Kawasaki disease in pediatric isolation ward during COVID-19 pandemic

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Research Article

Keywords: Kawasaki disease, pediatric, isolation ward, COVID-19

Posted Date: November 19th, 2020

DOI: <https://doi.org/10.21203/rs.3.rs-111880/v1>

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Abstract

Background: To our knowledge, a link between an emergence of Kawasaki disease and the ongoing COVID-19 pandemic has not been reported in China.

Methods: This study retrospectively analyzed the clinical data of Kawasaki patients admitted to Maternal and Child Health Hospital of Hubei Province from January 1, 2015 to July 31, 2020. Kawasaki patients admitted to the isolation ward from January 1, 2020 to July 31, 2020 as the current cohort and Kawasaki patients admitted to the general wards from January 1, 2015 to December 31, 2019 as the historical cohort were analyzed.

Results: The current cohort comprised 15 patients (10 boys and 5 girls, median age 11 months) without severe form. SARS-CoV-2 nucleic acid test was performed in 13 cases and SARS-CoV-2 antibodies (IgM and IgG) was conducted in 11 cases, but no positive results were found. The historical cohort included 89 patients (54 boys and 35 girls, median age 15 months). Comparison between the historical cohort and the current cohort demonstrated that there were no significant differences in age, sex, clinical manifestations, blood routine examination, blood biochemistry, cardiac ultrasound and treatment, but the incidence and the abnormal chest imaging in the current cohort were significantly higher than those in the historical cohort.

Conclusion: This study suggested that there may be an association between the emergence of Kawasaki disease with non-severe form and COVID-19 pandemic in Wuhan.

Impact Statement

Studies in Europe demonstrated COVID-19 was associated with high incidence of a severe form of Kawasaki disease. A link between an emergence of Kawasaki disease and the ongoing COVID-19 pandemic has not been reported in China.

The aim of this study was to explore the incidence and features of Kawasaki disease admitted to the isolation ward of a tertiary pediatric referral centre during COVID-19 pandemic in Wuhan, China.

Introduction

In December 2019, an outbreak of pneumonia caused by infection with a new type of coronavirus (severe acute respiratory syndrome coronavirus 2, SARS-CoV-2) occurred in Wuhan, Hubei Province, China. The disease has spread rapidly to other parts of China and many other countries and became a global health emergency [1]. The World Health Organization (WHO) named the illness associated with SARS-CoV-2 as the 2019 coronavirus disease (COVID-19) [2]. Because of its characteristics of human-to-human transmission, the National Health Commission of China has published the corresponding guidelines for diagnosis, treatment, prevention, and control of COVID-19 [3,4]. According to this guideline, Kawasaki disease with fever as the main manifestation was admitted to the isolation ward during COVID-19 pandemic. In the past few months, alerts on paediatric multisystem inflammatory syndrome temporally linked to SARS-CoV-2 in UK and multisystem inflammatory syndrome in children associated with COVID-19 in USA have been reported [5,6]. An observational cohort study in Italy and a multicenter cohort study in France also demonstrated COVID-19 was associated with high incidence of a severe form of Kawasaki disease [7,8]. There were also several case reports mentioned that the relationship between Kawasaki disease and COVID-19 [9-11]. To our knowledge, a link between an emergence of Kawasaki disease and the ongoing COVID-19 pandemic has not been reported in China. In the present study, the clinical characteristics of patients with Kawasaki disease in isolation ward from January 1, 2020 to July 31, 2020 in Maternal and Child Health Hospital of Hubei Province were analyzed retrospectively. The aim of this study was to explore the incidence and features of Kawasaki disease admitted to our isolation ward during COVID-19 pandemic in Wuhan.

Methods

Patients involvement

This study retrospectively analyzed the clinical data of Kawasaki patients admitted to Maternal and Child Health Hospital of Hubei Province from January 1, 2015 to July 31, 2020. Kawasaki patients admitted to the isolation ward from January 1, 2020 to July 31, 2020 as the current cohort and Kawasaki patients admitted to the general wards from January 1, 2015 to December 31, 2019 as the historical cohort were analyzed. As a tertiary pediatric referral centre in Wuhan, Hubei Province, China, Maternal and Child Health Hospital of Hubei Province has undertaken the diagnosis and treatment of the majority of febrile children in Wuhan and surrounding area. All the Kawasaki patients were admitted to the isolation ward due to fever during COVID-19 pandemic. Kawasaki disease was diagnosed according to the diagnostic criteria of the American Heart Association [12]. This study was approved and patient informed consent was waived by the Medical Ethics Committee of Maternal and Child Health Hospital of Hubei Province.

