Correspondence to 'Paediatric multisystem inflammatory syndrome temporally associated with SARS-CoV-2 mimicking Kawasaki disease (Kawa-COVID-19): a multicentre cohort'

We read with interest the clinical study entitled 'Paediatric multisystem inflammatory syndrome temporally associated with SARS-CoV-2 mimicking Kawasaki disease (Kawa-COVID-19): a multicentre cohort' by Pouletty *et al*.[1] In this series, the authors suggest that paediatric multisystem inflammatory syndrome temporally associated with SARS-CoV-2 (PMIS-TS) may represent a new inflammatory syndrome, different from classical Kawasaki disease (KD) as it occurs at an older age, and with a higher frequency of severe myocarditis.[1]

Likewise to this study, our Pediatric Tuscany Network (PTN)—16 paediatric units serving a region of 593 606 people aged less than 18 years—worked out the COVASAKI survey to detect the incidence of PMIS-TS cases and the eventual rise of KD in Tuscany during COVID-19 pandemic. Between 1 February 2000 and 30 June 2020, we tracked children with PMIS-TS and KD, aiming to compare the number of KD cases in the same 5 months of the previous 5 years and overall with the total number in the last 5 years.

No PMIS-TS cases were reported in our region. Ten KD children were diagnosed in 5 units (incidence two per month). Demographics, clinical and imaging findings, treatment and outcome of patients are reported in table 1. No specific intensive support was required. No coronary involvement was reported. Nasopharyngeal swabs (performed in 7/10) and serological test (available in 6/10) for SARS CoV-2 resulted negative.

From 1 January 2015 to 31 January 2020, 165 KD were diagnosed (incidence 2.7 per month): 59 were incomplete; 3 developed macrophage activation syndrome (MAS) and 1 KD shock syndrome (KDSS). Thirty-eight showed coronary involvement, with persistent ectasia/aneurisms in five. Eleven children

Table 1 Demographics, clinical findings, imaging findings, treatment and outcome of patients with Kawasaki disease

	Age weight comorbidities	Clinical presentation	Pharmacological treatment	Imaging results	Laboratory results	SARS CoV-2 tests	Hospital length of stay	Outcome
Patient 1 (female, Caucasian)	3 years, 15 kg no comorbidities	5 days fever (T>38°C), rash, palm-plantar oedema, conjunctivitis, cheilitis, lymphadenopathy, irritability, arthralgia	IVIG, aspirin and intravenous antibiotics	Normal abdominal US and echocardiography	WCC 14.38 10^9/L, ESR 53 mm/hour, CRP 12.5 mg/dL, ALT 238 UI/l	Nasopharyngeal swab: negative Serological test: negative	8 days	Complete recovery
Patient 2 (male, Caucasian)	4 years, 15 kg, no comorbidities	6 days fever (T>38°C), rash, conjunctivitis, cheilitis, lymphadenopathy, irritability, vomiting	IVIG, aspirin and intravenous antibiotics	Normal abdominal US and echocardiography	WCC 25.57 10^9/L PLT 528, ESR 120 mm/hour, CRP 16.4 mg/dL, fibrinogen 937 mg/dL	Not performed	7 days	Complete recovery
Patient 3 (male, Caucasian)	4 years, 17 kg, no comorbidities	9 days fever (T>38°C), rash, palm-plantar oedema cheilitis, lymphadenopathy, irritability, myalgia	IVIG, aspirin and intravenous antibiotics	Normal echocardiography	WCC 11.55 10^9/L, ESR 63 mm/hour, CRP 10 mg/dL, ferritin 116 ng/mL	Nasopharyngeal swab: negative Serological test: negative	8 days	Complete recovery
Patient 4 (female, Caucasian)	2 years, 11 kg, congenital hypothyroidism	5 days fever (T>38°C), rash, conjunctivitis, cheilitis, dyspnoea, irritability	IVIG, aspirin and intravenous antibiotics	Normal echocardiography, reactive lymphadenopathy at neck US, pneumonitis at chest US	WCC 3.47 10^9/L, L 0.7 10^9/L, ESR 4 mm/hour, CRP 2.1 mg/dL	Not performed	16 days	Complete recovery
Patient 5 (female, Caucasian)	2 years, 11 kg, no comorbidities	5 days fever (T>38°C), rash, conjunctivitis, cheilitis, lymphadenopathy, irritability	Methylprednisolone, IVIG, aspirin and intravenous antibiotics	Normal abdominal US and echocardiography, pneumonitis at chest XR	WCC 9.36 10^9/L, PLT 277 10^9/L Hb 8.3 g/dL, ESR 76 mm/hour, CRP 4.61 mg/dL, ferritin 866 ng/dL, triglycerides 419 mg/dL, albumin 1.98 g/dL	Nasopharyngeal swab: negative Serological test: negative	15 days	Complete recovery
Patient 6 (female, Asiatic)	2 years, 12 kg, no comorbidities	5 days fever (T>38°C), febrile seizures, rash, conjunctivitis, cheilitis, palm-plantar oedema lymphadenopathy, arthritis	IVIG (2 courses), aspirin and intravenous antibiotics	Normal echocardiography, pneumonitis at chest XR, hydrops of the gallbladder at abdominal US	WCC 12.60 10^9/L, ESR 59 mm/hour, CRP 26.02 mg/dL, ALT 485 UI/L, AST 536 UI/L, fibrinogen 924 mg/dL, ferritin 227 ng/mL	Nasopharyngeal swab: negative Serological test: negative	11 days	Complete recovery
Patient 7 (male, Caucasian)	1.5 years, 10.4 kg, no comorbidities	5 days fever (T>38°C), rash, conjunctivitis, cheilitis	IVIG, aspirin and intravenous antibiotics	Normal echocardiography	WCC 17.28 10^9/L, ESR 31 mm/hour, Hb 9.8 g/dL CRP 5.96 mg/dL	Not performed	10 days	Complete recovery
Patient 8 (female, Caucasian)	4 years, 15.5 kg, no comorbidities	5 days fever (T>38°C), rash, conjunctivitis, cheilitis lymphadenopathy	IVIG and aspirin	Normal echocardiography, hydrops of the gallbladder at abdominal US	WCC 19.90 10^9/L, ESR 120 mm/hour, CRP 25.72 mg/dL, fibrinogen 620 mg/dL, ferritin 183 ng/mL	Nasopharyngeal swab: negative Serological test: not performed	9 days	Complete recovery
Patient 9 (male, Hispanic)	4 years, 16 kg, no comorbidities	5 days fever (T>38°C), rash, conjunctivitis, cheilitis, palm-plantar oedema, lymphadenopathy	IVIG and aspirin	Normal echocardiography, hydrops of the gallbladder at abdominal US	WCC 21.36 10^9/L, ESR 120 mm/hour, CRP 12.00 mg/dL, fibrinogen 566 mg/dL, ALT 123 UI/L	Nasopharyngeal swab: negative Serological test: negative	16 days	Complete recovery
Patient 10 (female, Hispanic)	4 years, 15 kg, no comorbidities	5 days fever (T>38°C), rash, conjunctivitis, cheilitis lymphadenopathy	IVIG and aspirin	Normal echocardiography	WCC 21.29 10^9/L, ESR 89 mm/hour, CRP 9.16 mg/dL, fibrinogen 709 mg/dL, ALT 12 UI/L, AST 77 UI/L	Nasopharyngeal swab: negative Serological test: negative	13 days	Complete recovery

