Severe acute respiratory syndrome coronavirus 2-related multisystem inflammatory syndrome in children mimicking Kawasaki disease

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Abstract:	SARS-CoV-2 pandemics has been characterized by a high level of infectivity and high mortality in adults at risk (age >70 years, obesity, diabetes, systemic hypertension, and other underlying diseases). Following a common viral pneumonia, a multisystem inflammatory syndrome can occur usually in the second week of the disease including Acute Respiratory Distress Syndrome (ARDS) carrying a high mortality. Contrary to most common respiratory viruses, children seem less susceptible to SARS-CoV-2 infection and generally develop a mild disease with low mortality. However, clusters of severe shock associated with high levels of cardiac biomarkers and unusual vasoplegia requiring inotropes, vasopressors and volume loading have been recently described. Both clinical symptoms (i.e., high and persistent fever, gastrointestinal disorders, skin rash, conjunctival injection and dry cracked lips) and biological signs (e.g., elevated CRP/PCT, high levels of ferritinemia) resembled Kawasaki disease. In most instances, intravenous immunoglobin therapy improved the cardiac function and led to full recovery within a few days. Adjunctive steroid therapy and sometimes biotherapy (e.g., anti-IL-1Ra, anti-IL-6 monoclonal antibodies) were often necessary. Although almost all children fully recovered within a week, some of them later developed coronary artery dilation or aneurysm. Thus, a new 'Multisystem Inflammatory Syndrome in Children (MIS-C)' related to SARS-CoV-2 has been recently described mimicking Kawasaki disease, and questioned about a common or dissimilar pathophysiology. (215 words)
Suggested Reviewers:	
Opposed Reviewers:	
Response to Reviewers:	Professor Ariel Cohen Associate Editor Archives of Cardiovascular Diseases Paris, 30 March 2021 Dear Associate Editor, First of all, I would like to present to you and the Editors of the Archives of

	Cardiovascular Diseases my sincere condolences for Professor Yves Juillière's death, as he asked me to write this review entitled 'COVID-19 in children' for a special issue of ACVD to be published in April 2021, about one month ago. I will deeply think of him tomorrow afternoon, when his funerals takes place in Nancy. Secondly, we made every effort to follow our Reviewers' suggestions. Thus, find enclosed a revised version where all changes have been highlighted in yellow, and a clean one for better reading. In order to avoid the fastidious enumeration of the different clinical studies reported in the literature, we skipped the Italian report in the Lancet 2020, and several other studies published in France and the US. However, were retained the first original description of this new disease by the South Thames Retrieval Service, London and the clinical study led by Damien Bonnet et al, since it mainly focused on cardiogenic shock associated with depressed left ventricular function and elevated cardiac biomarkers. However, the unusual diastolic hypotension should have suggested this new disease as either some kind of "Toxic-Shock Syndrome" or Systemic Inflammatory Response Syndrome (SIRS). Furthermore, almost one third of the early children with MIS-C went rapidly on ECMO, though IVIGs and/or steroids were actually more appropriate and efficient to recover quickly the cardiac function. We also kept the original work from Ouldali et al. who were the first group to link MIS-C both with SARS-CoV-2 pandemics in 2020, but also Influenza A H1N1 pandemics in 2009. Then, we focused on both the UK experience (PIMS-TS) and the US ones (MIS-C) which further analyzed clinical and biological features as compared with Kawasaki Disease (KD), KD shock syndrome, and Toxic-Shock Syndrome (TSS). A table 1 has been added in order to sum up the diagnostic criteria of the above syndromes, upon your request. It was also important to highlight the unusual delay of 2 to 4 weeks between SARS-CoV-2 peak waves and the occurrence of MIS-C that strongly suggests an auto-immune phenomenon. Lastly, the chapter MIS-C and Kawasaki disease: similar or dissimilar pathophysiology? has been totally rewritten in order to take into account the most recent scientific publications regarding both Kawasaki disease and MIS-C advances in the understanding of their physiopathology. Hoping these significant changes have fully fulfilled the requested changes, on the name of my co-authors, I send you my best regards. Yours sincerely, Prof. emeritus Jean-Christophe Mercier jean-christophe.mercier-ext@aphp.fr OR jean-christophe.mercier@sfr.fr

SARS-CoV-2-related Multisystem Inflammatory Syndrome in Children (MIS-C) mimicking a Kawasaki Disease

Syndrome Multi-systémique Inflammatoire lié à SARS-CoV-2 chez l'Enfant (MIS-C) mimant un syndrome de Kawasaki.

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Les auteurs déclarent n'avoir aucun conflit d'intérêt en relation avec le contenu de cet article.

SUMMARY

SARS-CoV-2 pandemics has been characterized by a high level of infectivity and high mortality in adults at risk (age >70 years, obesity, diabetes, systemic hypertension, and other underlying diseases). Following a common viral pneumonia, a multisystem inflammatory syndrome can occur usually in the second week of the disease including Acute Respiratory Distress Syndrome (ARDS) carrying a high mortality. Contrary to most common respiratory viruses, children seem less susceptible to SARS-CoV-2 infection and generally develop a mild disease with low mortality. However, clusters of severe shock associated with high levels of cardiac biomarkers and unusual vasoplegia requiring inotropes, vasopressors and volume loading have been recently described. Both clinical symptoms (i.e., high and persistent fever, gastrointestinal disorders, skin rash, conjunctival injection and dry cracked lips) and biological signs (e.g., elevated CRP/PCT, high levels of ferritinemia) resembled Kawasaki disease. In most instances, intravenous immunoglobin therapy improved the cardiac function and led to full recovery within a few days. Adjunctive steroid therapy and sometimes biotherapy (e.g., anti-IL-1Ra, anti-IL-6 monoclonal antibodies) were often necessary. Although almost all children fully recovered within a week, some of them later developed coronary artery dilation or aneurysm. Thus, a new 'Multisystem Inflammatory Syndrome in Children (MIS-C)' related to SARS-CoV-2 has been recently described mimicking Kawasaki disease, and questioned about a common or dissimilar pathophysiology. (215 words)

KEYWORDS : COVID-19 ; CHILDREN; MULTISYSTEM INFLAMMATORY SYNDROME TEMPORALLY ASSOCIATED WITH SARS-COV-2; CARDIOGENIC SHOCK; KAWASAKI SYNDROME.

RÉSUMÉ

La pandémie due à SARS-CoV-2 est caractérisée par une haute contagiosité et une mortalité élevée chez les adultes à risque (âge supérieur à 70 ans, obésité, diabète, hypertension, autres pathologies associées). Au décours d'une pneumonie virale, peut survenir une phase hyper-inflammatoire compliquée d'une défaillance multi-viscérale avec Syndrome de Détresse Respiratoire Aiguë (SDRA). Contrairement à la majorité des virus respiratoires, les enfants apparaissent moins susceptibles à SARS-CoV-2 et développent généralement une forme peu sévère, avec une faible mortalité. Cependant, des cas groupés d'états de choc associés à des biomarqueurs cardiaques élevés et à une vasoplégie inhabituelle nécessitant un traitement par inotropes, vasopresseurs et un remplissage vasculaire ont été récemment décrits. Les symptômes cliniques observés (fièvre élevée et durable, troubles digestifs, rash cutané, injection conjonctivale, chéléite) et le profil biologique (CRP/PCT élevées, hyperferritinémie) évoquent un syndrome de Kawasaki qui répond à un traitement par perfusion intraveineuse d'immunoglobulines complété si besoin par une corticothérapie et/ou une biothérapie anti-IL-1Ra ou anti-IL-6. La majorité des enfants guérit en quelques jours avec cependant une possible dilatation des artères coronaires. Ainsi, un nouveau syndrome inflammatoire multi-systémique associé à SARS-CoV-2 mimant un syndrome de Kawasaki a été récemment identifié chez l'enfant et questionne sur sa physiopathologie proche ou dissemblable de ce syndrome d'étiologie restée jusqu'ici inconnue. (208 mots)

MOTS-CLEFS : COVID-19 ; ENFANT ; SYNDROME INFLAMMATOIRE MULTI-SYSTEMIQUE TEMPORELLEMENT ASSOCIE A SARS-COV-2 ; CHOC CARDIOGENIQUE ; SYNDROME DE KAWASAKI.

INTRODUCTION

While SARS-CoV-2 pandemic was spreading worldwide with as to February 2021 more than 100 million infected persons and a death toll of more than 2.3 million people, children were representing only a small fraction (~0.2%) of infected patients [1]. Often, they presented with mild symptoms of viral upper and/or lower respiratory disease including short-lasting fever, dry cough, fatigue, myalgias and/or cephalalgia requiring at the most low-flow oxygen therapy and on average a few days of hospitalization [2]. Furthermore, mortality was low: 0.02% in 5,015 children with mild disease, and 2% in 319 children with severe disease [3].

However, clusters of children developing *'cardiogenic shock'* since shock was associated with low left ventricular ejection fraction and elevated cardiac biomarkers, but also unusually low diastolic pressure suggestive of *'toxic shock'* [4], and also other features, e.g. high fever, cutaneous rash, and conjunctival injection quite similar to Kawasaki disease (KD), were first described in England, Italy, then France and the US. Striking were two facts: this new syndrome called either '*Paediatric Inflammatory Multisystem Syndrome temporally-associated with SARS-CoV-2*' (PIMS-TS) in the UK or '*Multisystem Inflammatory Syndrome in Children'* (MIS-C) in the US, was actually occurring about 2 to 3 weeks after an episode of SARS-CoV-2 infection, and associated with high levels of inflammatory markers, e.g., CRP, ferritin, D-dimers, suggestive of *'cytokine storming'* [5]. Although inotropes or vasopressors were initially prescribed in most of the cases, hypotension was often amenable to volume loading. Furthermore, cardiac function rapidly improved after intravenous immunoglobulins and often steroids, and a few times use of biotherapies. Lastly, contrary to the adults, cardiac function rapidly normalized within a few days. However, coronary artery wall ultrasound brightness and sometimes dilation of its proximal part as seen in KD justify a long-term follow-up.

