Clinical and laboratory characteristics of 58 children with a pediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2.

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KEY POINTS:

Question: What are the clinical and laboratory characteristics of critically ill children who developed an inflammatory multisystem disorder during the COVID-19 pandemic?

Findings: This case series included 58 hospitalized children, a subset of whom required intensive care, and met definitional criteria for pediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2 (PIMS-TS), including fever, inflammation, and organ dysfunction. Of these children, all had fever and non-specific symptoms such as vomiting, 31 (53%) had rash and conjunctival injection, 29 (50%) developed shock and required inotropic support or fluid resuscitation, 13 (22%) met diagnostic criteria for Kawasaki disease, and 8 (14%) had coronary artery dilatation or aneurysms . Some of the clinical and laboratory characteristics had important differences compared with Kawasaki disease, Kawasaki disease shock syndrome, and toxic shock syndrome.

Meaning: These findings help characterize the clinical features of hospitalized, critically ill children with PIMS-TS and may provide insights into this apparently novel syndrome.

ABSTRACT

Importance

In communities with high rates of COVID-19, reports have emerged of children with an unusual syndrome of fever and inflammation.

Objectives

To describe the clinical and laboratory characteristics of hospitalized patients who met criteria for the pediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2 (PIMS-TS) and compare these characteristics with other pediatric inflammatory disorders.

Design, Setting, and Participants

Case series of 58 children from 8 hospitals in England who were admitted between March 23 and May 16, 2020, with persistent fever, and laboratory evidence of inflammation meeting recently published definitions for pediatric inflammatory multisystem syndromes temporally associated with SARS-CoV-2; the final date of followup was May 22, 2020. Clinical and laboratory characteristics were abstracted by chart review and summarized, and were compared with clinical characteristics of patients with Kawasaki disease (n=1132), Kawasaki disease shock syndrome (n=45), and toxic shock syndrome (n=37) who had been in patient cohorts admitted to hospitals in Europe and the United States from 2002-2019.

Exposures.

Signs, symptoms and investigation findings that met definitional criteria for PIMS-TS based on definitions from the United Kingdom, the United States, or the World Health Organization.

Main Outcomes and Measures

Clinical and laboratory characteristics of children meeting definitional criteria for PIMS-TS, and comparison with the characteristics of other pediatric inflammatory disorders.

Results

Fifty-eight children (median age 8 years, IQR 5.7-14; 33 (57%) female) were identified who met the criteria for PIMS-TS. SARS-CoV-2 PCR was positive in 15/58 patients and SARS-CoV-2-IgG positive in 40/46 tested. In total, 45/58 patients had evidence of current or prior SARS-CoV-2 infection. All presented with fever and non-specific symptoms, including vomiting 26/58 (45%)

abdominal pain 31/58 (53%) and diarrhea 30/59 (52%). Rash was present in 30/58 (52%), and conjunctival injection in 26/58 (45%) of cases. Laboratory evaluation was consistent with marked inflammation, for example CRP 229 mg/L (IQR 156-338), ferritin 610 µg/L (IQR 359-1280) and neutrophilia 13 x10*^{9}/L (IQR 10-19). Of the 58 children, 29 developed shock requiring inotropic support and fluid resuscitation (including 23/29 [79%] who received mechanical ventilation; 13 who met the American Heart Association definition of Kawasaki disease, and 23 who had fever and inflammation without features of shock or Kawasaki disease. Patients who developed shock (n=29) had biochemical evidence of myocardial dysfunction, including 19 of 28 tested with elevated serum troponin [median 124 ng/L; IQR 45-97] and 11 of 11tested with elevated serum N-terminal pro B-type natriuretic peptide(NT-pro-BNP) concentrations [median pg/ml 14017; IQR 7004-35000)]. Comparison with Kawasaki disease and with Kawasaki disease shock syndrome, showed differences in clinical and laboratory features including older age (PIMS-TS-median age 8 years, IQR 5.7-14; 33 ;Kawasaki disease – 2.7yrs; IQR 1.4-4.7, Kawasaki disease with shock syndrome 3.8yrs; IQR 0.2-18yrs), and greater elevation of inflammatory markers such as CRP (PIMS-TS median 229 mg/L (IQR 156-338) , Kawasaki disease – 67g/L; IQR 40-150 g/L, Kawasaki shock syndrome median 193 mg/L(IQR83-237)).

Conclusions and relevance

In this case series of hospitalized children who met criteria for PIMS-TS, there was a wide spectrum of presenting signs and symptoms and disease severity, ranging from fever and inflammation to myocardial injury, shock, and development of coronary artery aneurysms. The comparison with patients with Kawasaki disease and Kawasaki disease shock syndrome may provide insights into this syndrome, and suggests this disorder differs from other pediatric inflammatory entities.

Background

From March through May 2020, during the COVID-19 pandemic, pediatricians in the UK and elsewhere noted hospitalizations of children who developed fever and multisystem inflammation. Some of these children were critically ill with shock and multi-organ failure and required intensive care[1-3], and some had characteristics that were similar to Kawasaki disease or Kawasaki disease shock syndrome[4,5]. The clinical evidence suggested the emergence of a pediatric multisystem inflammatory syndrome temporally associated with SARS-CoV-2 (PIMS-TS) [6-8]. The purpose of this study was to describe the clinical and laboratory characteristics of patients who met criteria for the pediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2 (PIMS-TS) and assess its similarity to other pediatric inflammatory disorders.

Methods

The study had approval from local clinical research offices in the United Kingdom. The review of patient records was registered as an audit (Great Ormond Street Hospital , and anonymized patient data were collated without informed consent.

Inclusion of patients with Kawasaki Disease and Kawasaki Disease shock syndrome was approved by the Institutional Review Board at the University of San Diego following informed consent from parents/guardians. Inclusion of patients with toxic shock syndrome from the EUCLIDS and PERFORM studies was approved by the UK research ethics bodies and ethics board of individual partners. Informed consent from parents/guardians was obtained for these patient cohorts.