Data collection

Demographic information (age, sex, and residential location), clinical features (medical history, exposure history, symptoms and sign), [imageological examination](#) (chest CT or X-ray, echocardiography), electrocardiograph, laboratory results (white blood cell counts, platelet counts, neutrophils, lymphocytes, C-reactive protein, procalcitonin, erythrocyte sedimentation rate, serum ferritin, alanine transaminase, [aspartate](#) transaminase, albumin, Mycoplasma pneumoniae, Epstein-Barr virus, influenza A, influenza B, adenovirus, SARS-CoV-2 nucleic acid and antibodies), treatment (immunoglobulin, aspirin, corticosteroid, antiviral therapy), length of hospital stay and response to treatment of each patient were obtained from the electronic medical record system of Maternal and Child Health Hospital of Hubei Province. The laboratory data of SARS-CoV-2 nucleic acid and SARS-CoV-2 antibodies for some patients were missing due to the absence of detection reagent. The data was reviewed by three physicians.

The counting data are described as percentage(%), non-normally distributed continuous data are presented as medians and interquartile ranges (25-75th). The Mann-Whitney U test or χ^2 test were performed for comparison between the current cohort and the historical cohort. Statistical analyses were performed using the SPSS software v.19.0 (IBM Corp.). $P < 0.05$ was considered statistically significant.

Results

15 patients with Kawasaki disease were admitted to the isolation ward between January 1, 2020 and July 31, 2020. The incidence was 2.14 per month. There were 10 males and 5 females, and the male-to-female ratio was 2:1. The median age was 11 months (IQR 4 to 17), ranging from 1 month to 4 years and 8 months. The majority (87%) of them were less than 2 years old, and 8 (53%) cases were less than 1 years old. 8 (53%) patients were admitted to hospital between January 23 and April 8, which was the period when Wuhan was closed down. All patients were local residents of Wuhan, who lived in Wuhan during COVID-19 pandemic. All patients had no direct exposure history of Huanan Seafood Wholesale Market or wildlife animals (The first COVID-19 were confirmed to be linked to Huanan Seafood Wholesale Market) [13]. All patients had no close contact with the confirmed or suspected COVID-19 patients. Only 2 (13%) patients had a history of eczema, and none of the others had a history of allergy. One patient had favism (glucose-6-phosphate dehydrogenase deficiency). One patient was preterm and the rest were full-term.

All 15 patients had hyperpyrexia with body temperature more than 39°C. 13 (87%) cases were classic Kawasaki disease and 2 (13%) cases were incomplete Kawasaki disease. Patients presenting with the classic form had polymorphic rash ($n=14$, 93%), bilateral conjunctival congestion ($n=15$, 100%), erythema and cracking of lips ($n=12$, 80%), strawberry tongue ($n=7$, 47%), cervical lymphadenopathy ($n=11$, 73%), erythema and edema of the hands and feet in acute phase ($n=6$, 40%) or periungual desquamation in subacute phase ($n=1$, 7%). One patient presenting with the incomplete form had coronary dilations (Z score > 2.5) without typical manifestations of Kawasaki disease except bilateral conjunctival congestion. One patient presenting with the incomplete form had rash, bilateral conjunctival congestion and several laboratory abnormalities (significantly elevated white blood cell count, platelet count, C-reactive protein, erythrocyte sedimentation rate, alanine transaminase, aspartate transaminase and urine leucocyte, and decreased albumin and hemoglobin).

All 15 patients underwent chest CT examination, cardiac ultrasound and electrocardiogram (ECG). No abnormality was found on chest CT in 6 cases. The other 9 cases had different degree of abnormal lung imaging. Fibrous strips were observed in 3 (20%) cases. Bilateral pleural thickening was found in 2 (13%) cases. The right interlobular fissure was thickened in 1 (7%) case. Subpleural nodules were observed in 1 (7%) case. Patchy consolidation was found in 1 (7%) case. The pulmonary texture was coarse in 1 (7%) case. Typical chest CT findings are shown in Figure 1. Echocardiography showed no abnormality in 5 (33%) cases. Coronary artery dilatation was observed in 4 (27%) cases. Mitral regurgitation was observed in 1 (7%) patients. Tricuspid regurgitation was observed in 5 (33%) patients. Pericardial effusion was found in 2 (13%) case. Atrial septal defect was found in 4 (27%) case. Ejection fractions were normal in all 15 patients. The ECG of 6 (40%) patients was normal. Sinus tachycardia was showed in 8 (53%) cases. ST segment changes was showed in 3 (20%) cases. Cardiac electric axis toward right deviation was showed in 1 (7%) case.