CHILDREN ARE INDEED LESS SUSCEPTIBLE TO SARS-CoV-2

Several explanations have been raised in order to explain the apparent paradox between the frequent viral respiratory diseases observed in children all-around the year, but particularly during winter, e.g., human rhinoviruses (Group A, B, and C >100 serotypes), respiratory syncytial viruses (RSV A & B), influenza virus (A & B, several subtypes), para-influenza viruses (type 3 most common), human metapneumoviruses (subgroups A & B), adenoviruses

(>50 serotypes), enteroviruses (echo & coxsackie), and common coronaviruses (OC43, 229E, NL63, and HKU1) [6], and the new SARS-CoV-2 that infects epithelial respiratory cells through Angiotensin Converting Enzyme-2 Receptors which are less numerous and mature in children as compared with adults [7].

The degree to which children and adolescents are infected by and transmit severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is unclear. The role of children and adolescents in transmission of SARS-CoV-2 is dependent on susceptibility, symptoms, viral load, social contact patterns and behavior. To systematically review the susceptibility to and transmission of SARS-CoV-2 among children and adolescents compared with adults, a total of 13,926 studies were identified through PubMed or medRxiv up to July 28, 2020 [8]. A total of 32 studies comprising 41,640 children and adolescents and 168,945 adults met inclusion criteria, including 18 contact-tracing studies and 14 population screening studies. The pooled odds ratio of being an infected contact in children compared with adults was 0.56 (95%CI 0.37-0.95) with substantial heterogeneity (I^2=94.6%). Three school-based contact-tracing studies found minimal transmission from child cases, although seroprevalence in adolescents appeared similar to adults. However, the studies were before the occurrence of new variants.

MULTISYSTEM INFLAMMATORY SYNDROME IN CHILDREN (MIS-C)

Mid-April 2020, the *South Thames Retrieval Service, London* referred eight children with shock associated with elevated cardiac biomarkers (i.e., troponin and BNP) and inflammatory markers (e.g., CRP, ferritine, and D-dimers) over just 10 days, as compared to usually 1-2 cases maximum a month [9]. Remarkable were both clinical features (e.g., high fever >4 days, diarrhea, cutaneous rash, conjunctivitis) similar to Kawasaki Disease (KD), and the unusually low diastolic pressure, as seen in toxic-shock syndrome due to TSS-1 released by Methicillin-Resistant *Staphylococcus aureus* or Group A *Streptococcus* [4]. Six of these children were of Afro-Caribbean descent, and 4 of them obese (BMI>25 kg/m^2). Although there was no primary respiratory failure, most of children were intubated and mechanically ventilated because of shock. Most of them required vasopressors (i.e., norepinephrine and/or milrinone), and one of them ultimately Extra-Corporeal Membrane Oxygenation (ECMO) support. All children tested negative for SARS-CoV-2 in nasopharyngeal swabs or bronchoalveolar lavage, but 4 of them had a known parental exposure. All children were given intravenous immunoglobulins (2g/kg) within the first 24h and antibiotic cover including ceftriaxone and

clindamycin. Subsequently, six children had been given orally 50mg/kg aspirin. A common echocardiographic finding was echo-bright coronary vessels which progressed to giant coronary aneurysms in one patient, one week after discharge home. All the children, except the one on ECMO who died from brain hemorrhage, were actually discharged from the pediatric intensive care unit (PICU) after 4-6 days.

In Italy, Bergamo was the most affected area by COVID-19 pandemic. All children diagnosed with a Kawasaki disease at John-Paul XXIII Hospital in Bergamo was retrospectively reviewed over the last 5 years, before (n=19) and after (n=10 of which 8 had a IgM and/or IgG-positive COVID-19 serology) [10]. The two groups differ both by the incidence (0.3 *vs.* 10 per month), mean age (3.0 *vs.* 7.5 years), myocardial disease (2/19 *vs.* 5/10), "Kawasaki Disease Shock Syndrome" (KDSS 0/19 *vs.* 5/10) and "Macrophage Activation Syndrome" (MAS 0/19 *vs.* 5/10), and the need to complete intravenous immunoglobulins by oral steroids (3/9 *vs.* 8/10), P<0.01.

In France, 35 children with shock associated with severe left ventricular dysfunction and marked inflammatory syndrome were retrospectively identified in 14 French PICUs over two months [11]. Median age at admission was 10 years (range 2-16). Comorbidities were present in 28%, including asthma and overweight. Gastrointestinal symptoms were predominant at the early stage. Furthermore, other clinical signs suggestive of Kawasaki disease were also observed (Fig. 1). Left ventricular ejection fraction was <30% in one-third of the cases; 80% required inotropic support and 28% treated with ECMO. Inflammatory markers were suggestive of cytokine storm (interleukin-6 median 135 pg/mL) and macrophage activation (D-dimers median 5284 ng/mL). Mean B-type natriuretic peptide (BNP) was markedly elevated (5743 pg/mL). Thirty-one of 35 (88%) patients tested positive for SARS-CoV-2 infection by PCR of nasopharyngeal swabs or serology. All patients received intravenous immunoglobulin, with adjunctive steroid therapy in one-third of them. Left ventricular function was restored in 25 of 35 discharged from the PICU. No patient died, and all patients supported by ECMO were successfully weaned off.

Twenty-one children and adolescents (median age 7.9 years [range 3.7-16.6]; 12 (57%) of African ancestry) with features of KDSS, including 16 (76%) with myocarditis, were admitted at "Hôpital des Enfants Malades" in Paris between 27 April and 11 May 2020, i.e., within only 2 weeks, as compared with just 1 case of KD on the average in the previous two years

[12]. All 21 patients had noticeable gastrointestinal symptoms during the early stage of the illness and high inflammatory markers. Nineteen (90%) had evidence of recent SARS-CoV-2 infection (positive PCR in 8/21, positive IgG serology in 19/21). All 21 patients received intravenous immunoglobulins and 10 (48%) also received corticosteroids. Clinical outcome was favorable in all patients, but moderate coronary artery dilations were detected in 5 (24%) of the patients.

A time-series analysis at another pediatric hospital (Hôpital Robert Debré) in the Paris region, a French epicentre of the COVID-19 first wave outbreak, recorded the number of hospital admissions from the Pediatric Emergency Department for Kawasaki disease over the past 15 years [13]. Between Dec 1, 2005 and May 20, 2020, 230 patients diagnosed as Kawasaki disease estimated by the quasi-Poisson model was 1.2 per month [IQR, 1.1-1.3]. In April 2020, a rapid increase of KD related to SARS-CoV-2 (six cases per month; 497% increase [95% CI 72-1082], p=0.0011) was identified, starting 2 weeks after the peak of the epidemy. SARS-CoV-2 was the only virus circulating during the period and was found in 8 of 10 patients (80%) with Kawasaki disease with positive PCR or serology, since April 15, 2020. A second peak of hospital admissions due to Kawasaki disease was also observed in December 2009 (six cases per month; 365% increase [31-719], p=0.0053), concomitant with the influenza A H1N1 pandemic.

A case series of 58 children (median age 9 years [IQR 5.7-14.0]); 33 (57%) girls; 40 (60%) of African or Asian descent) from 8 hospitals in England admitted between March 23 and May 16, 2020, with persistent fever and laboratory evidence of inflammation meeting the published definition of "*Pediatric Inflammatory Syndrome Temporally Associated with SARS-CoV-2*" (PIMS-TS) was later reported [14]. Clinical and laboratory characteristics were compared with those in patients with Kawasaki disease (KD) (n=1132), Kawasaki disease shock syndrome (KDSS) (n=45) and toxic-shock syndrome (n=37) who had been admitted to hospitals in Europe and the US from 2002 to 2019 [SARS-CoV-2 PCR was positive in 15 of 58 patients (26%), and SARS-CoV-2 IgG test results were positive in 40 of 46 (87%). All children presented with fever and nonspecific symptoms including vomiting (26/58 [45%]), abdominal pain (31/58 [53%]), and diarrhea (30/58 [52%]). Rash was present in 30 of 58 (52%), and conjunctival injection in 26 of 58 (45%) cases. Laboratory evaluation was consistent with marked inflammation with median CRP 229 mg/L [IQR 156-338] and ferritin (610 µg/L [IQR 359-1280]. Of the 58 children, 29 developed shock (with biochemical

evidence of myocardial dysfunction) and required inotropic support and fluid resuscitation (including 23/29 [79%] who received mechanical ventilation); 13 met the American Heart definition of Kawasaki disease [15], and 23 had fever and inflammation without features of shock and Kawasaki disease. Eight patients (14%) developed coronary artery dilatation or aneurysm. Comparison of PIMS-TS with KD and KDSS showed differences in clinical and laboratory features, including older age (median age 9 years [IQR, 5.7-14.0] *vs.* 2.7 years [IQR, 1.4-4.7] and 3.8 years [IQR, 0,2-18], respectively), and greater elevation of inflammatory markers such as CRP (median 229 mg/L [IQR, 156-338] *vs.* 67 mg/L [IQR, 40-150] and 193 mg/L [IQR, 83-237], respectively. The comparison with patients with KD and KDSS suggested this new disorder differs from other pediatric inflammatory entities.