Case ascertainment

Following the initial National Health Service (UK) alert and publication of the Royal College of Paediatrics and Child Health definition[7] the World Health Organisation (WHO), and US Centers for Disease Control and Prevention (CDC) and European Centre for Disease Prevention and Control[6,8,9] have all produced definitions for the childhood inflammatory disorder which has emerged as the COVID-19 pandemic evolved in different countries (Table 1). All definitions had been developed based on a limited number of unpublished cases. The CDC and WHO definitions include laboratory

evidence of SARS-CoV-2 exposure, or history of contact with SARS-CoV-2 in the preceding month. In this study, we included children who met the UK, CDC or WHO definitions for (PIMS-TS), without requiring proof of SARS-CoV-2 exposure, and investigated the value of this requirement in our analysis. Admission notes and transfer documents, including transfer letters and copies of referring hospital medical notes when available, were reviewed. Data was extracted from both electronic and paper records. Any report of mucocutaneous features during the course of the illness was recorded. Race/Ethnicity was determined by parent report. The American Heart Assocation (AHA) criteria for Kawasaki disease were used to define cohorts as follows -persistent fever and 4/5 mucocutaneous features: Erythema and cracking of lips, strawberry tongue, and/or erythema of oral and pharyngeal mucosa; bilateral bulbar conjunctival injection without exudate; rash: maculopapular, diffuse erythroderma; erythema and edema of the hands and feet in acute phase and/or periungual desquamation in subacute phase; cervical lymphadenopathy (>1.5cm diameter) [10]. Clinical Patterns were established by defining shock (inotrope use or fluid resuscitation >20ml/kg), meeting AHA criteria with 4/5 mucocutaneous clinical features of Kawasaki disease as described above, coronary artery aneurysms (z score >2 in the acute phase or >2.5 in the sub-acute or late phase) were considered dioagnostic of Kawasaki disease in children without 4/5 clinical features. A final cohort of fever and inflammation included all those children who did not have shock, nor met the clinical criteria for Kawasaki disease. SARS-CoV-2 IgG was measured using EDI Novel Coronavirus COVID-19 IgG ELISA Kit.

Comparison with Kawasaki disease, and Kawasaki disease shock syndrome and toxic shock syndrome.

Because some features of the children who met criteria for PIMS-TS overlapped with features of Kawasaki disease and the Kawasaki disease shock syndrome, clinical features of cases were compared with patients with Kawasaki Disease and those with Kawasaki disease shock syndrome, seen between 2002 and 2019 at Rady Children's Hospital San Diego. Clinical features also were compared with those of children with toxic shock syndrome from the PERFORM and EUCLIDS studies of febrile children in the European Union who were seen between 2012 and 2020 (details in eAppendix).

Statistical analysis.

Clinical characteristics and laboratory and other measurements were compared descriptively between the children who met criteria for PIMS-TS and children with Kawasaki disease, Kawasaki disease shock syndrome, and toxic shock syndrome cases from the previous cohorts. Because of the small number of cases and large number of comparisons, formal statistical testing was not conducted; the findings should be interpreted as descriptive and exploratory. Descriptive statistics were analyzed in R. [11]

Results

Between March 25th and May 20th 2020, 58 children who had been admitted to 8 hospitals in England were identified by invited survey and considered to meet the PIMS-TS criteria (Table 1). Eight of the children in this study have previously been reported[2].

Clinical characteristics of patients

The median age was nine years (IQR 5.7-14, range 3 months to 17 years), 33/58 (57%) were female, and 40/58 (69%) of patients were from Black, Asian, and minority ethnic groups (Table 2). The majority were previously healthy and only 7 had comorbidities, including 3 with asthma, 1 with neurodisability, 1 with epilepsy, 1 with sickle cell trait and 1 with alopecia.

All patients presented with persistent fever for 3 to 19 days and variable combinations of sore throat, 6 (10%), headache, 15 (26%) and abdominal pain, 31 (53%). Erythematous rashes (one patient had purpuric features) were present in 30 (52%). Conjunctival injection was noted in 26 (45%); lymphadenopathy in 9 (16%); mucus membrane changes and red cracked lips in 17 (29%), swollen hands and feet in 9 (16%). Admission to pediatric critical care units was required in 29 (50%) of the patients. Shock requiring inotropic support was present in 27 (47%) of the patients. Mechanical or non-invasive ventilation was used for respiratory support in 25 (43%) of the patients (Table 3).

SARS-CoV-2 Test results.

PCR tests to detect SARS-CoV-2 were positive in 26% (15) (Table 4). IgG antibody against SARS-CoV-2 was tested in 46 of the patients and was positive in 40 (87%) of these (IgG antibody was not tested in 21% (12/58) and was negative in 13% (6/46). There were no meaningful differences in clinical and laboratory features between patients who either were not tested for SARS-CoV-2

antibody, or who had negative results on both antibody and PCR tests compared with patients who tested positive for SARS-CoV-2, or between patients with or without confirmed exposure to SARS-CoV-2 (eFigure 1,eTable1)

Laboratory Investigations

All patients had evidence of a marked inflammatory state. (Table 4). For example, CRP (median 229mg/L; (IQR 156-338), neutrophilia (13x10*9/L; IQR 10-19) and ferritin (610ug/L; IQR 359-1280). Troponin concentrations were elevated in 68% (34/50), and N-terminal pro B-type natriuretic peptide (NT-pro-BNP) in 83% (24/29). This included two children who required extracorporeal membrane oxygenation (ECMO) for severe myocardial dysfunction.

Microbiological and virological investigations

Blood cultures, surface swabs and cultures to detect staphylococci and streptococci in all patients were negative. Respiratory viral screening, undertaken using a multiplex panel for a range of common respiratory viruses, identified adenovirus and enterovirus in one patient. One patient had significant EBV viremia; genetic and functional screening tests for familial hemophagocytic lymphocytic histiocytosis in this patient were negative.

Clinical course following admission

Examination of the clinical course suggested 3 provisional clinical patterns (Table 2, eFigure 2):

First, 23 children had persistent fever, elevated inflammatory markers, but no features of organ failure or mucocutaneous features suggestive of Kawasaki disease or toxic shock syndrome.

Second, 29 children developed shock, often associated with evidence of left ventricular dysfunction on echocardiography (62%, 18/29) and with elevation of troponin (66%, 19/29) and NT-Pro-BNP (100% and 11/11 tested). Four patients developed arrhythmia; one had first degree atrioventricular block with frequent supraventricular ectopic beats, another intractable broad complex tachycardia, associated with low cardiac output, necessitating extra corporeal membrane oxygenation (ECMO), one patient had atrial fibrillation managed with amiodarone and one had 2nd degree heart block, which resolved without treatment.

Third, 7 children fulfilled the AHA diagnostic criteria for Kawasaki disease. Of these, one progressed to shock. A total of 13 children met the criteria for Kawasaki disease when coronary artery aneurysms

were included. Of note only 55 children underwent echocardiography to assess for coronary artery aneurysms. Eight children had abnormally dilated coronary arteries (z score >2), including 7 with z score above 2.5. (Table 3) . Giant coronary artery aneurysms (z-score >10) were documented in two patients. Coronary artery aneurysms developed in a total of 8 children: 1(4%) in the fever and inflammation group, 6 (21%) in the group with shock, and 2 (29%) in those with mucocutaneous features of Kawasaki disease, one of whom was shocked.

Comparison of laboratory findings in patients with shock and coronary artery aneurysms

Children with PIMS-TS who developed shock (n=29) had numerically higher CRP and neutrophil counts, lower albumin, lower lymphocyte counts, and elevated troponin and NT-pro-BNP concentrations compared to those without shock. (Table 4; eFigure 3, eTable1). Laboratory findings among children who developed coronary artery dilatation or aneurysms were not meaningfully different from those without coronary artery aneurysms (eFigure 4, eTable1); neither were those in children who did and did not meet the clinical diagnostic criteria for Kawasaki disease (eFigure 5, eTable1).