White blood cell counts were elevated in 13 (87%) patients with median $15.07 \times 10^9/L$ (IQR 11.07 to 17.88). platelet counts were elevated in 8 (53%) patients with median $301 \times 10^9/L$ (IQR 251 to 413). Neutrophil counts were increased in 10 (67%) patients with median $8.02 \times 10^9/L$ (IQR 5.78 to 12.86). Lymphocyte counts were decreased in 7 (47%) patients with median $4.52 \times 10^9/L$ (IQR 2.95 to 5.02). Platelet counts were increased in 8 (53%) patients with median $301 \times 10^9/L$ (IQR 251 to 413). Inflammatory biomarkers were significantly elevated in all 15 patients with median C-reactive protein (CRP) 66.29 mg/L (IQR 37.25 to 108.77) and median Erythrocyte sedimentation rate (ESR) 81 mm/h (IQR 52 to 104). Procalcitonin was elevated in 7 (47%) patients with median 0.49 ng/mL (IQR 0.17 to 1.33). Aspartate transaminase was increased in 6 (40%) patients with median 31.8 U/L (IQR 23.4 to 82.2) and alanine transaminase was increased in 3 (20%) patients with median 23.5 U/L (IQR 19.8 to 38.6). Albumin was decreased in 7 (47%) patients with median 35.3 g/L (IQR 32.7 to 40.3). Sodium concentration was decreased in 8 (53%) patients with median 133 mmol/L (IQR 128 to 139). All 15 cases were negative in blood culture. 3 (20%) cases were complicated with Mycoplasma pneumoniae infection. 1 (7%) patient was associated with Epstein-Barr virus infection. None of the 15 children was infected with adenovirus, influenza A or influenza B. SARS-CoV-2 nucleic acid test was performed in 13 cases, but no positive results were found. 11 children were tested for SARS-CoV-2 antibodies (IgM and IgG), but there was still no positive result. None of the 15 children met the biological criteria for macrophagic activation syndrome (MAS) according to hemophagocytic lymphohistiocytosis MAS criteria [14], and none developed Kawasaki disease shock syndrome (KDSS) characterized by hypotension or signs of hypoperfusion [15].

All 15 patients received 2g/kg intravenous immunoglobulin (IVIG) and 50-80mg/kg aspirin per day. After 3 days of normal temperature, aspirin was reduced to 3-5mg/kg per day for 6-8 weeks or till dilated arteries return to normal. All 15 children received neither corticosteroid or other second-line treatment, nor antiviral therapy. 15 patients were sensitive to IVIG because the body temperature decreased to normal on the same day and the inflammation biomarkers decreased gradually. The median of length of hospital stay was 10 days (IQR 10 to 13). So far, 12 patients have been revisited at least once without special complications. Clinical and laboratory features of 15 patients with Kawasaki disease in isolation ward was shown in Table 1.

89 patients diagnosed with Kawasaki disease from January 1, 2015 to December 31, 2019 were analyzed in this study as historical cohort. 22 patients lived outside Wuhan and 67 patients were local residents of Wuhan. The total incidence in the past 5 years was 1.48 per month and the incidence of Wuhan local children was 1.12 per month. There were 34731 patients admitted to the general wards from January 1, 2015 to December 31, 2019 and 1462 patients admitted to the isolation ward and the general wards from January 1, 2020 to July 31, 2020. The incidence was significantly different between the two cohorts (< 0.001). The total number of Kawasaki disease cases in different months in the historical cohort was shown in Figure 2. The higher incidence was found in summer (May, June and July) over the past five years. Among the 89 patients, 54 boys and 35 girls with the median age 15 months (IQR 7.5 to 30.5). 55 (62%) patients were less than 2 years old, and 34 (38%) patients were less than 1 years old. 78 (88%) patients presented with a classic form of the disease, and 11 (12%) patients with an incomplete form. Coronary artery dilatation was observed in 25 (28%) cases. Mitral regurgitation was observed in 12 (13%) patients.

