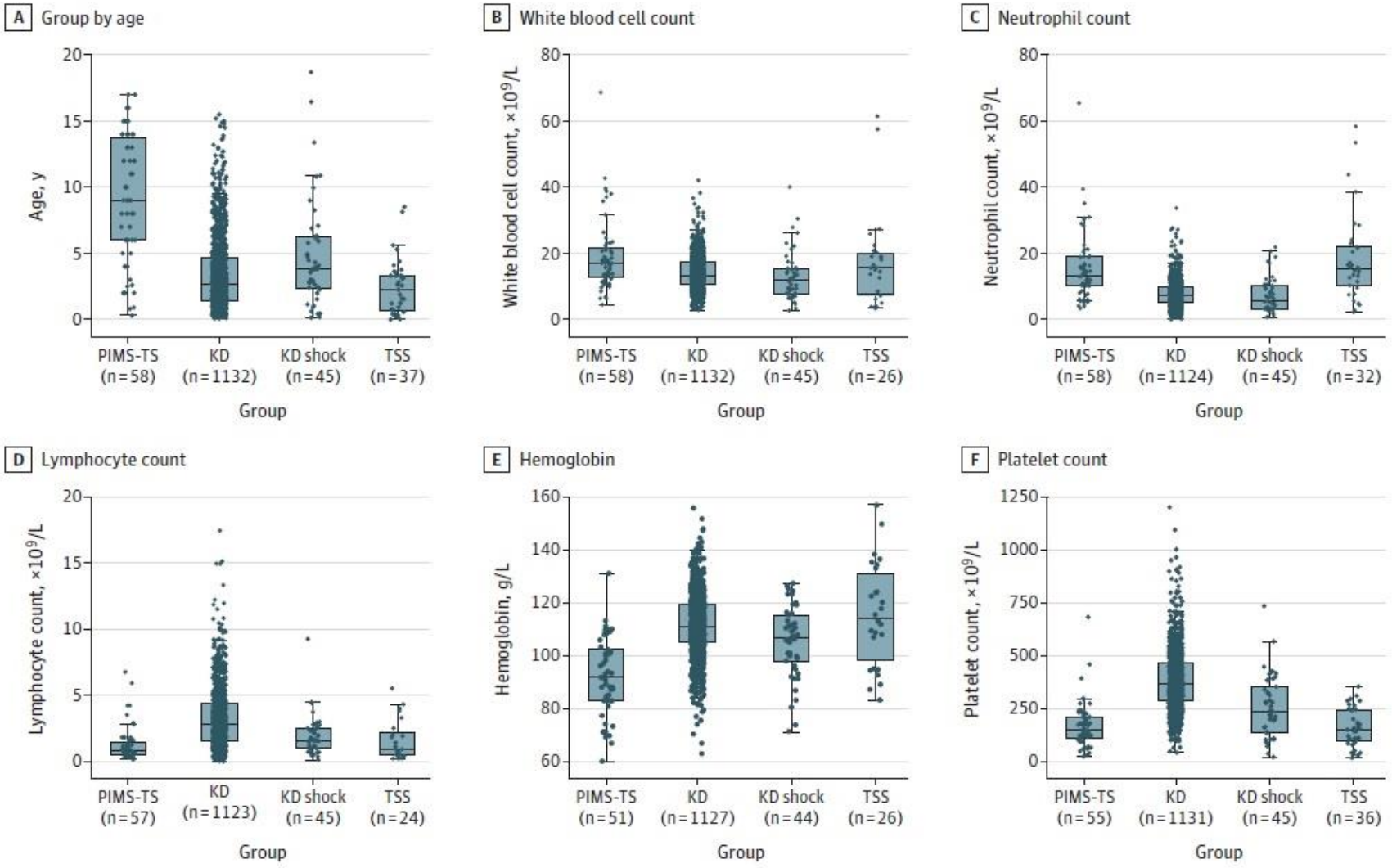
DOI: 10.1093/jpids/piaa112

Therapeutic Interventions	Number of positives (n)	Number of Reported Cases (n)	Percent
IVIG	389	498	78.1%
aspirin	73	158	46.2%
methylprednisolone/prednisone	288	500	57.6%
anticoagulation	197	362	54.4%
infliximab	8	133	6.0%
anakinra	45	375	12.0%
tocilizumab	24	380	6.3%
ionotropic agents	288	502	57.4%
mechanical ventilation	128	490	26.1%
extracorporeal membrane oxygenation	26	490	5.3%
Outcome			
survived	415	505	82.2%
died	7	505	1.4%
unresolved at time of report	82	505	16.2%