Treatment

Inotropic support was required in 47%; 71% were treated with intravenous immunoglobulin and 64% with corticosteroids. Three patients received anakinra and eight infliximab (Table 3); 22% of the patients recovered with supportive care alone.

Comparison with other childhood inflammatory diseases.

The comparison groups of children from cohorts with other inflammatory diseases included 1132 patients (mean age 2.7yrs, range 0.1-15.5 yrs) with Kawasaki disease, 45 (mean age 3.8yrs, range 0.2-18yrs) with Kawasaki disease shock syndrome, and 37 (mean age 7.3yrs, range 2.4-15.4yrs) with toxic shock syndrome. Patients with PIMS-TS were generally older than those with Kawasaki disease or Kawasaki disease shock syndrome and had higher WBC, higher neutrophil count, and CRP, and more profound lymphopenia and anemia (Figure 1, eTables 1,2). They also tended to have lower platelet counts, higher fibrinogen levels, and greater elevation of troponin. Alanine aminotransferase

(ALT) levels and D-dimer levels were similar between PIMS-TS and Kawasaki disease and PIMS-TS and Kawasaki disease shock syndrome. Patients with PIMS-TS tended to be older than those with toxic shock syndrome. Hemoglobin levels were lower, while CRP and ALT were higher. Ferritin and troponin results were not available in the toxic shock syndrome group.

eFigure 6 shows that, overall, the children meeting the diagnostic criteria of Kawasaki disease in the PIMS-TS group (n=13) differed from those with Kawasaki disease pre-COVID-19; the PIMS-TS group who met the diagnostic criteria for Kawasaki disease tended to have higher age, neutrophil counts, CRP, ferritin, fibrinogen, troponin and lower lymphocyte counts.

Discussion

In this case series of 58 hospitalized children who met broad definitions for childhood inflammatory multisystem disorders recently proposed in the UK, USA, or by the WHO, [7-9] there was a wide spectrum of presenting signs and symptoms, including fever, gastrointestinal symptoms, and rash; and of disease severity, including myocardial injury, shock, and development of coronary artery aneurysms. Comparison with patients from other cohorts with Kawasaki disease, Kawasaki disease shock syndrome, and toxic shock syndrome provides additional insights into this syndrome, and suggests that PIMS-TS differs from other pediatric inflammatory entities.

Since the first reports of an unusual inflammatory illness in children that emerged in the months following the onset of COVID 19, there have been additional reports from many countries of children with fever and inflammation, for which no cause could be identified, first in health alerts and web exchanges between professional groups, and then in case reports and small case-series in rapid publications[2-4]. As these cases have emerged in temporal association with the pandemic, a link with SARS-CoV-2 is likely.

The cases reported in this study provide evidence of a wider spectrum of illness than identified in the initial UK definition and the early reports. In addition, there provisionally appears to be 3 main groups within the PIMS-TS spectrum. One group of children had persistent fever and elevated levels of inflammatory markers, but without features of Kawasaki disease, shock or organ failure. A second group fulfilled the diagnostic criteria for Kawasaki disease. A third group had shock and clinical,

echocardiographic, and laboratory evidence of myocardial injury. The clinical and laboratory features of these groups may provide useful insights to the new syndrome.

The initial reports of PIMS-TS were largely based on critically ill children who required intensive care support (including ECMO) for severe myocardial failure, and included fatal cases and cases with coronary artery aneurysms[1-4]. These reports raised concern among pediatricians and pediatric intensivists and among the public, as the likelihood of individual children progressing to shock or developing coronary artery aneurysms was unknown. Reports of these cases also raised questions as to whether all children with fever and elevated inflammatory markers required transfer to tertiary centres where ECMO or intensive cardiac support was available; what interventions were needed to prevent progressive myocardial involvement and development of coronary artery aneurysms; and whether treatment with intravenous immunoglobulin, (the established treatment for Kawasaki disease) or other immune modulating agents should be given based on the observed similarities to Kawasaki disease.

The current study provides some information that may be helpful in addressing various questions that have arisen with respect to PIMS-TS. PIMS-TS cases generally occurred in children older than those with Kawasaki disease and Kawasaki disease shock syndrome, and with different laboratory features. When PIMS-TS cases with coronary artery aneurysms were compared with pre-COVID-19 Kawasaki disease cases that developed coronary artery aneurysms, they tended to have higher age, more intense inflammation, and higher levels of markers of cardiac injury, suggesting that these are two separate entities. Treatment for PIMS-TS may need to be different than that for Kawaski's disease. Various biomarkers, including CRP, ferritin; troponin and NT-pro-BNP levels may be helpful in predicting progression of disease. Comparison of children with PIMS-TS who developed coronary artery dilatation or aneurysms with those who did not, failed to identify any differences in clinical or laboratory markers. Of particular concern was the finding that coronary artery aneurysms were found in a subset of all three groups of PIMS-TS. The lack of association either between the levels of inflammation in these groups, or markers of cardiac injury and development of coronary artery aneurysms, suggest that the coronary changes are not solely a consequence of severity of inflammation. The lack of any clinical and laboratory markers that identify patients who develop

coronary artery aneurysms, and the occurrence of coronary aneurysms in all three groups has implications for treatment and cardiac investigation. Children with Kawasaki disease require coronary echocardiography to detect coronary artery aneurysms, and the echocardiographic changes may either worsen or resolve, leading to recommendations for both acute echocardiographic studies, as well as sequential follow up at 2 and 6 weeks[10].The high NT-proBNP and troponin levels raise concern as to myocardial cell injury, and follow up of cardiac function as well echocardiographic studies to detect coronary artery aneurysms are warranted across the spectrum of PIMS-TS in both the acute and convalescent phases.

As an uncontrolled case series, this study does not provide evidence on effectiveness of treatment of PIMS-TS. Patients were treated with a range of immunomodulatory medications, according to local practice. Further studies will be needed to establish optimal treatment, and whether the same agents that show benefit in Kawasaki disease reduce both risk of coronary artery aneurysms and progression to severe illness, or whether other agents targeting specific inflammatory pathways or cells may be preferable.

This study has not addressed the mechanisms underlying PIMS-TS. However, the timing of the disorder emerging in relation to the epidemic, and the finding that the majority of patients were negative for detection of the virus but positive for antibody against SARS-CoV-2, raises the possibility that the disorder may involve an aberrant development of acquired immunity. There is evidence from SARS-CoV-1 that antibodies accentuate disease either through antibody enhancement of viral entry or replication as has been observed in Dengue[12], or through triggering of a host inflammatory response either through formation of immune complexes or direct anti-tissue or cellular activation. Anti-spike antibodies against SARS-CoV-1 have been shown to accentuate inflammation in primates and in human macrophages[13] and it is therefore possible that as antibodies develop against SARS-CoV-2 they may trigger an inflammatory process through a similar mechanism. The possibility that PIMS-TS arises from an unusual acquired immune response to SARS-CoV-2 (either antibody or T cell) has implications for development of vaccines, and thus the mechanisms require additional investigation.