ALT, alanine aminotransferase; AST, aspartate aminotransferase; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; Hb, haemoglobin; IVIG, intravenous immunoglobulins; L, lymphocytes; PLT, platelets; US, ultrasonography; WCC, white cell count; XR, radiography.

received steroid pulses and additional three biological therapy. No significant difference has been shown regarding the incidence/month (RR 1.21, 95% CI 0.60 to 2.20), neither limiting the analysis to the 56 children with KD diagnosed during the same corresponding 5 months of the last 5 years: 2.2 versus 2.0 incidence/month (RR 0.89, 95% CI 0.42 to 1.69).

The KD incidence rate adjusted for the 3801 children hospitalised in Tuscany in the 2020 index 5 months resulted 0.26%.

No significant differences were detected among the principal KD outcomes during the COVID-19 time and in the last 5 years: incomplete KD 59 versus 2, $\chi^2=1.03$; KDSS 1 versus 0, $\chi^2=0.06$; MAS: 3 versus 1, $\chi^2=2.81$; coronary involvement 38 versus 0, $\chi^2=2.92$. The same results have been observed limiting the analysis to the corresponding index 5 months of the last 5 years (p=n.s, Fisher's exact test).

From 1 February to 30 June, 8,637 nasopharyngeal swabs have been performed to the Tuscan children admitted to the hospitals: 157 resulted positive for SARS CoV-2. Serological tests have been performed in 2100 children: 127 were positive for antibodies.

Although the 10,500 COVID-19 Tuscany positive cases represent the fifth Italian highest number, our region reported a lower prevalence of infection compared with other high-prevalence areas in the North of Italy.[2] This epidemiological context may explain the lack of patients with PIMS-TS. However, our survey, as previously reported in other cohorts,[1 3–6] provides epidemiological evidence that the clinical spectrum of PMIS-TS differs from classical KD: median age of our patients with KD was lower (3.5 years), gastrointestinal symptoms were absent, any myocarditis was reported and all patients presented a benign disease course, responsive to a single dose of intravenous immunoglobulins in most of cases. Additionally, no significant increase of KD cases has been documented.