DOI: 10.1093/jpids/piaa112


patient history
DIFFERENTIAL DIAGNOSIS
DDx??
MISC
KDSS
TSS
KD

Whittaker and colleagues. *JAMA*. doi:10.1001/jama.2020.10369



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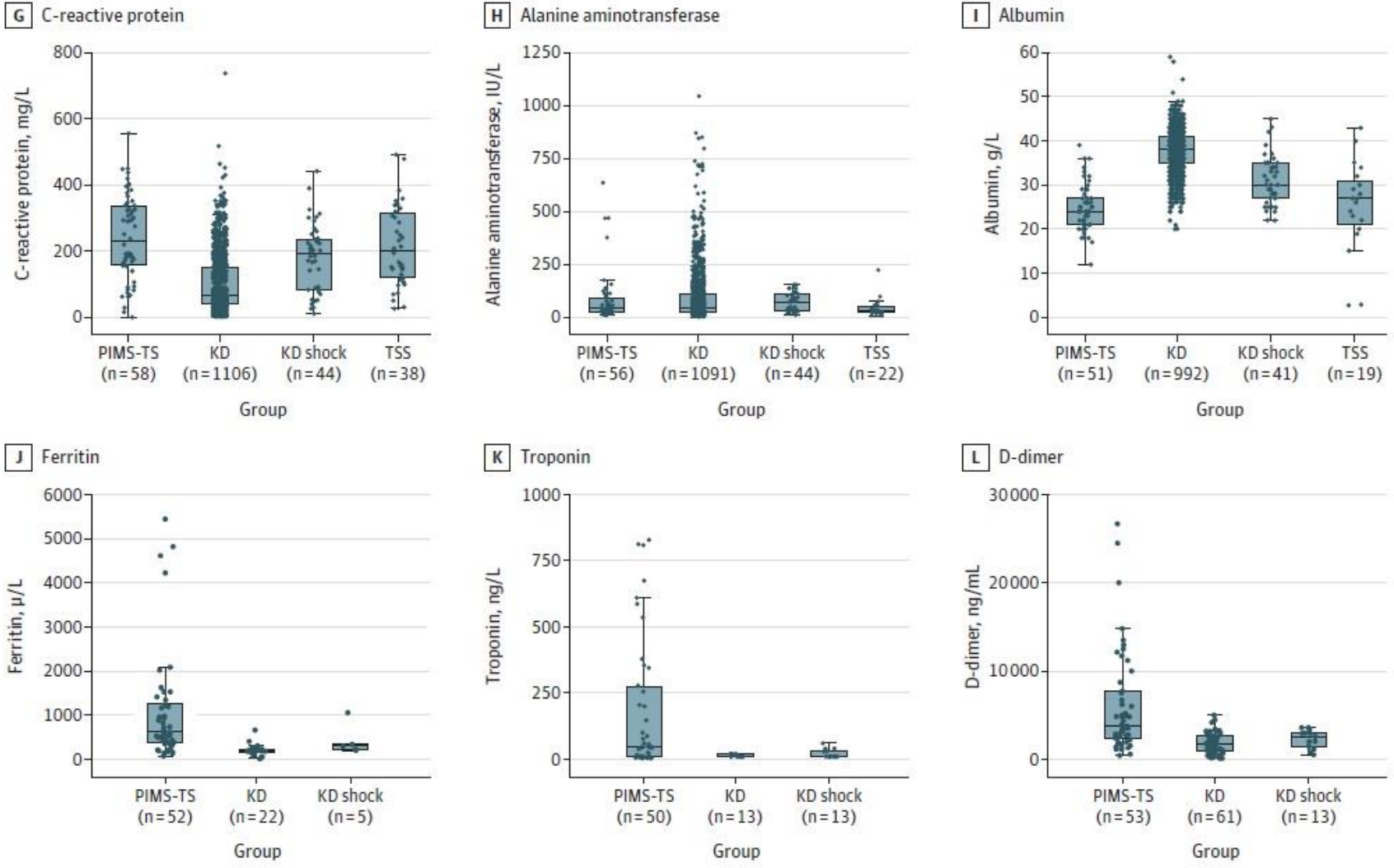

Differences in medians	Age (years)	Total white cell count *10^9/L	Neutrophil count *10^9/L	Lymphocyte count *10^9/L	Haemoglobin g/L	Platelet number (*10^9/L)	CRP (mg/L)	ALT (IU/L)	Albumin (g/L)	FerritiN (mg/L)	NT-Pro-BNP (pg/ml)	Troponin (ng/L)	D-dimer (ng/ml)	LDH (U/L)
PIMS-TS — KD	6.30	3.60	5.92	-1.96	-1.90	-214.00	161.95	-0.50	-14.00	420.50	35.05	2100.00	NA	NA
PIMS-TS — KDshock	5.18	4.90	7.56	-0.76	-1.45	-84.00	36.45	-31.00	-6.00	319.50	35.05	1170.00	NA	NA
PIMS-TS — TSS	6.75	1.38	-2.36	-0.09	-2.20	6.00	27.60	11.50	-3.00	NA	NA	NA	NA	NA

Differences in median values for all categories on the x-axis in Figure 1 and eFigures 1,3,4,5,6,7. Red indicates an increase in median value between comparisons and blue indicates a decrease in median value. Colour coding by each column, in a 3-color scale with red indicating the highest value for the column, blue indicating the lowest value for the column and grey for 0 values. WBC = white blood cell count Hb= haemoglobin, PLT = platelet number, CRP = C reactive protein, ALT = alanine aminotransferase, BNP = N terminal pro B-type natriuretic peptide, LDH Lactate dehydrogenase KD = Kawasaki disease TSS =toxic shock syndrome CAA = coronary artery aneurysm

Whittaker and colleagues. *JAMA*. doi:10.1001/jama.2020.10369