Although this study has shown that PIMS-TS has differences from pre-COVID-19 Kawasaki disease, the similarity in clinical features in some cases and development of coronary artery aneurysms in both disorders may provide clues to the underlying mechanisms of both. Immune complexes have been well documented in Kawasaki disease[14,15] and may also mediate vascular injury, through activation of inflammatory responses through Fc Gamma receptor[16] or neutrophil activation[17]. In this study, the majority of patients with PIMS-TS were treated with intravenous immunoglobulin (IVIG) and/ or corticosteroids, and fewer patients received a range of other immunomodulating agents. In view of the extremely high CRP levels, IL6 may have a role in the myocardial depression[18,19], but clinicans are cautious about the use of toculizimab (anti-IL6) in those who meet criteria for Kawasaki disease[20].

Limitations

This study has several limitations. First, it was based on retrospective data collection from a number of hospitals, during a period before and during the development of the case definition. Investigations and management were individualized by centre and patient rather than following a standardized protocol. In addition, during this time PCR testing of stool was not routinely undertaken; hence, this was measured only in a very small group of children in this cohort, so conclusions could not be drawn. It is possible that viral replication is occurring in the gastrointestinal tract, endothelium, or myocardial tissue, but as these samples were not available, this mechanism cannot be explored.

Second, seroprevalence data in children within the UK are unavailable, so it is difficult to be certain of the background rate of SARS-CoV-2 IgG positivity in the population.

Third, there is no diagnostic test for Kawasaki disease, so it is not possible to exclude that the cohort includes children who have Kawasaki disease rather than a newer emerging condition associated with COVID-19. We attempted to distinguish between the cohort who met the criteria of Kawasaki disease from other children in the cohort.

Fourth, there is no national registry of Kawasaki disease or toxic shock syndrome in England, so comparing numbers of children with PIMS-TS to usual prevalence of Kawasaki disease is not possible.

Conclusion

In this case series of hospitalized children who met criteria for PIMS-TS, there was a wide spectrum of presenting signs and symptoms and disease severity, ranging from fever and inflammation, to myocardial injury, shock, and development of coronary artery aneurysms. The comparison with patients with Kawasaki disease and Kawasaki disease shock syndrome may provide insights into this syndrome, and suggests this disorder differs from other pediatric inflammatory entities.

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Study Concept and Design: Whittaker, Bamford, Kenny, Lyall, Levin

Acquisition, analysis or interpretation of data: Whittaker, Bamford, Kenny, Lyall, Levin, Kaforou Shah, Jones, Ramnarayan, Fraisse, Miller, Davies, Kucera, Brierley, McDougall, Carter, Tremoulet, Shimizou, Herberg, Burns and the PIMS-TS Study team.

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Critical revision of the manuscript for important intellectual content: All authors

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World Health Organisation	**Royal College of Paediatrics and Child Health (UK)**	**Center for Disease Control (USA)**
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 (diarrhoea, 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,	1. A child presenting with persistent fever, inflammation (neutrophilia, elevated CRP and lymphopaenia) and evidence of single or multi-organ dysfunction (shock, cardiac, respiratory, renal, gastrointestinal or neurological disorder) with additional features (see listed in eAppendix 1) This may include children fulfilling full or partial criteria for Kawasaki disease. 2. Exclusion of any other microbial cause, including bacterial sepsis, staphylococcal or streptococcal shock syndromes, infections associated with myocarditis such as enterovirus (waiting for results of these investigations should not delay seeking expert advice). 3. SARS-CoV-2 PCR testing may be positive or negative	• 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 Additional comments

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.		• Some individuals may fulfill full or partial criteria for Kawasaki disease but should be reported if they meet the case definition for MIS-C • Consider MIS-C in any pediatric death with evidence of SARS-CoV-2 infection
https://www.who.int/publications-detail/multisystem-inflammatory-syndrome-in-children-and-adolescents-with-covid-19	https://www.rcpch.ac.uk/resources/guidance-paediatric-multisystem-inflammatory-syndrome-temporally-associated-covid-19	https://emergency.cdc.gov/han/2020/han00432.asp

Table 1 Case definitions for emerging inflammatory condition during COVID-19 pandemic from World Health Organisation, Royal College of Paediatrics and Child Health and Center for Disease Control (USA). eAppendix 1 is in the supplement

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Characteristic n (%)	PIMS-TS all cases[a] N=58	Febrile and Inflamm-atory[b] N=23	Stratification by Shock[c]		Stratification by Kawasaki disease[d]		Stratification by Kawasaki clinical criteria		Stratification by Coronary artery aneurysm[e]		Stratification by evidence of SARS-CoV-2 infection[f]	
			Shocked N=29	Not Shocked N=29	Kawasaki disease N=13	Not Kawasaki disease N=45	Criteria met N=7	Criteria not met N=51	CAA + N=8	CAA - n=50	SARS-CoV-2 Testing positive N=45	SARS-CoV-2 Testing negative N=13
Age, median (Interquartile range) year	9 (5.7-14)	10 (5.5-14)	10.5 (7-14)	10 (3-14)	8 (5-11)	10.5 (5.7-14)	6 (2-8)	10 (6-14)	9.5 (8-12.3)	9 (5-11)	10 (6-14)	7 (2.5-14)
Male	25 (43)	17 (74)	16 (55)	22 (76)	10 (77)	29 (64)	6 (86)	32 (63)	6 (75)	32 (64)	19 (43)	8 (61)
Female	33 (57)	6 (26)	13 (45)	7 (24)	3 (23)	25 (36)	1 (14)	19 (37)	2 (25)	19 (36)	26 (57)	5 (49)
Ethnicity												
Black	22 (38)	7 (30)	14 (48)	8 (28)	8 (62)	15 (33)	2 (29)	20 (39)	7 (87.5)	15 (30)	18 (40)	4 (31)
Asian	18 (31)	6 (26)	6 (21)	6 (21)	0	12 (27)	0	12 (24)	0	12 (24)	11 (24)	1 (8)
White	12 (21)	8 (35)	6 (21)	12 (42)	4 (31)	14 (31)	4 (57)	14 (27)	1 (12.5)	17 (34)	13 (29)	5 (38)
Other	6 (10)	2 (9)	3 (10)	3 (10)	1 (8)	5 (11)	1 (14)	5 (10)	0	6 (12)	3 (7)	3 (23)
Clinical Features at Presentation												
Abdominal pain	31 (53)	13 (57)	18 (62)	11 (38)	2 (15)	29 (64)	1 (14)	30 (59)	2 (33)	29 (58)	24 (55)	7 (50)
Diarrhoea	30 (52)	10 (44)	19 (66)	10 (34)	7 (54)	23 (51)	2 (29)	28 (55)	4 (67)	22 (44)	25 (75)	5 (36)