Tricuspid regurgitation was observed in 20 (22%) patients. Pericardial effusion was found in 3 (3%) case. 31 (35%) cases were complicated with bronchitis or pneumonia. 11 (12%) cases were complicated with *Mycoplasma pneumoniae* infection. 3 (3%) cases were complicated with enterovirus infection (two were rotavirus and one was norovirus). 3 (3%) cases were complicated with Epstein-Barr virus infection. 1 (1%) cases were complicated with adenovirus infection. None of the 89 children were complicated with influenza infection. As shown in Table 2, comparison between the historical cohort and the current cohort suggested that the incidence and the abnormal chest imaging in the current cohort were significantly higher than those in the historical cohort ($p < 0.001$ and $p = 0.003$ respectively). There were no significant differences in age, sex, clinical manifestations, blood routine examination, blood biochemistry, cardiac ultrasound and treatment between the two cohorts ($p > 0.05$ for all).

Discussion

Kawasaki disease, also called as mucocutaneous lymph node syndrome, was first reported by a Japanese pediatrician, Dr. Tomisaku Kawasaki in 1967 [16]. Kawasaki disease often occurs in young children, mostly under 5 years of age, with 1.5 times more in boys compared to girls [17]. Consistent with this literature report, our study found that the median age of children with Kawasaki disease in the historical cohort was 15 months with the male-to-female ratio 1.54:1. We haven't observed significant differences in age and sex between the patients with Kawasaki disease admitted to the isolation ward from January 1, 2020 to July 31, 2020 during COVID-19 pandemic and the historical cohort. An observational cohort study in Italy demonstrated the mean age of children with Kawasaki disease was 7.5 years [7], which is different from our findings. Epidemiological patterns vary widely from different regions, with incidence varying by race and season. The highest incidence has been reported in Japan with 239/1000000, followed by Korea with 113.1/100000 and Taiwan, China with 69/100000 [18]. The incidence of Kawasaki disease hospitalizations has been reported in USA with 19/100,000 in children below 5 years of age [19]. In Japan, Kawasaki disease is most prevalent in January (winter) and July (summer), as well as in Korea [20]. In USA, the higher incidence in winter and spring has been discovered [21]. Our data showed the higher incidence in summer (May, June and July) over the past five years. But the highest incidence in the current cohort was in March, two months after COVID-19 outbreak in Wuhan.

The pathogenesis of Kawasaki disease is not fully understood, which may be related to infection, immunity and genetic susceptibility [22]. Nationwide epidemics of Kawasaki disease have occurred in Japan in the years 1979, 1982, and 1986 [23-25]. Seasonal variation have also been observed in many other countries, including but not limited to Europe. These findings suggested that infection may be a trigger for Kawasaki disease. So far, no specific pathogen has been confirmed to be absolutely associated with Kawasaki disease. Several case reports have linked Kawasaki disease with many pathogens such as *Mycoplasma pneumoniae* [26], cytomegalovirus [27], adenovirus, rhinovirus, enterovirus [28], bocavirus [29], parainfluenza type 3 and coronavirus OC43/HKU1 [30]. Consistent with these reports, Kawasaki disease has been found to be associated with *Mycoplasma pneumoniae*, enterovirus, Epstein-Barr virus and adenovirus in our historical cohort and *Mycoplasma pneumoniae* and Epstein-Barr virus in our current cohort. In the past few months several case reports and a time-series analysis have demonstrated that Kawasaki disease is linked to a SARS-CoV-2 infection [31]. SARS-CoV-2 nucleic acid test was performed in 13 cases and SARS-CoV-2 antibodies (IgM and IgG) was conducted in 11 cases in our current cohort, but no positive results were found. However, the incidence of Kawasaki disease during COVID-19 pandemic was significantly higher than that before COVID-19 pandemic, and Kawasaki disease associated with abnormalities of chest CT were also significantly increased. As shown in figure 1, ground-glass opacity (GGO) which is the initial chest CT feature of COVID-19 has not been found in our current cohort, but pleural thickening, fibrous strips, and subpleural nodules which are the follow-up chest CT changes of COVID-19 have been observed [32,33]. SARS-CoV-2 RT-PCR test results of pharyngeal swab specimens are variable and potentially unstable [34], the false-negative rate is as high as 66% on day 21 after infection [35]. At present, there are insufficient studies to evaluate the duration of SARS-CoV-2 antibodies [36]. Considering that Kawasaki disease mainly occurred two months after COVID-19 outbreak in the current cohort, it is possible that these children with CT abnormalities have been previously infected with SARS-CoV-2.