Similar cases quoted as "*Multisystem Inflammatory Syndrome related to COVID-19*" (MIS-C) were described in New York City hospitals [16, 17], then rapidly followed by a targeted surveillance funded by the CDC for MIS-C in pediatric health centers across the US from March 15 to May 20, 2020 [18]. Case definition included six criteria: age lower than 21 years, fever that lasted for at least 24 hours, laboratory evidence of inflammation, evidence of infection with SARS-CoV-2 based on RT-PCR, antibody testing, or exposure to persons with COVID-19 in the past month, multisystem organ involvement, and serious illness leading to hospitalization. In 26 US states, 186 patients with MIS-C were identified from March 15 to May 20, 2020: 115 patients (62%) were male; 135 (73%) have been previously healthy, 131 (70%) were positive for SARS-CoV-2 by RT-PCR or antibody testing. Most patients (171 [92%]) had elevations in at least four markers of inflammation. Organ-system involvement included the gastrointestinal system in 171 patients (92%), cardiovascular in 149 (80%), hematologic in 142 (76%), mucocutaneous in 137 (74%), and respiratory in 131 (70%). The median duration of hospitalization was 7 days [IQR 4-10]: 148 patients (80%) were admitted into intensive care, 37 (20%) were mechanically ventilated, 90 (48%) received vasoactive support, and 4 (2%) died. Kawasaki disease-like features were documented in 74 patients (40%), and coronary-artery aneurysms (z scores $\geq$2.5) in 15 (8%). The use of immunomodulating therapies was common: intravenous immune globulin (IVIG) was used in 144 (77%), glucocorticoids in 91 (49%), and interleukin-6 or -1RA inhibitors in 38 (20%). Remarkedly, the MIS-C peaked about one month after the nadir of the pandemic first wave in the US.

To address the burden of MIS-C in France, a nationwide surveillance program was launched by "Santé Publique France" and the French Pediatric Society on April 30, 2020 [19]. As of June 21, 2020, a total of 195 cases (i.e., hospitalizations) had been reported, with 138 classified as being related with SARS-CoV-2. Likewise, a sharp decrease in the incidence of MIS-C cases occurred 3 to 4 weeks after the decrease of the outbreak in France (Fig. 2). Taking advantage of this national database, it was recently shown that treatment with IVIG and methylprednisolone *vs.* IVIG alone was associated with a more favorable fever course [20].

Multisystem inflammatory syndrome in children associated with SARS-CoV-2 and Kawasaki disease: a similar or dissimilar pathophysiology?

The epidemiology, putative pathophysiology, clinical and biological features (Fig. 3), and current treatment protocols for MIS-C associated with SARS-CoV-2 have been recently reviewed [21]. Key messages are the followings:

- Although SARS-CoV-2 infections in children are generally mild and non-fatal, there is a growing recognition of a paediatric inflammatory multisystem syndrome-temporally associated with SARS-CoV-2 (PIMS-TS), also known as multisystem inflammatory syndrome in children (MIS-C) associated with COVID-19, which can lead to serious illness and long-term side-effects.
- Clinical and laboratory features of MIS-C (Fig. 3) are similar to those of Kawasaki disease, Kawasaki disease shock syndrome, and toxic shock syndrome, but the disorder has some distinct features, and it needs a clear clinical and pathophysiological definition.
- MIS-C might be distinct from Kawasaki disease, with features including age at onset of more than 7 years of age, a higher proportion of African or Hispanic children affected, and diffuse cardiovascular involvement suggestive of a generalized immune-mediated disease.
- Pathophysiology of MIS-C is still unclear and possible mechanisms include antibody or T-cell recognition of self-antigen (viral mimicry of the host) resulting in auto-antibodies, antibody or T-cell recognition of viral antigens expressed on infected cells, formation of immune complexes which activate inflammation, and viral superantigen sequences that activate host immune cells.

- Most cases of MIS-C associated with COVID-19 were managed using the standard protocols for Kawasaki disease, with inotropic and vasoactive agents often required in patients with cardiac dysfunction and hypotension and anticoagulation also used frequently; clinical research is required to prove the effectiveness and safety of those treatments.
- The medium-term to long-term outcomes of MIS-C, such as the sequelae of coronary artery aneurysm formation, remain unknown and close follow-up is important.

The immunology of MIS-C associated with COVID-19 has been recently assessed by peripheral blood mononuclear cell phenotypes using flow cytometry in 51children with MIS-C and 28 with Kawasaki disease [22]. Differences were found in the distributions of subpopulations of CD4+ T cells and the frequency of T-follicular helper cells. Furthermore, IL-17A is important in Kawasaki disease, but was significantly lower in MIS-C patients, indicating a difference in the underlying pathology. Likewise, peripheral leukocyte phenotyping has been performed in 25 children with MIS-C, in the acute stage (n=23), resolution (n=14), and convalescent (n=10) phases of the illness [24]. In the acute phase of MIS-C, high levels of interleukin-1β (IL-1β), IL-6, IL-8, IL-10, IL-17, interferon-γ, and differential T and B cell subset lymphopenia. High CD64 expression on neutrophils and monocytes, and high HLA-DR expression on γδ and $CD4^{+}CCR7^{+}$ T cells in the acute phase, suggested that these immune cells were activated. Antigen-presenting cells have low HLA-DR and CD86 expression, potentially indicative of impaired antigen presentation. These features normalized over the resolution and convalescent phases. Overall, MIS-C presents as an immunopathogenic illness, and appears distinct from Kawasaki disease. Altogether, MIS-C and Kawasaki disease share in common an overexuberant autoimmune component, although differences exist not only in the initial trigger [25], but also in the intrinsic pathophysiology [26].

CONCLUSIONS:

Although children are generally less susceptible to SARS-CoV-2 and less sick with very low mortality, a few of them may develop shock with cardiac dysfunction and systemic hypotension that requires vasoactive agents and fluid resuscitation. The 2 to 3 weeks gap between the initial COVID-19 viral phase and the hyperinflammatory phase leads to speculate on the complex interplay between the host immune response, viral antigens, and auto-

immunity and similarities or dissimilarities between MIS-C and Kawasaki disease. However, both entities share common therapeutic approaches including intravenous immune globulins and/or corticosteroids, with sometimes requirement to biotherapies. Nevertheless, the medium- and long-term outcomes of this new disease, particularly of coronary artery aneurysms, remain unknown and close follow-up is important up to the adult age.

(7 pages; 25 paragraphs; 232 lines; 2,686 words; 15,637 characters; 18,338 characters including spaces)

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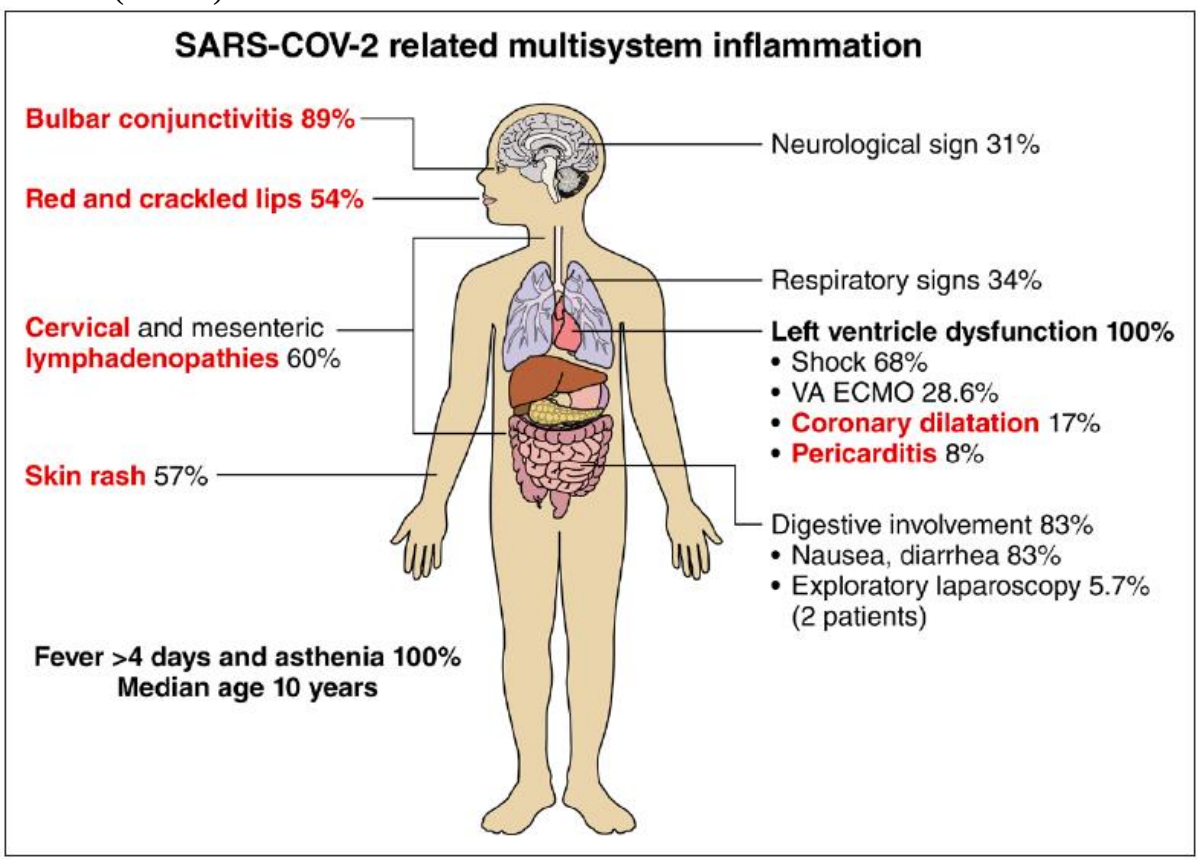
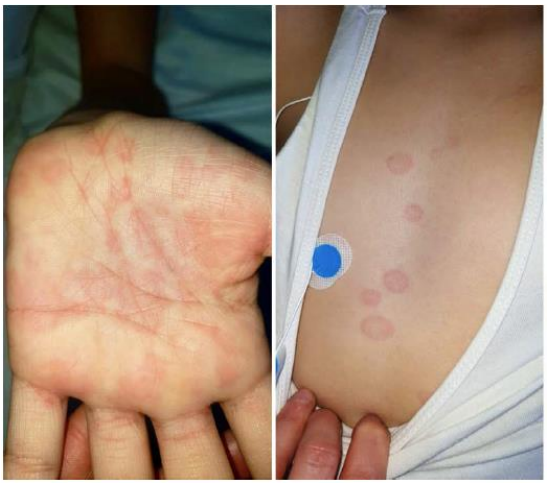
Legends

Fig. 1 – Schematic distribution of the clinical signs in multisystem inflammatory syndrome in children (MIS-C) associated with SARS-CoV-2.