[a] Fever >38 C for >72 hours was an entry point to the study

[b] Febrile and inflammatory only – this cohort of children were those who did not meet the criteria for shock (footnote c) or the clinical diagnostic criteria for Kawasaki disease (footnote d)

[c] Shock was defined as needing inotrope support or fluid resuscitation >20ml/kg

[d] AHA Criteria for definition of Kawasaki Disease is to have 4 of 5 mucocutaneous features as follows: Persistent fever and 4/5 mucocutaneous features : Erythema and cracking of lips, strawberry tongue, and/or erythema of ofral and pharyngeal mucosa; bilateral bulbar conjunctival injection without exudate; rash: maculopapular, diffuse erythroderma; erythema and edema of the hands and feet in acute phase and/or periungual desquamation in subacute phase; cervical lymphadenopathy (>1.5cm diameter). Patients with less than 4 features were stratified as Kawasaki disease if coronary artery aneurysms were present. In the absence of coronary artery changes, stratification by Kawasaki clinical criteria required 4/5 features to be present.

[e] Coronary artery aneurysm (CAA) is dilatation of any coronary artery seen on echocardiogram with a z score of >2.0 in the acute phase

[f] SARS-CoV-2 Infection includes positive SARS-CoV-2 PCR or positive SARS-CoV-2 IgG serology

Rash	30 (52)	9 (39)	15 (52)	14 (48)	10 (77)	20 (44)	7 (100)	23 (45)	5 (83)	20 (40)	21 (48)	9 (64)
Shock	29 (50)	0	29 (100)	0	6 (46)	23 (51)	1 (14)	28 (55)	6 (75)	23 (46)	25 (56)	4 (31)
Vomiting	26 (45)	13 (57)	15 (52)	14 (48)	5 (38)	21 (47)	2 (29)	23 (45)	3 (50)	21 (42)	20 (45)	6 (43)
Conjunctival injection	26 (45)	9 (39)	11 (38)	18 (62)	11 (85)	16 (36)	7 (100)	19 (37)	4 (67)	16 (32)	20 (45)	6 (43)
Mucus membrane changes	17 (29)	5 (22)	6 (21)	23 (79)	6 (46)	11 (24)	6 (86)	11 (22)	1 (17)	11 (22)	11 (25)	6 (43)
Headache	15 (26)	4 (17)	11 (38)	18 (62)	4 (31)	11 (24)	1 (14)	14 (27)	3 (50)	11 (22)	13 (30)	2 (14)
Respiratory symptoms	12 (21)	2 (13)	9 (31)	20 (69)	2 (15)	9 (20)	1 (14)	11 (22)	2 (33)	9 (18)	9 (20)	3 (21)
Lymphadenopathy	9 (16)	3 (13)	2 (7)	27 (93)	5 (38)	4 (9)	4 (57)	5 (10)	2 (33)	4 (8)	8 (18)	1 (7)
Swollen hands and feet	9 (16)	2 (13)	4 (14)	25 (86)	4 (31)	5 (11)	4 (57)	5 (10)	1 (17)	5 (8)	7 (16)	2 (14)
Sore throat	6 (10)	1 (4)	5 (17)	24 (83)	0	5 (11)	0	6 (12)	0	5 (10)	6 (14)	0
Confusion	5 (9)	0	5 (17)	24 (83)	1 (8)	4 (9)	0	5 (10)	1 (17)	4 (8)	5 (11)	0

Table 2. Demographics and clinical features of the whole PIMS-TS cohort. Clinical features are listed in order of frequency. In addition, pairwise comparison is included dividing the cohort by: Febrile and Inflammatory, Shock, Kawasaki Disease, Clinical diagnostic criteria of Kawasaki, Presence of coronary artery aneurysm, laboratory evidence for SARS-CoV-2 infection. Values shown as number (percentage) or median (interquartile range (IQR)) as indicated in the table. AHA = American Heart Association.

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Characteristic n (%)	PIMS-TS all cases[a] N=58	Febrile and Inflamm-atory[b] N=23	Stratification by Shock[c]		Stratification by Kawasaki disease[d]		Stratification by Kawasaki clinical criteria		Stratification by Coronary artery aneurysm[e]		Stratification by evidence of SARS-CoV-2 infection[f]	
			Shocked N=29	Not Shocked N=29	Kawasaki disease N=13	Not Kawasaki disease N=45	Criteria met N=7	Criteria not met N=51	CAA + N=8	CAA - n=50	Shocked N=29	Not Shocked N=29
Cardiac / circulatory/renal												
Acute Kidney Injury[g]	13 (22)	2 (9)	11 (38)	2 (7)	3 (23)	0	0	0	3 (38)	0	11 (24)	2 (67)
Vasoactive support	27 (47)	0	27 (93)	0	6 (46)	20 (44)	1 (14)	26 (51)	6 (75)	21 (42)	23 (52)	4 (29)
Extracorporeal membrane oxygenation (ECMO)	3 (5)	0	3 (10.3)	0	0	3 (7)	0	3 (60)	0	3 6)	3 (7)	0
Respiratory												
Intubation	25 (43)	2 (9)	23 (79)	2/29 (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)	20/29 (69)	13 (100)	29 (64)	7 (100)	34 (68)	8 (100)	33 (66)	33 (75)	8 (57)
Corticosteroids	37 (64)	12 (52)	19 (66)	18/29	12 (92)	23 (51)	7 (100)	30 (59)	7 (88)	30 (60)	33 (75)	4 (29)

[a] Fever >38 C for >72 hours was an entry point to the study

[b] Febrile and inflammatory only – this cohort of children were those who did not meet the criteria for shock (footnote c) or the clinical diagnostic criteria for Kawasaki disease (footnote d)

[c] Shock was defined as needing inotrope support or fluid resuscitation >20ml/kg

[d] AHA Criteria for definition of Kawasaki Disease is to have 4 of 5 mucocutaneous features as follows: Persistent fever and 4/5 mucocutaneous features : Erythema and cracking of lips, strawberry tongue, and/or erythema of ofral and pharyngeal mucosa; bilateral bulbar conjunctival injection without exudate; rash: maculopapular, diffuse erythroderma; erythema and edema of the hands and feet in acute phase and/or periungual desquamation in subacute phase; cervical lymphadenopathy (>1.5cm diameter). Patients with less than 4 features were stratified as Kawasaki disease if coronary artery aneurysms were present. In the absence of coronary artery changes, stratification by Kawasaki clinical criteria required 4/5 features to be present.