The relationship between COVID-19 and Kawasaki disease macrophage activation and Kawasaki disease shock has been reported in Italy and France [6-8]. In contrast, our data showed no increase in severe form of Kawasaki disease during COVID-19 pandemic in Wuhan. There were no significant differences in age, sex, clinical manifestations, blood routine examination, blood biochemistry, cardiac ultrasound and treatment between the historical cohort and the current cohort. The reason for this inconsistency may be related to race and genetic difference. We also compared our data with those of Europe, and we found the median age of children with Kawasaki disease in Wuhan were significantly younger than that reported in Europe [6-8]. We presumed that the immune response in younger children was not as strong as in older children, so there was no severe form of Kawasaki disease or multisystem inflammatory syndrome reported in Wuhan.

The present study has some limitations. This is not a multicenter retrospective analysis and may not perfectly represent the overall incidence of Kawasaki disease during COVID-19 pandemic in Wuhan. Further clinical studies with larger cohorts in China are required to confirm the findings of this study.

In conclusion, the present study retrospectively analyzed the characteristics of Kawasaki disease in isolation ward from January 1, 2020 to July 31, 2020 in a tertiary pediatric referral centre in Wuhan, China. This study found that Kawasaki disease mainly occurred in young children (87% were less than 2 years old) in Wuhan, and there were no MAS and KDSS during COVID-19 pandemic. All children with Kawasaki disease responded well to IVIG and aspirin. Although no definitive evidence of SARS-CoV-2 infection in these children with Kawasaki disease has been found, but the incidence of Kawasaki disease during COVID-19 pandemic was significantly higher than that before COVID-19 pandemic, and Kawasaki disease associated with abnormalities of chest CT were also significantly increased. This study suggested that there may be an association between the emergence of Kawasaki disease with non-severe form and COVID-19 pandemic in Wuhan.

Declarations

Acknowledgments

The authors thank Dr. Zhen Long and Dr. Xiaoqin Zhou for their clinical advice and assistance and Mr. Xinfeng Lu for data collection.

Statement of financial support:

None

Disclosure statement:

The authors have indicated they have no potential conflicts of interest to disclose.

Consent Statement:

This study was approved and patient informed consent was waived by the Medical Ethics Committee of Maternal and Child Health Hospital of Hubei Province.

Authors contribution:

Xia Chen designed the study, performed statistical analysis, and wrote the first draft of the manuscript. Xiuzhen Chen, Junhua Shu and Yang Huang participated in the design of the study, acquired the data, and contributed intellectually to the manuscript. Yabin Wu designed the study, acquired the data, assisted with the interpretation of data, and revised the manuscript. All authors reviewed the manuscript and approved the submission.