VA-ECMO = veno-arterial Extra-Corporeal Membrane Oxygenation



Maculopapular rash in a 12-year-old girl.
Circulation 2020;142:429-36. (with permission)

Conjunctival injection

Figure 2 – Temporal distribution of Hospitalizations for COVID-19 and MIS-C in France

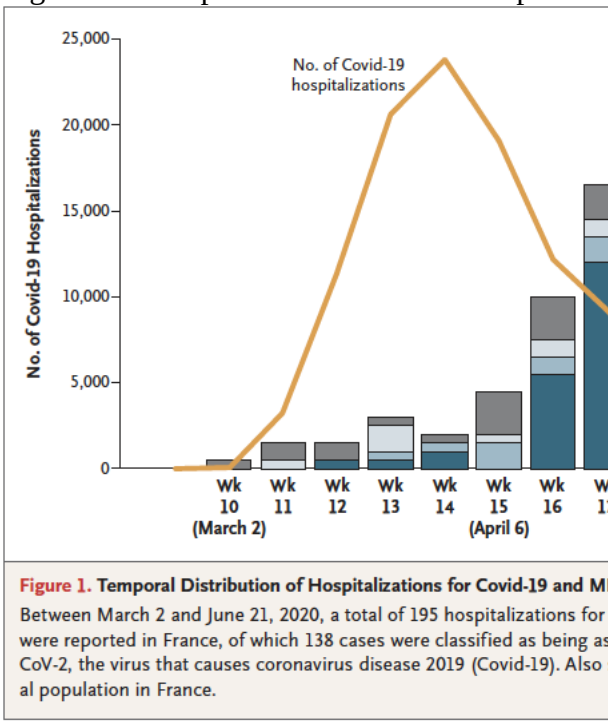
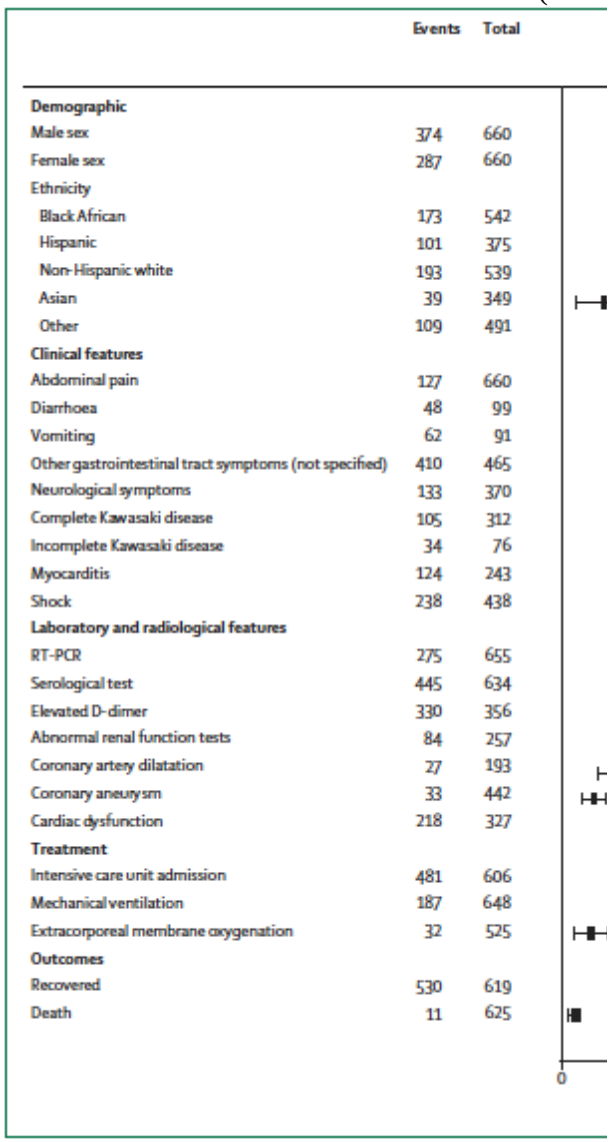


Figure 1. Temporal Distribution of Hospitalizations for Covid-19 and M
Between March 2 and June 21, 2020, a total of 195 hospitalizations for
were reported in France, of which 138 cases were classified as being as
CoV-2, the virus that causes coronavirus disease 2019 (Covid-19). Also
al population in France.

(N Engl J Med 2020 Oct 29;383(18):1793-4. with permission)

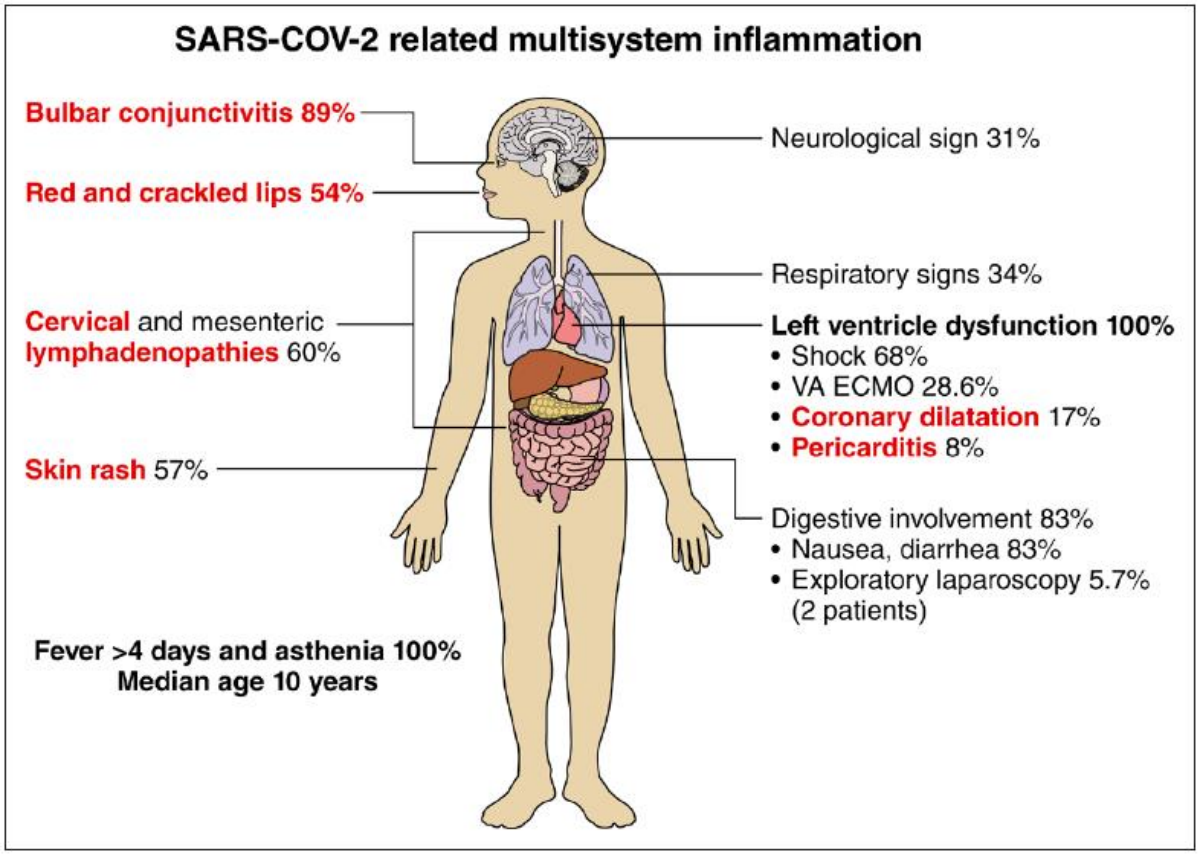
Fig. 3 – Pooled meta-analysis of patient characteristics in multisystem inflammatory syndrome in children associated with SARS-CoV-2 (Lancet Infect Dis 2020;20:e276-88. with permission)



	Events	Total
Demographic		
Male sex	374	660
Female sex	287	660
Ethnicity		
Black African	173	542
Hispanic	101	375
Non-Hispanic white	193	539
Asian	39	349
Other	109	491
Clinical features		
Abdominal pain	127	660
Diarrhoea	48	99
Vomiting	62	91
Other gastrointestinal tract symptoms (not specified)	410	465
Neurological symptoms	133	370
Complete Kawasaki disease	105	312
Incomplete Kawasaki disease	34	76
Myocarditis	124	243
Shock	238	438
Laboratory and radiological features		
RT-PCR	275	655
Serological test	445	634
Elevated D-dimer	330	356
Abnormal renal function tests	84	257
Coronary artery dilatation	27	193
Coronary aneurysm	33	442
Cardiac dysfunction	218	327
Treatment		
Intensive care unit admission	481	606
Mechanical ventilation	187	648
Extracorporeal membrane oxygenation	32	525
Outcomes		
Recovered	530	619
Death	11	625

Legends

Fig. 1 – Schematic distribution of the clinical signs in multisystem inflammatory syndrome in children (MIS-C) associated with SARS-CoV-2.