[e] Coronary artery aneurysm (CAA) is dilatation of any coronary artery seen on echocardiogram with a z score of >2.0 in the acute phase

[f] SARS-CoV-2 Infection includes positive SARS-CoV-2 PCR or positive SARS-CoV-2 IgG serology

[g] Acute kidney injury – creatinine greater than upper limit for age

				(62)								
Anakinra (IL-1 receptor antagonist)	3 (5)	1 (4)	2 (7)	1/29 (3.4)	0	2 (4)	0	3 (6)	0	3 (6)	2 (5)	1 (8)
Infliximab (TNF-alpha antagonist)	8 (14)	4 (17)	2 (7)	6/29 (21)	4 (31)	4 (9)	3 (43)	5 (19)	3 (38)	5 (10)	7 (16)	1 (8)
2 immunomodulatory agents[h]	35 (60)	11 (48)		17	12 (92)	23 (51)	7 (100)	28 (55)	7 (88)	28 (56)	32 (71)	3 (23)
3 immunomodulatory agents[i]	9 (16)	4 (17)	3 (10)	6/29 (21)	4 (31)	7 (16)	3 (43)	6 (12)	3 (38)	6 (12)	9 (20)	1 (8)
Outcomes												
Coronary artery aneurysms (z score >2)	8 (14)	1/23	5 (17)	3/29 (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

Table 3 Clinical outcomes and management. In addition, pairwise comparison is included dividing the cohort by: Febrile and Inflammatory, Shock, Kawasaki Disease, Clinical diagnostic criteria of Kawasaki, Presence of coronary artery aneurysm, laboratory evidence for SARS-CoV-2 infection. Values shown as number (percentage) or median (interquartile range (IQR)) as indicated in the table. AHA = American Heart Associatio

[h] Two agents of intravenous immunoglobulin, corticosteroids, anakinra, or infliximab were given in order to manage inflammation
[i] Three agents of intravenous immunoglobulin, corticosteroids, anakinra, or infliximab were given in order to manage inflammation

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		PIMS-TS all cases[p] N=58	Febrile and Inflamm-atory[q] N=23	Stratification by Shock[r]		Stratification by Kawasaki disease[s]		Stratification by Kawasaki clinical criteria		Stratification by Coronary artery aneurysm[t]		Stratification by evidence of SARS-CoV-2 infection[u]	
				Shocked N=29	Not Shocked N=29	Kawasaki disease N=13	Not Kawasaki disease N=45	Criteria met N=7	Kawasaki criteria not met N=51	Coronary artery aneurysm N=8	Shocked N=29	Not Shocked N=29	Kawasaki disease N=13
Virology		**Number (%)**											
Sars-CoV-2 respiratory PCR positive		15 (26)	5/23 (22)	10 (35)	5 (17)	0	15 (33)	0	15 (29)	0	15 (30)	15 (33)	0
Sars-CoV-2 IgG antibody		40/48 (83)	15/18 (83)	22/25 (88)	18/23 (78)	8/12 (67)	32/36 (89)	4/6 (67)	36/42 (86)	6 (75)	34/40 (75)	40/42 (95)	0
Any Sars-CoV-2 PCR or IgG positive		45/58 (78)	17 (74)	25 (86)	20 (69)	8 (62)	32(64)	4 (57)	41 (80)	6 (75)	39 (78)	45 (100)	0
No positive test		13 (22)	6 (26)	4 (14)	9 (31)	5 (39)	8 (18)	3 (43)	10 (20)	2 (25)	11 (22)	0	13/13 (100)
Characteristic	Reference range	Median (IQR)											
Haematology													
Total white cell count	4-13.5	17 (12-22)	16 (11.2-19)	18 (14-28)	17 (11.3-	17 (13.5-	17 (12.15-	17 (11-17)	17.4 (12.5-	20 (15-29)	17 (11.6-	17 (12-23)	17 (13-21)

[p] Fever >38 C for >72 hours was an entry point to the study

[q] Febrile and inflammatory only – this cohort of children were those who did not meet the criteria for shock (footnote c) or the clinical diagnostic criteria for Kawasaki disease (footnote d)

[r] Shock was defined as needing inotrope support or fluid resuscitation >20ml/kg

[s] AHA Criteria for definition of Kawasaki Disease is to have 4 of 5 mucocutaneous features as follows: Persistent fever and 4/5 mucocutaneous features : Erythema and cracking of lips, strawberry tongue, and/or erythema of ofral and pharyngeal mucosa; bilateral bulbar conjunctival injection without exudate; rash: maculopapular, diffuse erythroderma; erythema and edema of the hands and feet in acute phase and/or periungual desquamation in subacute phase; cervical lymphadenopathy (>1.5cm diameter). Patients with less than 4 features were stratified as Kawasaki disease if coronary artery aneurysms were present. In the absence of coronary artery changes, stratification by Kawasaki clinical criteria required 4/5 features to be present.

[t] Coronary artery aneurysm (CAA) is dilatation of any coronary artery seen on echocardiogram with a z score of >2.0 in the acute phase

[u] SARS-CoV-2 Infection includes positive SARS-CoV-2 PCR or positive SARS-CoV-2 IgG serology

(x10*9/L)					18.8)	26.4)	22.6)		22.4)		21.7)		
Neutrophil count (x10*9/L)	1.5-7	13 (10-19)	10.7 (7.4-16)	16 (11-25)	10.8 (6.8-16)	13.2 (10.2-16.4)	12.5 (8.5-19.5)	12.5 (6-14)	14 (10.1-19.2)	16 (13-26)	12 (7.9-18.9)	14 (9-20)	13 (8-18)
Lymphocyte count (x10*9/L)	1.5-4	0.8 (0.5-1.5)	1.1 (0.7-2.8)	0.7 (0.4-0.9)	1.3 (0.7-2.5)	1.2 (0.5-1.6)	0.81 (0.5-1.4)	1.3 (0.5-1.8)	0.8 (0.5-1.3)	0.6 (0.4-1.3)	0.83 (0.6-1.6)	0.8 (0.4-1.4)	0.8 (0.5-2.6)
Haemoglobin (g/L), n=51	111-147	92 (83-103)	97 (87-108)	85 (74-100)	99.5 (88-109)	92.5 (70.75-109.3)	92.5 (83-102)	109 (84-110)	91 (83-101.5)	80 (70-95)	93 (83-106)	93 (83-103)	88 (79-106)
Platelet number (x10*9/L), n=55	200-450	151 (104-210)	175.5 (101-209)	136 (75-214)	176 (118-210)	391 (272-581)	147.5 (93-195)	176 (106-302)	150 (101-210)	173 (123-230)	151 (97-209)	142 (91-201)	180 (129-332)
Inflammatory markers													
C reactive protein (CRP) (mg/L)	0-5	229 (156-338)	176 (82-192)	321 (223-371)	176 (83-229)	237.9 (164.9-366)	206 (151-331)	238 (106-339)	220 (156-338)	301 (205-361)	191 (132-330.5)	251 (158-342)	220 (131-323)
Ferritin (ug/L), n=53	7-140	610 (359-1280)	379.5 (195-831)	888 (556-1530)	378 (180-907)	620 (306.3-1254)	592 (373-1443)	357 (146-1078)	631 (381-1342)	637 (376-1076)	574 (355-1378)	679 (374-1249)	495 (190-1627)
Biochemistry													
Lactate dehydrogenase (U/L), n=41	125-243	419 (319-887)	327 (274-463)	764 (291-989)	327 (273.5-451.8)	373 (309-828)	448 (319-912.5)	359 (246-373)	434 (323-906)	615 (371-905)	408 (311-900)	414 (310-915)	1104 (327-1209)
ALT (U/L) n=56	0-34	42 (26-95)	40 (21-79)	47 (30-107)	31.5 (20-77)	36.5 (18.75-117.8)	42 (27-97)	26 (12-141)	43 (28-96)	86 (34-129)	40 (25-77)	42 (30-95)	28 (22-273)
Albumin (g/L), n=51	35-5-	24 (21-27)	27 (24-33)	22 (20-24)	27 (25-32)	25.5 (20-27)	24 (21-29)	27 (23-28)	24 (21-28)	21 (18-26)	25 (21-29)	24 (21-27)	27 (21-31)
Creatinine (umol/L), n=48	30-80 (varies with age)	71 (43-108)	62 (42-93)	78 (42-104)	61 (45-92)	76 (46-122)	71 (42-101)	42 (40-46)	76 (40-118)	72 (46-122)	71 (40-101)	67 (44-116)	76 (40-96)
Cardiac Markers													