References

1. World Health Organization (WHO). Coronavirus disease (COVID-2019) situation reports. <https://www.who.int/emergencies/diseases/novel-coronavirus-2019/situation-reports>. Accessed 19 February 2020
2. World Health Organization. WHO Director-General's remarks at the media briefing on 2019-nCoV on 11 February 2020. <https://www.who.int/dg/speeches/detail/who-director-general-s-remarks-at-the-media-briefing-on-2019-ncov-on-11-february-2020>. Published 11 February 2020
3. National Health Committee of the People's Republic of China. Diagnosis and Treatment of New Coronavirus Pneumonia (Trial Version 7). <http://www.nhc.gov.cn/yzygj/s7653p/202003/46c9294a7dfe4cef80dc7f5912eb1989/files/ce3e6945832a438eaae415350a8ce964.pdf>. Accessed 31 March 2020
4. National Health Committee of the People's Republic of China. Technical guide for prevention and control of novel coronavirus infection in medical institutions (1st edition). <http://www.nhc.gov.cn/yzygj/s7659/202001/b91fdab7c304431eb082d67847d27e14.shtml>. Accessed 31 March 2020
5. 2020 Health Alert #13: Pediatric Multi-System Inflammatory Syndrome Potentially Associated with COVID-19 2020. Available from: <https://www1.nyc.gov/assets/doh/downloads/pdf/han/alert/2020/covid-19-pediatric-multi-system-inflammatory-syndrome.pdf>
6. Riphagen S, Gomez X, Gonzalez-Martinez C, Wilkinson N, Theocharis P (2020) Hyperinflammatory shock in children during COVID-19 pandemic. *Lancet* 395:1607-1608. [https://doi.org/10.1016/S0140-6736\(20\)31094-1](https://doi.org/10.1016/S0140-6736(20)31094-1)
7. Verdoni L, Mazza A, Gervasoni A, Martelli L, Ruggeri M, Ciuffreda M, Bonanomi E, D'Antiga L (2020) An outbreak of severe Kawasaki-like disease at the Italian epicentre of the SARS-CoV-2 epidemic: an observational cohort study. *Lancet* 395:1771-1778. [https://doi.org/10.1016/S0140-6736\(20\)31103-X](https://doi.org/10.1016/S0140-6736(20)31103-X)
8. Pouletty M, Borocco C, Ouldali N, Caseris M, Basmaci R, Lachaume N, Bensaid P, Pichard S, Kouider H, Morelle G, Craiu I, Pondarre C, Deho A, Maroni A, Oualha M, Amoura Z, Haroche J, Chommeloux J, Bajolle F, Beyler C, Bonacorsi S, Carcelain G, Koné-Paut I, Bader-Meunier B, Faye A, Meinzer U, Galeotti C, Melki I (2020) Paediatric multisystem inflammatory syndrome temporally associated with SARS-CoV-2 mimicking Kawasaki disease (Kawa-COVID-19): a multicentre cohort. *Ann Rheum Dis* 79:999-1006. <https://doi.org/10.1136/annrheumdis-2020-217960>
9. Licciardi F, Pruccoli G, Denina M, Parodi E, Taglietto M, Rosati S, Montin D (2020) SARS-CoV-2-Induced Kawasaki-like hyperinflammatory syndrome: a novel COVID phenotype in children. *Pediatrics* 146:e20201711. <https://doi.org/10.1542/peds.2020-1711>
10. Jones VG, Mills M, Suarez D, Hogan CA, Yeh D, Segal JB, Nguyen EL, Barsh GR, Maskatia S, Mathew R (2020) COVID-19 and Kawasaki disease: novel virus and novel case. *Hosp Pediatr* 10:537-540. <https://doi.org/10.1542/hpeds.2020-0123>
11. Rivera-Figueroa EI, Santos R, Simpson S, Garg P (2020) Incomplete Kawasaki disease in a child with Covid-19. *Indian Pediatr* 57:680-681. <https://doi.org/10.1007/s13312-020-1900-0>
12. McCrindle BW, Rowley AH, Newburger JW, Burns JC, Bolger AF, Gewitz M, Baker AL, Jackson MA, Takahashi M, Shah PB, Kobayashi T, Wu MH, Saji TT, Pahl E, American Heart Association Rheumatic Fever, Endocarditis, and Kawasaki Disease Committee of the Council on Cardiovascular Disease in the Young; Council on Cardiovascular and Stroke Nursing; Council on Cardiovascular Surgery and Anesthesia; and Council on Epidemiology and Prevention (2017) Diagnosis, Treatment, and Long-Term Management of Kawasaki Disease: A Scientific Statement for Health Professionals From the American Heart Association. *Circulation* 135:e927-e999. <https://doi.org/10.1161/CIR.0000000000000484>
13. Li Q, Guan X, Wu P, Wang X, Zhou L, Tong Y, Ren R, Leung KSM, Lau EHY, Wong JY, Xing X, Xiang N, Wu Y, Li C, Chen Q, Li D, Liu T, Zhao J, Liu M, Tu W, Chen C, Jin L, Yang R, Wang Q, Zhou S, Wang R, Liu H, Luo Y, Liu Y, Shao G, Li H, Tao Z, Yang Y, Deng Z, Liu B, Ma Z, Zhang Y, Shi G, Lam TTY, Wu JT, Gao GF, Cowling BJ, Yang B, Leung GM, Feng Z (2020) Early Transmission Dynamics in Wuhan, China, of Novel Coronavirus-Infected Pneumonia. *N Engl J Med* 382:1199-1207. <https://doi.org/10.1056/NEJMoa2001316>
14. Henter J-I, Horne A, Aricó M, Egeler RM, Filipovich AH, Imashuku S, Ladisch S, McClain K, Webb D, Winiarski J, Janka G (2007) HLH-2004: diagnostic and therapeutic guidelines for hemophagocytic lymphohistiocytosis. *Pediatr Blood Cancer* 48:124-131. <https://doi.org/10.1002/psc.21039>