VA-ECMO = veno-arterial Extra-Corporeal Membrane Oxygenation

SARS-CoV-2-related Multisystem Inflammatory Syndrome in Children (MIS-C) mimicking Kawasaki Disease

Syndrome Multi-systémique Inflammatoire lié au SARS-CoV-2 chez l'Enfant (MIS-C) mimant un syndrome de Kawasaki.

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SUMMARY

The SARS-CoV-2 pandemic has been characterized by high transmission rates and high mortality in adults with predisposing factors including age >70 years, obesity, diabetes, systemic hypertension, and other underlying diseases. During the second week of viral pneumonia, Acute Respiratory Distress Syndrome (ARDS) can occur and carries high mortality. Unlike most common respiratory viruses, children seem to be less susceptible to SARS-CoV-2 infection and generally develop mild disease with low mortality. However, clusters of severe shock associated with high levels of cardiac biomarkers and unusual vasoplegia requiring inotropes, vasopressors and volume loading have recently been described. Both clinical symptoms (i.e., high and persistent fever, gastrointestinal disorders, skin rash, conjunctival injection and dry cracked lips) and biological signs (e.g., elevated CRP/PCT, high levels of ferritinemia) mimicked Kawasaki disease. In most cases, intravenous immunoglobin therapy improved the cardiac function and led to full recovery within a few days. Adjunctive steroid therapy and sometimes biotherapy (e.g., anti-IL-1Ra, anti-IL-6 monoclonal antibodies) were often necessary. Although almost all children fully recovered within a week, some of them later developed coronary artery dilation or aneurysm. Thus, a new 'Multisystem Inflammatory Syndrome in Children (MIS-C)' related to SARS-CoV-2 has recently been described. Similarities with Kawasaki disease and understanding of its physiopathology still needs further explorations. (215 words)

KEYWORDS : COVID-19 ; CHILDREN; MULTISYSTEM INFLAMMATORY SYNDROME TEMPORALLY ASSOCIATED WITH SARS-COV-2; CARDIOGENIC SHOCK; KAWASAKI SYNDROME.

RÉSUMÉ

La pandémie due à SARS-CoV-2 est caractérisée par une haute contagiosité et une mortalité élevée chez les adultes à risque (âge supérieur à 70 ans, obésité, diabète, hypertension, autres pathologies associées). Au décours d'une pneumonie virale, peut survenir une phase hyper-inflammatoire compliquée d'une défaillance multi-viscérale avec Syndrome de Détresse Respiratoire Aiguë (SDRA). Contrairement à la majorité des virus respiratoires, les enfants apparaissent moins susceptibles à SARS-CoV-2 et développent généralement une forme peu sévère, avec une faible mortalité. Cependant, des cas groupés d'états de choc associés à des biomarqueurs cardiaques élevés et à une vasoplégie inhabituelle nécessitant un traitement par inotropes, vasopresseurs et un remplissage vasculaire ont été récemment décrits. Les symptômes cliniques observés (fièvre élevée et durable, troubles digestifs, rash cutané, injection conjonctivale, chéléite) et le profil biologique (CRP/PCT élevées, hyperferritinémie) évoquent un syndrome de Kawasaki qui répond à un traitement par perfusion intraveineuse d'immunoglobulines complété si besoin par une corticothérapie et/ou une biothérapie anti-IL-1Ra ou anti-IL-6. La majorité des enfants guérit en quelques jours avec cependant une possible dilatation des artères coronaires. Ainsi, un nouveau syndrome inflammatoire multi-systémique associé à SARS-CoV-2 mimant un syndrome de Kawasaki a été récemment identifié chez l'enfant et questionne sur sa physiopathologie proche ou dissemblable de ce syndrome d'étiologie restée jusqu'ici inconnue. (208 mots)

MOTS-CLEFS : COVID-19 ; ENFANT ; SYNDROME INFLAMMATOIRE MULTI-SYSTEMIQUE TEMPORELLEMENT ASSOCIE A SARS-COV-2 ; CHOC CARDIOGENIQUE ; SYNDROME DE KAWASAKI.

INTRODUCTION

While SARS-CoV-2 pandemic was spreading worldwide with as to April 2021 more than 130 million infected persons and a death toll of more than 2.7 million people, children only accounted for a small fraction (~0.2%) of infected patients [1]. Most of the time, they presented with mild symptoms of viral upper and/or lower respiratory tract infection including short-lasting fever, dry cough, fatigue, myalgias and/or cephalalgia requiring in worst cases low-flow oxygen therapy and a few days of hospitalization [2]. Mortality rates were low, ranging from 0.02% in 5,015 children with mild disease to 2% in 319 children with severe disease and/or underlying chronic diseases including obesity [3].

However, clusters of children developing *'cardiogenic shock'* (i.e., shock associated with low left ventricular ejection fraction and elevated cardiac biomarkers) together with unusually low diastolic pressure suggestive of associated *'toxic shock'* [4] and other features similar to Kawasaki disease (KD) (high fever, cutaneous rash, and conjunctival injection) were described in England, Italy, France and the US. Two facts were particularly striking: i) this new syndrome called either '*Paediatric Inflammatory Multisystem Syndrome temporally-associated with SARS-CoV-2*' (PIMS-TS) in the UK or '*Multisystem Inflammatory Syndrome in Children'* (MIS-C) in the US occurred 2 to 4 weeks after an episode of SARS-CoV-2 infection, ii) the syndrome included high levels of inflammatory markers like CRP, ferritin, D-dimers, highly suggestive of *'cytokine storming'* [5]. Although inotropes or vasopressors were initially prescribed in most cases, hypotension was often responsive to fluid resuscitation. Furthermore, cardiac function rapidly improved after intravenous immunoglobulins and often steroids, and sometimes biotherapies. Lastly, unlike adults, cardiac function rapidly normalized within a few days. However, coronary artery wall ultrasound brightness and sometimes dilation of its proximal part as seen in KD was noticed, justifying a long-term follow-up.

CHILDREN ARE INDEED LESS SUSCEPTIBLE TO SARS-CoV-2

Several explanations have been raised in order to explain the apparent paradox between the frequent viral respiratory diseases observed in children all-around the year, but particularly during winter, e.g., human rhinoviruses (Group A, B, and C >100 serotypes), respiratory syncytial viruses (RSV A & B), influenza virus (A & B, several subtypes), para-influenza viruses (type 3 most common), human metapneumoviruses (subgroups A & B), adenoviruses

(>50 serotypes), enteroviruses (echo & coxsackie), and common coronaviruses (OC43, 229E, NL63, and HKU1) [6], and the new SARS-CoV-2. One of them lies in the fact SARS-CoV-2 infects epithelial respiratory cells through Angiotensin Converting Enzyme-2 Receptors which are less numerous and mature in children than in adults [7].

The extent to which children and adolescents are infected by and transmit severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is unclear. The role of children and adolescents SARS-CoV-2's transmission depends on susceptibility, symptoms, viral load, social contact patterns and behavior. To systematically review the susceptibility to and transmission of SARS-CoV-2 among children and adolescents compared with adults, a total of 13,926 studies were identified through PubMed or medRxiv up to July 28, 2020 [8]. A total of 32 studies comprising 41,640 children and adolescents, and 168,945 adults met inclusion criteria, including 18 contact-tracing studies and 14 population screening studies. The pooled odds ratio of being an infected contact in children compared with adults was 0.56 (95%CI 0.37-0.95) with substantial heterogeneity (I^2=94.6%). Three school-based contact-tracing studies found minimal transmission from child cases, although seroprevalence in adolescents appeared similar to adults. The recent diffusion of SARS-CoV-2 new variants in the community such as B1.1.7 which is more contagious did not result in an appreciably different clinical course to the original strain in children and young people [9].

MULTISYSTEM INFLAMMATORY SYNDROME IN CHILDREN (MIS-C)

Mid-April 2020, the *South Thames Retrieval Service, London* referred eight children with shock associated with elevated cardiac biomarkers (i.e., troponin and BNP) and inflammatory markers (e.g., CRP, ferritine, and D-dimers) over just 10 days, as compared to the usual 1-2 monthly cases of KD [9]. Remarkable were both clinical features (e.g., high fever >4 days, diarrhea, cutaneous rash, conjunctivitis) similar to KD, and the unusually low diastolic pressure as seen in toxic-shock syndrome (TSS) due to TSS-1 released by Methicillin-Resistant *Staphylococcus aureus* or Group A *Streptococcus* [4]. Six of these children were of Afro-Caribbean descent, and 4 of them obese (BMI>25 kg/m^2). Although there was no primary respiratory failure, most children were intubated and mechanically ventilated because of shock. Most of them required vasopressors (e.g., norepinephrine and/or milrinone), and one of them ultimately Extra-Corporeal Membrane Oxygenation (ECMO) support. All children were tested negative for SARS-CoV-2 in either nasopharyngeal swabs or bronchoalveolar lavage, but 4 of them had a

known parental exposure. All children were given intravenous immunoglobulins (2g/kg) within the first 24h and antibiotic coverage including ceftriaxone and clindamycin. Subsequently, six children were given orally 50mg/kg/day aspirin. A common echocardiographic finding was echo-bright coronary vessels which progressed to giant coronary aneurysms in one patient, one week after hospital discharge. All the children, except the one on ECMO who died from brain hemorrhage, were actually discharged from the pediatric intensive care unit (PICU) after 4 to 6 days.