Troponin (ng/L) n=50	0-15	45 (8-294)	8 (5-45)	124 (45-497)	8 (5-45)	19.25 (7-153)	45.1 (8-355)	10 (5-38)	47.5 (11-353)	100 (25-379)	45 (7-278)	45 (8-202)	256 (9-598)
NT-pro-BNP (pg/ml), n=29	<100	788 (174-10548)	310.5 (106-1354)	14017 (7004-35000)	212.5 (70-876)	788 (56-32169)	921.5 (180-9962)	118 (23-636)	1833 (213-12868)	32169 (1994-35000)	629 (155-7597)	1140 (184-11719)	11 (10-12)
Coagulation													
Fibrinogen (g/L), n=51	1.99-4.09	5.7 (4.37-7)	4.8 (3.5-5.8)	6.1 (5-7.3)	4.88 (3.9-6.7)	7.08 (4.8-7.6)	5.7 (4.3-6.8)	6 (4.7-7.4)	5.7 (4.3-6.9)	6.9 (5.7-7.8)	5.54 (4.3-6.8)	5.8 (4.4-7.1)	5.5 (3.8-7.6)
D-Dimer (ng/ml), n=53	100-560	3578 (2085-8235)	2402 (1336-4248)	5935 (3548-12842)	2383 (1357-4360)	3238 (969-6262)	3578 (2205-10000)	3494 (1733-6650)	3578 (2205-8729)	4375 (2662-6906)	3564 (1964-10000)	3910 (2563-10000)	2094 (1379-5815)

Table 4 Laboratory results. In addition, pairwise comparison is included dividing the cohort by: Febrile and Inflammatory, Shock, Kawasaki Disease, Clinical diagnostic criteria of Kawasaki, Presence of coronary artery aneurysm, laboratory evidence for SARS-CoV-2 infection. Values shown as number (percentage) or median (interquartile range (IQR)) as indicated in the table. AHA = American Heart Association. NT-pro-BNP = N terminal pro B-type natriuretic peptide.

vwxyzaa

[v] Fever >38 C for >72 hours was an entry point to the study

[w] SARS-CoV-2 Infection includes positive SARS-CoV-2 PCR or positive SARS-CoV-2 IgG serology

[x] Shock was defined as needing inotrope support or fluid resuscitation >20ml/kg

[y] AHA Criteria for definition of Kawasaki Disease is to have 4 of 5 mucocutaneous features as follows: Persistent fever and 4/5 mucocutaneous features : Erythema and cracking of lips, strawberry tongue, and/or erythema of of oral and pharyngeal mucosa; bilateral bulbar conjunctival injection without exudate; rash: maculopapular, diffuse erythroderma; erythema and edema of the hands and feet in acute phase and/or periungual desquamation in subacute phase; cervical lymphadenopathy (>1.5cm diameter).

[z] Coronary artery aneurysm (CAA) is dilatation of any coronary artery seen on echocardiogram with a z score of >2.0 in the acute phase

[aa] Febrile and inflammatory only – this cohort of children were those who did not meet the criteria for shock or the clinical diagnostic criteria for Kawasaki disease