15. Kanegaye JT, Wilder MS, Molkara D, Frazer JR, Pancheri J, Tremoulet AH, Watson VE, Best BM, Burns JC (2009) Recognition of a Kawasaki disease shock syndrome. *Pediatrics* 123:e783-789. <https://doi.org/10.1542/peds.2008-1871>
16. Kontopoulou T, Kontopoulou DG, Vaidakis E, Mousoulis GP (2015) Adult Kawasaki disease in a European patient: a case report and review of literature. *J Med Case Rep* 9:75. <https://doi.org/10.1186/s13256-015-0516-9>
17. Singh S, Vignesh P, Burgner D (2015) The epidemiology of Kawasaki disease: a global update. *Arch Dis Child* 100:1084-1088. <https://doi.org/10.1136/archdischild-2014-307536>
18. Greco A, Virgilio AD, Rizzo MI, Tombolini M, Gallo A, Fusconi M, Ruoppolo G, Pagliuca G, Martellucci S, Vincentiis MD (2015) Kawasaki disease: an evolving paradigm. *Autoimmun Rev* 14:703-709. <https://doi.org/10.1016/j.autrev.2015.04.002>
19. Uehara R, Belay ED (2012) Epidemiology of Kawasaki disease in Asia, Europe, and the United States. *J Epidemiol* 22:79-85. <https://doi.org/10.2188/jea.je20110131>
20. Makino N, Nakamura Y, Yashiro M, Ae R, Tsuboi S, Aoyama Y, Kojo T, Uehara R, Kotani K, Yanagawa H (2015) Descriptive epidemiology of Kawasaki disease in Japan, 2011–2012: from the results of the 22nd nationwide survey. *J Epidemiol* 25:239-245. <https://doi.org/10.2188/jea.JE20140089>
21. Holman RC, Christensen KY, Belay ED, Steiner CA, Effler PV, Miyamura J, Forbes S, Schonberger LB, Melish M (2010) Racial/ethnic differences in the incidence of Kawasaki syndrome among children in Hawaii. *Hawaii Med J* 69:194-197
22. Agarwal S, Agrawal DK (2017) Kawasaki disease: etiopathogenesis and novel treatment strategies. *Expert Rev Clin Immunol* 13:247-258. <https://doi.org/10.1080/1744666X.2017.1232165>
23. Nakamura Y, Yashiro M, Uehara R, Oki I, Watanabe M, Yanagawa H (2008) Epidemiologic features of Kawasaki disease in Japan: results from the nationwide survey in 2005–2006. *J Epidemiol* 18:167-172. <https://doi.org/10.2188/jea.je2008001>
24. Burns JC, Herzog L, Fabri O, Tremoulet AH, Rodó X, Uehara R, Burgner D, Bainto E, Pierce D, Tyree M, Cayan D (2013) [Kawasaki Disease Global Climate Consortium](#). Seasonality of Kawasaki disease: a global perspective. *PLoS One* 8:e74529. <https://doi.org/10.1371/journal.pone.0074529>
25. Nakamura Y, Yashiro M, Uehara R, Sadakane A, Tsuboi S, Aoyama Y, Kotani K, Tsogzolbaatar EO, Yanagawa H (2012) Epidemiologic features of Kawasaki disease in Japan: results of the 2009–2010 nationwide survey. *J Epidemiol* 22:216-221. <https://doi.org/10.2188/jea.je20110126>
26. Lee MN, Cha JH, Ahn HM, Yoo JH, Kim HS, Sohn S, Hong YM (2011) *Mycoplasma pneumoniae* infection in patients with Kawasaki disease. *Korean J Pediatr* 54:123-127. <https://doi.org/10.3345/kjp.2011.54.3.123>
27. Usta Guc B, Cengiz N, Yildirim SV, Uslu Y (2008) Cytomegalovirus infection in a patient with atypical Kawasaki disease. *Rheumatol Int* 28:387-389. <https://doi.org/10.1007/s00296-007-0440-4>
28. Chang LY, Lu CY, Shao PL, Lee PI, Lin MT, Fan TY, Cheng AL, Lee WL, Hu JJ, Yeh SJ, Chang CC, Chiang BL, Wu MH, Huang LM (2014) Viral infections associated with Kawasaki disease. *J Formos Med Assoc* 113:148-154. <https://doi.org/10.1016/j.jfma.2013.12.008>
29. Bajolle F, Meritet JF, Rozenberg F, Chalumeau M, Bonnet D, Gendrel D, Lebon P (2014) Markers of a recent bocavirus infection in children with Kawasaki disease: “a year prospective study”. *Pathol Biol (Paris)* 62:365-368. <https://doi.org/10.1016/j.patbio.2014.06.002>
30. Giray T, Biçer S, Küçük Ö, Çöl D, Yalvaç Z, Gürol Y, Yılmaz G, Saç A, Mogol Y (2016) Four cases with Kawasaki disease and viral infection: aetiology or association. *Infez Med*. 24, 340-344
31. Ouldali N, Pouletty M, Mariani P, Beyler C, Blachier A, Bonacorsi S, Danis K, Chomton M, Maurice L, Bourgeois FL, Caseris M, Gaschignard J, Poline J, Cohen L, Faye A, Melki I, Meinzer U (2020) Emergence of Kawasaki disease related to SARS-CoV-2 infection in an epicentre of the French COVID-19 epidemic: a time-series analysis. *Lancet Child Adolesc Health* 4:662-668. [https://doi.org/10.1016/S2352-4642\(20\)30175-9](https://doi.org/10.1016/S2352-4642(20)30175-9)
32. Wu J, Wu X, Zeng W, Guo D, Fang Z, Chen L, Huang H, Li C (2020) Chest CT Findings in Patients with Corona Virus Disease 2019 and its Relationship with Clinical Features. *Invest Radiol* 55:257-261. <https://doi.org/10.1097/RLI.0000000000000670>
33. Carotti M, Salaffi F, Sarzi-Puttini P, Agostini A, Borgheresi A, Minorati D, Galli M, Marotto D, Giovagnoni A (2020) Chest CT features of coronavirus disease 2019 (COVID-19) pneumonia: key points for radiologists. *Radiol Med* 125:636-646. <https://doi.org/10.1007/s11547-020-01237-4>
34. Li Y, Yao L, Li J, Chen L, Song Y, Cai Z, Yang C (2020) Stability Issues of RT-PCR Testing of SARS-CoV-2 for Hospitalized Patients Clinically Diagnosed with COVID-19. *J Med Virol* 92:903-908. <https://doi.org/10.1002/jmv.25786>
35. Kucirka LM, Lauer SA, Laeyendecker O, Boon D, Lessler J (2020) Variation in False-Negative Rate of Reverse Transcriptase Polymerase Chain Reaction-Based SARS-CoV-2 Tests by Time Since Exposure. *Ann Intern Med* 173:262-267. <https://doi.org/10.7326/M20-1495>
36. Deeks JJ, Dinnes J, Takwoingi Y, Davenport C, Spijker R, Taylor-Phillips S, Adriano A, Beese S, Dretzke J, Ferrante di Ruffano L, Harris IM, Price MJ, Dittich S, Emperador D, Hooft L, Leeflang MM, Van den Bruel A; Cochrane COVID-19 Diagnostic Test Accuracy Group (2020) Antibody tests for identification of current and past infection with SARS-CoV-2. *Cochrane Database Syst Rev* 6:CD013652. <https://doi.org/10.1002/14651858.CD013652>