In France, 35 children with shock associated with severe left ventricular dysfunction and marked inflammatory syndrome were retrospectively identified in 14 French PICUs over two months [10]. Median age at admission was 10 years (range 2-16). Comorbidities were present in 28%, including asthma and overweight. Gastrointestinal symptoms were predominant at the early stage, associated with clinical signs suggestive of KD, i.e., skin rash, conjunctivitis, red and cracked lips. Left ventricular ejection fraction was <30% in one-third of the cases; 80% required inotropic support and 28% went on ECMO. Inflammatory markers were suggestive of cytokine storm (median interleukin-6 135 [Interquartile range IQR 87-115] pg/mL) and macrophage activation (D-dimers 5284 [4069-9095] ng/mL). B-type natriuretic peptide (BNP) was markedly elevated (5743 [2648-11,909] pg/mL), as well as high-sensitivity troponin (347 [186-1267] ng/L). Thirty-one of 35 (88%) patients tested positive for SARS-CoV-2 infection by PCR of nasopharyngeal swabs or serology. All patients received intravenous immunoglobulin, with adjunctive steroid therapy in one-third of them. No patient died, and all patients supported by ECMO were successfully weaned off. Median [IQR] time to full recovery was rather short two [2-5] days, as found in another case series of acute myocarditis and MIS-C who fully recovered without the need of ECMO [11].

A time-series analysis at Robert Debré Hospital in Paris area, a French epicentre of the COVID-19 first wave outbreak, recorded the number of hospital admissions from the Pediatric Emergency Department for Kawasaki disease over the past 15 years [12]. Between Dec 1, 2005 and May 20, 2020, 230 patients diagnosed as Kawasaki disease estimated by the quasi-Poisson model was 1.2 per month [IQR, 1.1-1.3]. In April 2020, a rapid increase of KD related to SARS-CoV-2 (six cases per month, 497% increase [95% CI 72-1082], p=0.0011) was identified, starting two weeks after the peak of the pandemics. SARS-CoV-2 was actually the only virus circulating during the period and was found in 8 of 10 patients (80%) with Kawasaki disease with positive PCR or serology. A second peak of hospital admissions due to Kawasaki disease

was also observed in December 2009 (six cases per month, 365% increase [31-719], p=0.0053), concomitant with the influenza A H1N1 pandemic.

Fifty-eight children (median age 9 years [IQR 5.7-14.0]); 33 (57%) girls; 40 (60%) of African or Asian descent) from 8 hospitals in England admitted between March 23 and May 16, 2020, with persistent fever and laboratory evidence of inflammation meeting the published definition of "*Pediatric Inflammatory Syndrome Temporally Associated with SARS-CoV-2*" (PIMS-TS) was later reported [13]. All children presented with persistent fever for 3 to 19 days and variable combination of vomiting (26/58 [45%]), abdominal pain (31/58 [53%]), and diarrhea (30/58 [52%]). Rash was present in 30 of 58 (52%), and conjunctival injection in 26 of 58 (45%) cases. Laboratory evaluation was consistent with marked inflammation with median CRP 229 [IQR 156-338] mg/L and ferritin 610 [359-1280] µg/L. Of the 58 children, 29 developed shock that required inotropic support and fluid resuscitation, including 23/29 [79%] who received mechanical ventilation. Thirteen children met the American Heart definition of Kawasaki disease [14]; 23 had fever and inflammation without features of shock and Kawasaki disease. Comparison of PIMS-TS (n=58) with other cohorts of KD (n=1132), KDSS (n=45), and toxic shock syndrome TSS (n=37) showed differences in clinical and laboratory features that suggest this new disorder differs from other pediatric inflammatory entities (Table 1). PIMS-TS generally occurred in children older than those with KD and KDSS, and with different laboratory features (Fig. 1).

Similar cases, this time quoted as "*Multisystem Inflammatory Syndrome related to COVID-19*" (MIS-C), were described in 53 pediatric health centers across the US [15]. Case definition included six criteria: age lower than 21 years, fever that lasted for at least 24 hours, laboratory evidence of inflammation, evidence of infection with SARS-CoV-2 based on RT-PCR, antibody testing, or exposure to persons with COVID-19 in the past month, multisystem organ involvement, and serious illness leading to hospitalization (Table 1). From March 15 to May 20, 2020, 186 children with MIS-C were identified: 115 patients (62%) were male; 135 (73%) previously healthy, 131 (70%) positive for SARS-CoV-2 by RT-PCR or antibody testing. Most patients had elevations in at least four markers of inflammation. Organ-system involvement included the gastrointestinal system in 171 patients (92%), cardiovascular in 149 (80%), hematologic in 142 (76%), mucocutaneous in 137 (74%), and respiratory in 131 (70%). Median duration of hospitalization was 7 days [IQR 4-10]: 148 patients (80%) were admitted to the PICU, 37 (20%) were mechanically ventilated, 90 (48%) received vasoactive support, and 4

(2%) died. KD-like features were documented in 74 patients (40%), and coronary-artery aneurysms (z scores ≥2.5) in 15 (8%). The use of immunomodulating therapies was common: intravenous immune globulin (IVIG) in 144 (77%), glucocorticoids in 91 (49%), and interleukin-6 or -1RA inhibitors in 38 (20%). Remarkedly, MIS-C peaked about one month after the nadir of the pandemic first wave in the US.

To address the burden of MIS-C in France, a nationwide prospective surveillance of children hospitalized with SARS-CoV-2 infection was supported by "Santé Publique France" and the French Pediatric Society [16]. Likewise, a sharp increase in the incidence of MIS-C cases occurred about 3 to 4 weeks after the first and second waves of the SARS-CoV-2 pandemic in France (Fig. 2) [17]. Taking advantage of this national database including 181 children with suspected MIS-C, treatment with IVIG and methylprednisolone *vs.* IVIG alone was associated with lower risk of treatment failure (OR=0.25 [95%CI 0.09 to 0.70], *P*=.008) and lower risk of use of second-line therapy (OR=0.21 [95%CI 0.06-0.61], *P*=.004), hemodynamic support, acute left ventricular dysfunction, and median duration of stay in the PICU (4 vs. 6 days) [18].

MIS-C and Kawasaki disease: similar or different pathophysiology?

The epidemiology, putative pathophysiology, clinical and biological features, and current treatment protocols for MIS-C associated with SARS-CoV-2 have been recently reviewed [19]. Key messages are the followings:

- Although SARS-CoV-2 infections in children are generally mild and non-fatal, there is a growing recognition of a paediatric inflammatory multisystem syndrome-temporally associated with SARS-CoV-2 (PIMS-TS), also known as multisystem inflammatory syndrome in children (MIS-C) associated with COVID-19, which can lead to serious illness and long-term side-effects.
- Clinical and laboratory features of MIS-C (Fig. 3) are similar to those of KD, KDSS, and TSS, but this syndrome has distinct features and needs a clear clinical and pathophysiological definition.
- MIS-C might be distinct from KD, with features including age at onset of more than 7 years of age, a higher proportion of African or Hispanic children affected, and diffuse cardiovascular involvement suggestive of a generalized immune-mediated disease.
- Pathophysiology of MIS-C is still unclear and possible mechanisms include antibody or T-cell recognition of self-antigen (viral mimicry of the host) resulting in autoantibodies, antibody or T-cell recognition of viral antigens expressed on infected cells, formation of

immune complexes which activate inflammation, and viral superantigen sequences that activate host immune cells.

- Most cases of MIS-C associated with COVID-19 were managed using the standard protocols for KD, with inotropic and vasoactive agents often required in patients with cardiac dysfunction and hypotension and anticoagulation also used frequently; clinical research is required to prove the effectiveness and safety of those treatments.
- The medium-term to long-term outcomes of MIS-C, such as the sequelae of coronary artery aneurysm formation, remain unknown and close follow-up is important [20].

For almost half a century, the etiology of Kawasaki disease has remained elusive. Interestingly, a prospective population survey has been carried out in the UK and Ireland from 2013 to 2015 [21]. Five hundred and fifty-three cases were notified: 389 had complete KD, 46 had atypical KD and 116 incomplete KD. Presentation was highest in January and in rural areas. Most children were white (64%), but Chinese and Japanese Asians were overrepresented as were black African or African mixed-race children. Many of these features are also seen in studies from other countries, including the majority of cases being less than five years old, seasonal occurrence with more cases in winter and spring, a higher proportion of cases living in rural areas relative to the population distribution, and increased proportions of Asians and Africans suggesting a genetic background. Recently, Rowley *et al*. isolated peripheral blood plasmablasts from children with KD 1-3 weeks after onset and prepared 60 monoclonal antibodies (mAbs) [22]. Thirty-two mAbs from 9 of 11 patients recognize antigens within intracytoplasmic inclusion bodies in ciliated epithelial cells of fatal cases. Five of these mAbs, from 3 patients with coronary artery aneurysms, recognize a specific peptide which blocks binding to inclusion bodies. Sera from 5/8 KD patients, day ≥8 after illness onset, compared with 0/7 infant controls (P<.01), recognized the KD peptide antigen. Whether the protein epitope derives from a previously unidentified virus remains to be determined. However, mAbs recognized related peptides of a hepacivirus C NS4A using protein phase array. Thus, many lines of evidence now support a ubiquitous viral agent as the cause of KD in genetically susceptible children.

The immunology of MIS-C with COVID-19 has been recently assessed by analyses of blood immune cells, cytokines, and auto-antibodies in healthy children, children with KD disease enrolled prior to COVID-19, children infected with SARS-CoV-2, and children presenting with MIS-C [23]. The inflammatory response in MIS-C differs from the cytokine storm of severe

acute SARS-CoV-2, shares several features with Kawasaki disease, but also differs from this condition with respect to T-cell subsets, interleukin IL-17A, and biomarkers associated with arterial damage. Finally, autoantibody profiling suggests multiple autoantibodies and identified endoglin, a glycoprotein expressed by endothelial cells and necessary for structural integrity of arteries, to be possibly involved into the pathogenesis of MIS-C.