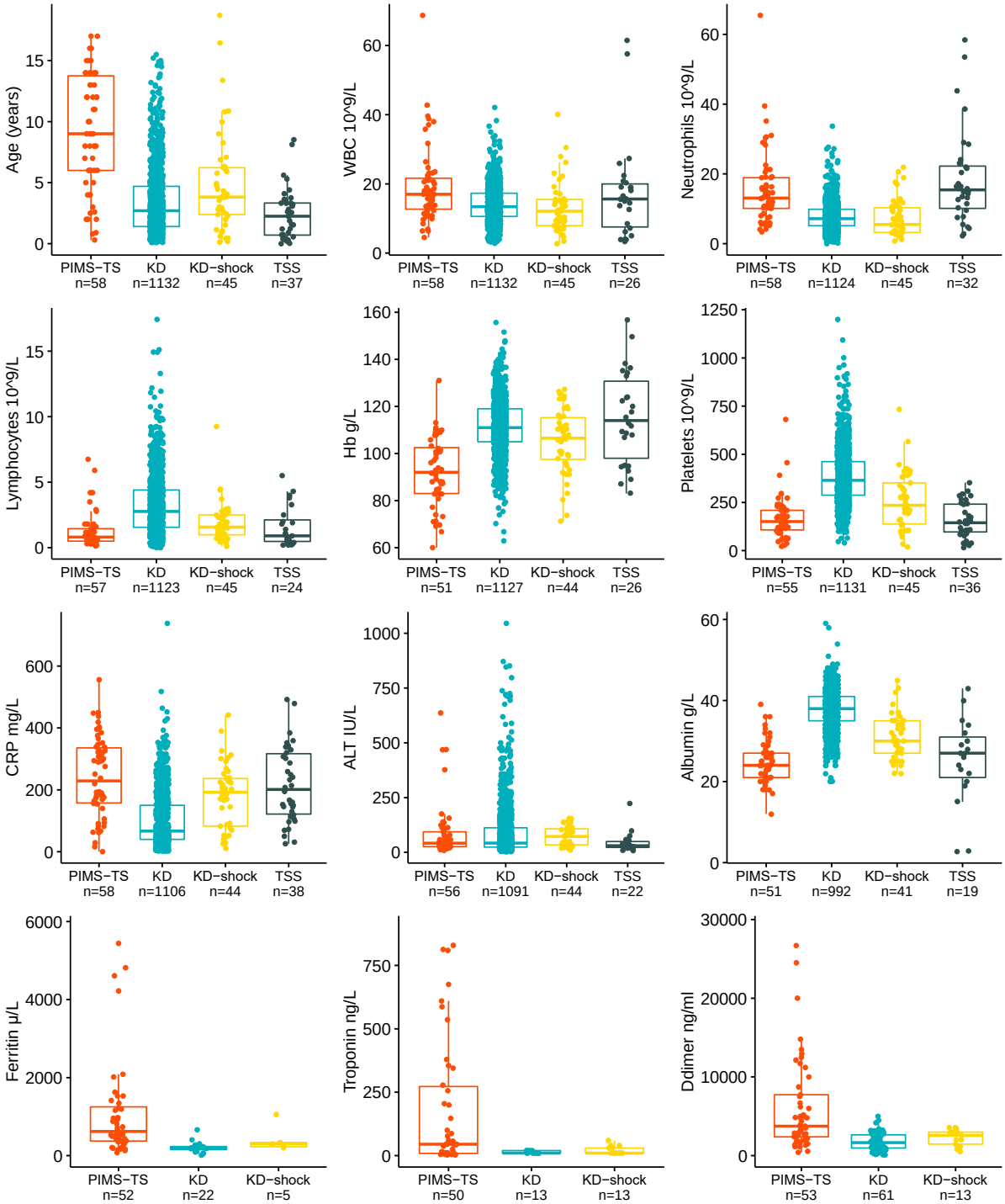

Figure 1 Comparison of age and laboratory results in 4 different patient groups. PIMS-TS - children meeting the case definition, n=58; KD – cohort of 1132 children with Kawasaki Disease, KD-shock – cohort of 45 children with Kawasaki Disease shock syndrome; TSS – children with toxic shock syndrome n=37. 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.

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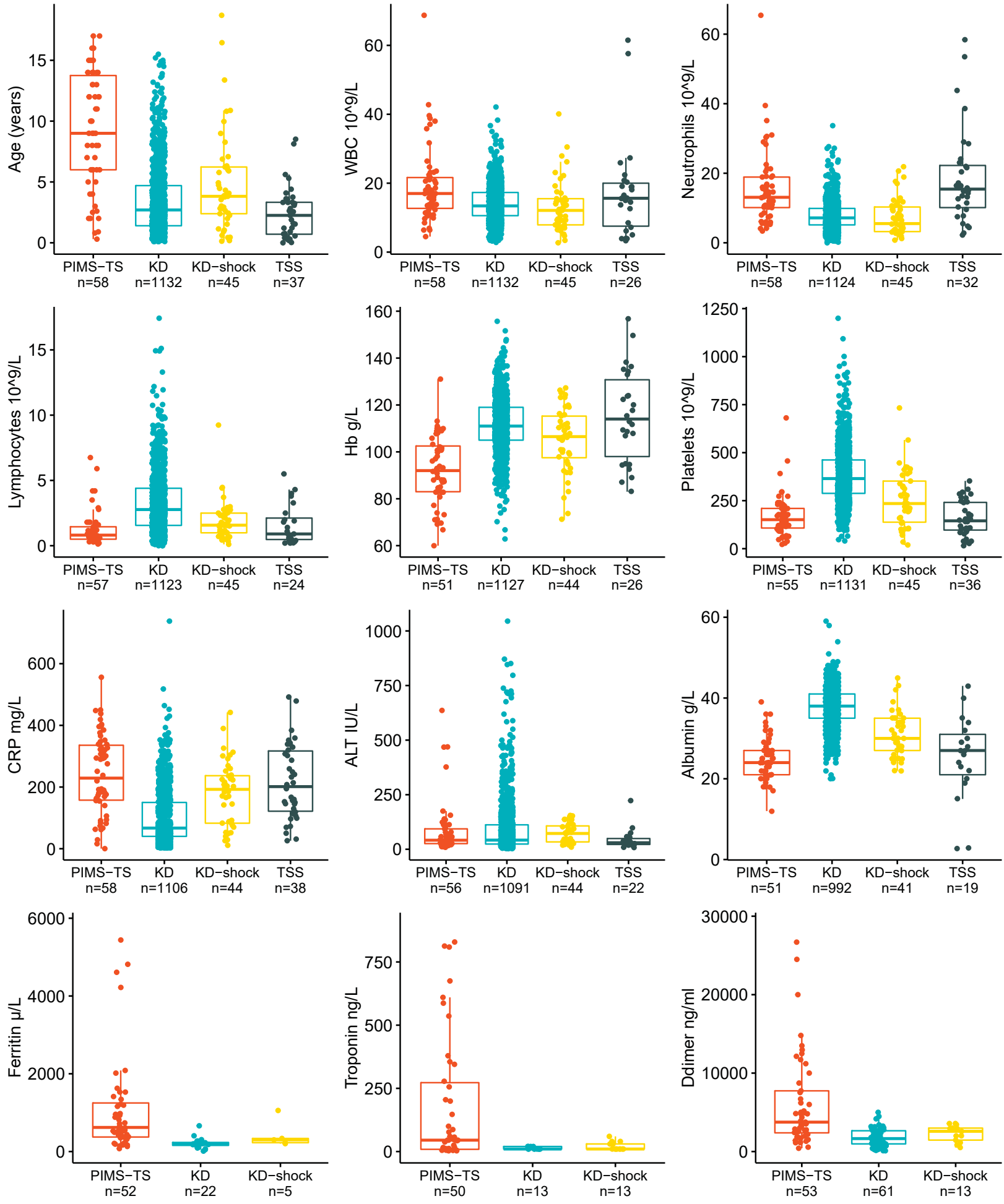
Age (years)
0
5
10
15
PIMS−TS n=58
KD n=1132
KD−shock n=45
TSS n=37
WBC 10^9/L
0
20
40
60
PIMS−TS n=58
KD n=1132
KD−shock n=45
TSS n=26
Neutrophils 10^9/L
0
20
40
60
PIMS−TS n=58
KD n=1124
KD−shock n=45
TSS n=32
Lymphocytes 10^9/L
0
5
10
15
PIMS−TS n=57
KD n=1123
KD−shock n=45
TSS n=24
Hb g/L
60
80
100
120
140
160
PIMS−TS n=51
KD n=1127
KD−shock n=44
TSS n=26
Platelets 10^9/L
0
250
500
750
1000
1250
PIMS−TS n=55
KD n=1131
KD−shock n=45
TSS n=36
CRP mg/L
0
200
400
600
PIMS−TS n=58
KD n=1106
KD−shock n=44
TSS n=38
ALT IU/L
0
250
500
750
1000
PIMS−TS n=56
KD n=1091
KD−shock n=44
TSS n=22
Albumin g/L
0
20
40
60
PIMS−TS n=51
KD n=992
KD−shock n=41
TSS n=19
Ferritin µ/L
0
2000
4000
6000
PIMS−TS n=52
KD n=22
KD−shock n=5
Troponin ng/L
0
250
500
750
PIMS−TS n=50
KD n=13
KD−shock n=13
Ddimer ng/ml
0
10000
20000
30000
PIMS−TS n=53
KD n=61
KD−shock n=13