The PIMS-TS may in some cases mimic KD at onset, even if its typical clinical manifestations are characterised by a greater framework of systemic inflammation and haemodynamic involvement. At this regard, Whittaker *et al* and Cheung *et al* reported that only 28% (21/75) of PMIS-TS children met the American Heart Association criteria for KD diagnosis.[3 4]

These clinical differences also lead to pathogenetic implications. Most of patients with PIMS-TS presented a low viral load at diagnosis and/or showed positivity to serological tests. The high rate of SARS CoV-2 IgG positivity, usually mirror of a past infection, seems to suggest a reactive immunological response to a previous viral infection rather to an acute one, that is, instead, traditionally assumed as potential causative trigger of KD.

These considerations pose the clinical question whether different treatment approaches, that is, the immunomodulating agents, may be preferable to that strategies, such as intravenous immunoglobulins, that evidenced benefits in KD.

In conclusion, the epidemiology COVASAKI survey showed a KD incidence rate during COVID-19 pandemic identical to what previously reported in Tuscany along with clinical characteristics of typical KD picture.[7]

The well-structured collaboration of our PTN has ensured a prompt recognition of children with suspected KD, thus avoiding diagnostic and treatment delay. Keeping updated our register, a comparison between the COVASAKI survey and the worldwide results will better define the multifaceted nature of the paediatric COVID-19 disease and, if any, the potential relationship between PIMS-TS and KD.

Maria Vincenza Mastrolia,[1] **Rino Agostiniani**,[2] **Chiara Azzari**,[3] **Roberto Bernardini**,[4] **Ugo Bottone**,[5] **Giovanni Battista Calabri**,[6] **Flavio Civitelli**,[7] **Rita Consolini**,[8] **Roberto Danieli**,[9] **Rosalia Di Silvio**,[10] **Susanna Falorni**,[11] **Luigi Gagliardi**,[12] **Salvatore Grosso**,[13] **Marco Martini**,[14] **Graziano Memmini**,[15] **Diego Peroni**,[16] **Marco Pezzati**,[17] **Giovanni Suriano**,[18] **Luca Tafi**,[19] **Angelina Vaccaro**,[20] **Pier Luigi Vasarri**,[21] **Gabriele Simonini**,[22] **On behalf of the Paediatric Tuscany Network**

[1]Rheumatology Unit, Meyer Children's University Hospital, Firenze, Italy
[2]Pediatric Unit, San Jacopo Hospital, Pistoia, Italy
[3]Department of Health Science, Pediatric Immunology Unit, Meyer Children's University Hospital, Firenze, Italy
[4]Pediatric Unit, San Giuseppe Hospital, Empoli, Italy
[5]Division of Neonatology and Pediatrics, Lotti Hospital, Pontedera, AUSL Toscana Nord Ovest, Pisa, Italy
[6]Cardiology Unit, Meyer Children's University Hospital, Firenze, Italy
[7]Division of Neonatology and Pediatrics, Montepulciano Hospital, Montepulciano, AUSL Toscana Sud Est, Siena, Italy
[8]Department of Clinical and Experimental Medicine, Section of Clinical and Laboratory Immunology, University of Pisa, Pisa, Italy
[9]Division of Neonatology and Pediatrics, Spedali Riuniti di Livorno, AUSL Toscana Nord Ovest, Livorno, Italy
[10]Pediatric Unit, Mugello Hospital, Borgo San Lorenzo, Firenze, Italy
[11]Pediatric Unit, Misericordia Hospital, Grosseto, Italy
[12]Division of Neonatology and Pediatrics, Versilia Hospital, Viareggio, AUSL Toscana Nord Ovest, Pisa, Italy
[13]Department of Molecular Medicine and Development, University of Siena, Clinical Pediatrics, Siena, Italy
[14]Pediatric Unit, San Donato Hospital, Arezzo, Italy
[15]Division of Neonatology and Pediatrics, Apuane Hospital, AUSL Toscana Nord Ovest, Massa Carrara, Italy
[16]Section of Pediatrics, Department of Clinical and Experimental Medicine, University of Pisa, Pisa, Italy
[17]Pediatric Unit, Santa Maria Annunziata Hospital, Bagno a Ripoli, AUSL Toscana Centro, Firenze, Italy
[18]Division of Neonatology and Pediatrics, Cecina Hospital, Cecina, AUSL Toscana Nord Ovest, Pisa, Italy
[19]Paediatric and Neonatal Unit, Valdarno Hospital, Montevarchi, Arezzo, Italy
[20]Division of Neonatology and Pediatrics, San Luca Hospital, AUSL Toscana Nord Ovest, Lucca, Italy
[21]Paediatric and Neonatologic Unit, Santo Stefano Hospital, Prato, Italy
[22]Rheumatology Unit, Department Neurofarba, Meyer Children's University Hospital, Firenze, Italy

Correspondence to Dr Gabriele Simonini, Rheumatology Unit, Meyer Children's University Hospital, Department NEUROFARBA, Firenze 50139, Italy; gabriele.simonini@unifi.it

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ORCID iD
Maria Vincenza Mastrolia http://orcid.org/0000-0002-9784-3543

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