CONCLUSIONS:

Although children are generally less susceptible to SARS-CoV-2 and less sick with very low mortality, a few of them may develop shock with cardiac dysfunction and diastolic hypotension that requires vasoactive agents and fluid resuscitation. The 2 to 4 weeks gap between the initial COVID-19 viral phase and the hyperinflammatory phase leads to speculate on the complex interplay between the host immune response, viral antigens, and auto-immunity and similarities or dissimilarities between MIS-C and KD. However, both entities share common therapeutic approaches including intravenous immune globulins and/or corticosteroids, with sometimes requirement to biotherapies. Nevertheless, the medium- and long-term outcomes of this new disease, particularly regarding coronary artery aneurysms, remain unknown and close follow-up is important up to the adult age.

(7 pages, 25 paragraphs, 221 lines, 2548 words, 14,945 characters, 17,495 characters including spaces)

Table 1 – Clinical and Laboratory Features of Multisystem Inflammatory Syndrome in Children (MIS-C) [15], Kawasaki Disease (KD) [14], Kawasaki Disease Shock Syndrome (KDSS) [14], and Toxic-Shock Syndrome (TSS) [4].

	MIS-C	**KD**	**KDSS**	**TSS**
Age	>8 years	<5 years		Any age
Fever	>5 days	>5 days		>39°C
Suggestive signs	At least 1 among: - Exanthem - Conjunctival hyperhemia - Cracked lips - Cervical adenopathy	At least 4 among: – Exanthem – Conjunctival – Cracked lips – Cervical adenopathy – Peeling extremities	At least 4 among: – Exanthem – Conjunctival – Cracked lips – Cervical adenopathy – Peeling extremities	At least 1 among - Diffuse erythrodermia - Desquamation of extremities - Conjunctival hyperhemia
Cardiac dysfunction	Acute myocarditis HypoTA (diastolic)	Acute myocarditis	Acute myocarditis Shock	HypoTA (diastolic)
Coronary dilation	~10%	~10%	~10%	None
Gastrointestinal	Diarrhea, vomiting	Diarrhea, vomiting	Diarrhea, vomiting	Diarrhea, vomiting
Musculoskeletal		Myalgias, arthralgias		Severe myalgias
Inflammatory markers	Elevated CRP Lymphopenia Elevated D-dimers Hypoalbuminemia	Elevated CRP Leukocytosis Thrombocytosis Hypoalbuminemia		Elevated CRP Leukocytosis or leukopenia Thrombocytopenia
Cardiac biomarkers	Elevated BNP, troponine			
Etiology	SARS-CoV-2 PCR or serology	So far none	So far none	Blood cultures : Strepto A or *Staph aureus* (TSS-1)
Treatment	Inotropes + fluids **IVIGs + steroids**	Antiplatelets **IVIGs ± steroids**	Inotropes **IVIGs ± steroids**	Inotropes + fluids IV **antibiotics** (C3G + Dalacine)

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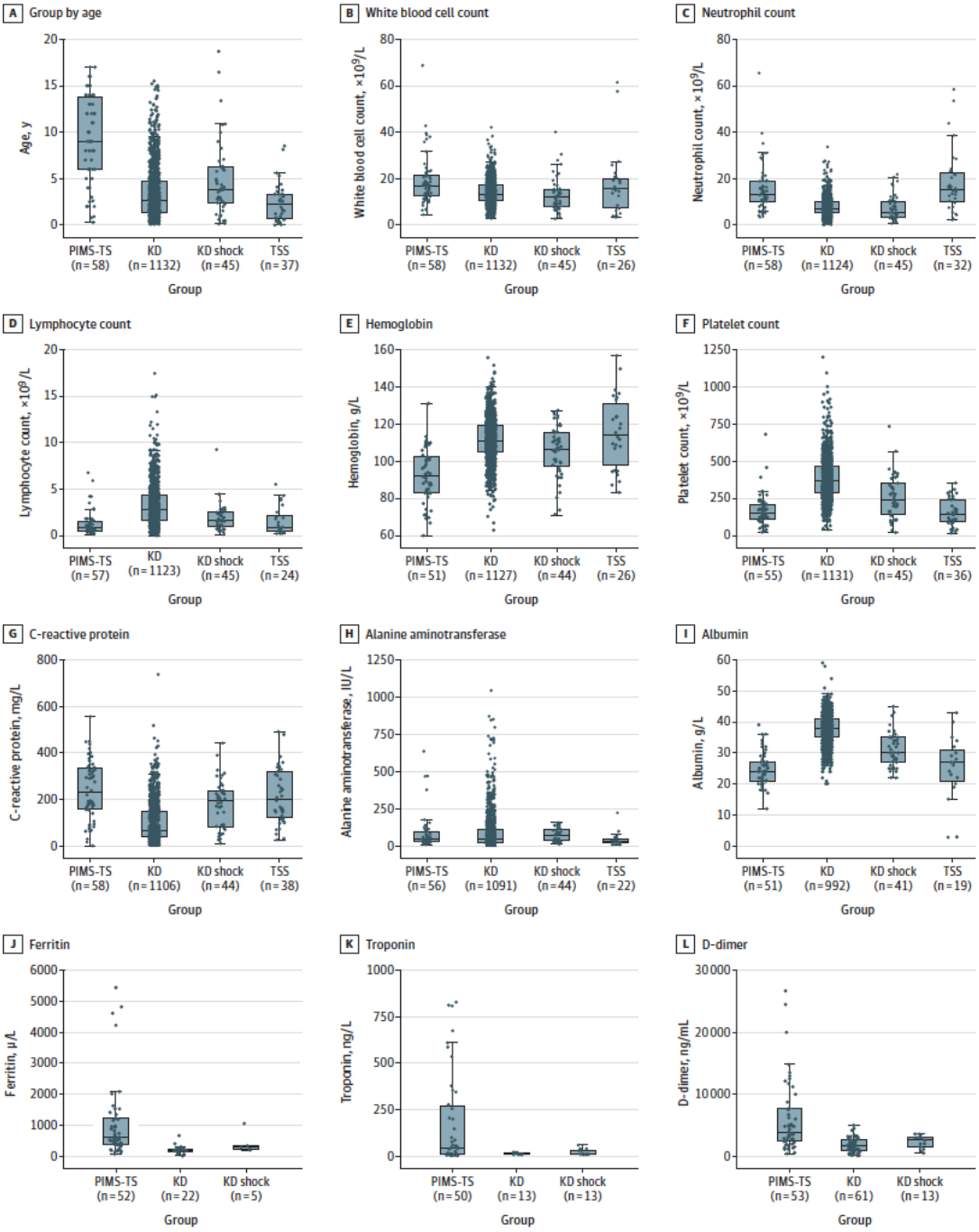
Legends

Fig. 1 – Comparison for age and laboratory results between PIMS-TS =Paediatric Inflammatory MultiSystem-Temporally associated with SARS-CoV-2 (n=58) KD = Kawasaki Disease (n=1132); KD shock = Kawasaki Disease Shock Syndrome (n=45); TSS= Toxic Shock Syndrome (n=37) [13] (with permission)



The horizontal lines in the boxes indicate medians; lower and upper edges of the boxes indicate interquartile range and the bars extend to the highest and lowest value within 1.5 times the interquartile range.

Figure 2 – Temporal distribution of Hospitalizations for COVID-19 and MIS-C in France [17]

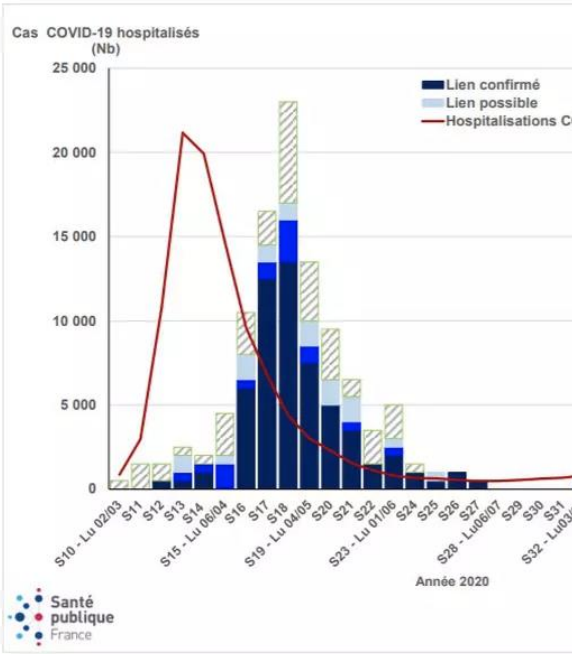
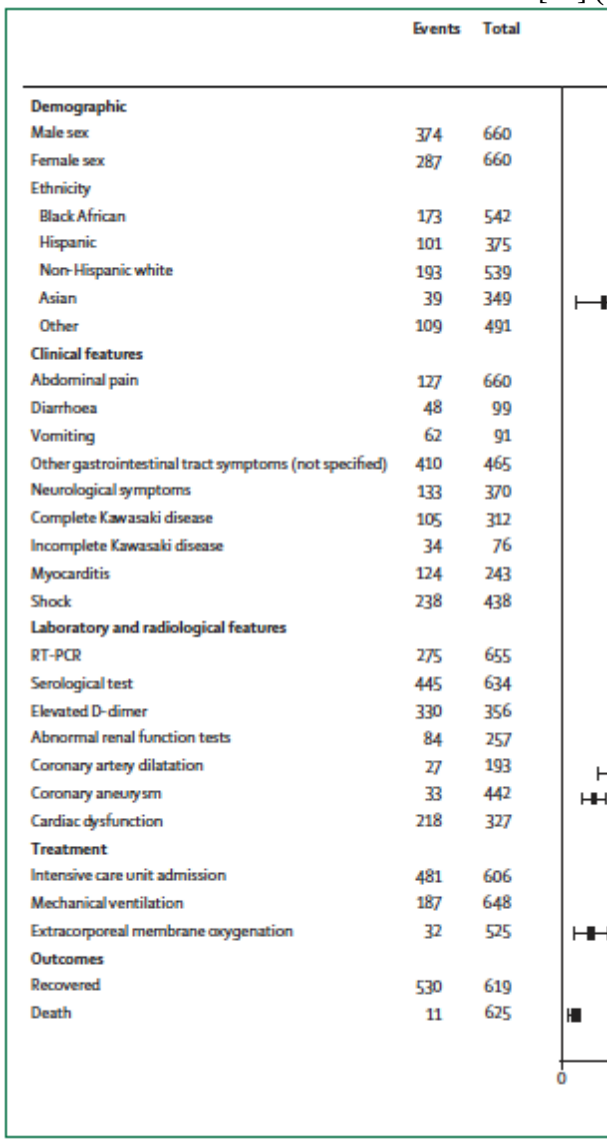


Fig. 3 – Pooled meta-analysis of patient characteristics in multisystem inflammatory syndrome in children associated with SARS-CoV-2 [19] (with permission)



	Events	Total
Demographic		
Male sex	374	660
Female sex	287	660
Ethnicity		
Black African	173	542
Hispanic	101	375
Non-Hispanic white	193	539
Asian	39	349
Other	109	491
Clinical features		
Abdominal pain	127	660
Diarrhoea	48	99
Vomiting	62	91
Other gastrointestinal tract symptoms (not specified)	410	465
Neurological symptoms	133	370
Complete Kawasaki disease	105	312
Incomplete Kawasaki disease	34	76
Myocarditis	124	243
Shock	238	438
Laboratory and radiological features		
RT-PCR	275	655
Serological test	445	634
Elevated D-dimer	330	356
Abnormal renal function tests	84	257
Coronary artery dilatation	27	193
Coronary aneurysm	33	442
Cardiac dysfunction	218	327
Treatment		
Intensive care unit admission	481	606
Mechanical ventilation	187	648
Extracorporeal membrane oxygenation	32	525
Outcomes		
Recovered	530	619
Death	11	625

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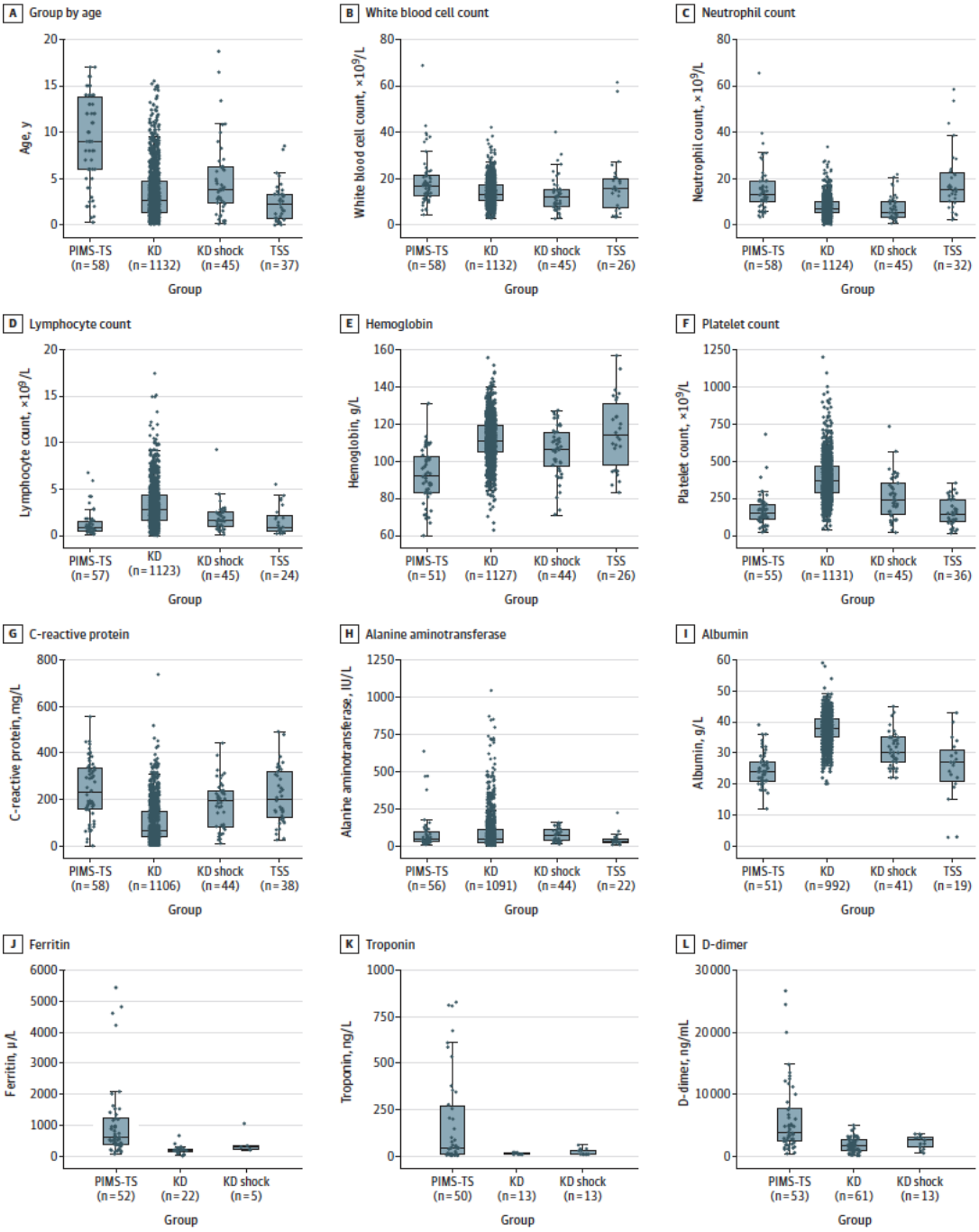

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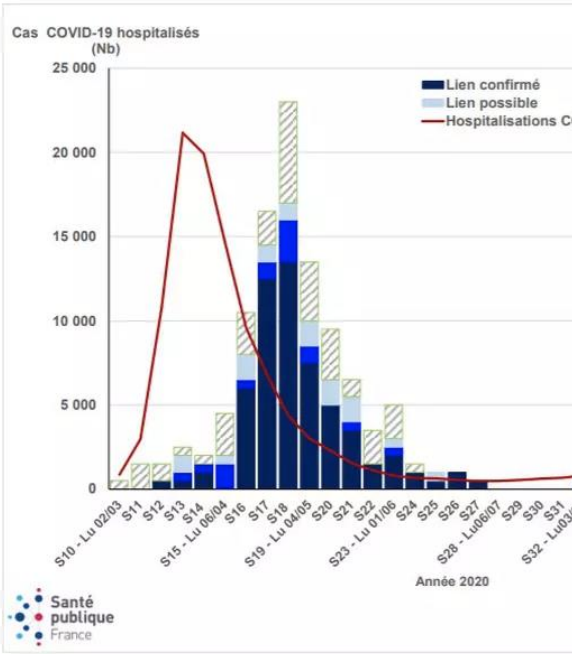

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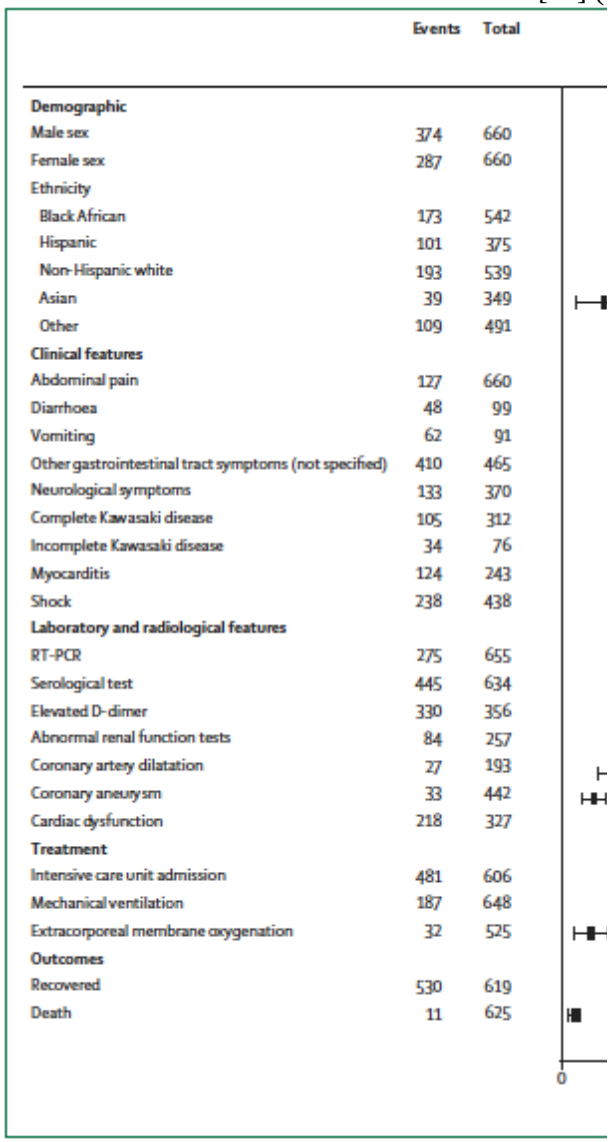

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