Tables

Table 1. Clinical and laboratory features of 15 patients with Kawasaki disease in isolation ward

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7
Date of admission	January 19, 2020	January 24, 2020	February 1, 2020	February 19, 2020	March 2, 2020	March 8, 2020	March 13, 2020
Age (months)	16	13	17	4	7	11	47
Sex	Male	Female	Female	Female	Male	Male	Male
contact with the confirmed or suspected COVID-19 patients	No	No	No	No	No	No	No
Chest CT	Pneumonia	Normal	Bronchitis	Pneumonia	Normal	Pneumonia	Normal
SARS-CoV-2 nasopharyngeal PCR	NA	NA	Negative	Negative	Negative	Negative	Negative
SARS-CoV-2 serology	NA	NA	NA	NA	Negative	Negative	Negative
Type of Kawasaki disease	Classic	Classic	Classic	Classic	Classic	Classic	Classic
Kobayashi score	3	1	2	2	2	4	5
MAS	No	No	No	No	No	No	No
KDSS	No	No	No	No	No	No	No
Coronary artery dilatation	No	No	No	Yes	No	No	Yes
Mitral regurgitation	No	No	No	No	No	No	No
Tricuspid regurgitation	No	No	No	No	No	Yes	Yes
Pericardial effusion	No	No	No	No	No	No	No
Treatment	IVIG plus aspirin	IVIG plus aspirin	IVIG plus aspirin	IVIG plus aspirin	IVIG plus aspirin	IVIG plus aspirin	IVIG plus aspirin
Response to treatment	Yes	Yes	Yes	Yes	Yes	Yes	Yes

Table 1 Continued

	Patient 8	Patient 9	Patient 10	Patient 11	Patient 12	Patient 13	Patient 14	Patient 15	
Date of admission	March 18, 2020	March 30, 2020	April 12, 2020	April 22, 2020	May 24, 2020	June 10, 2020	July 3, 2020	July 3, 2020	
Age (months)	17	4	9	56	10	18	1	2	
Sex	Male	Male	Male	Female	Male	Male	Female	Male	
contact with the confirmed or suspected COVID-19 patients	No	No	No	No	No	No	No	No	
Chest CT	Pleural thickening	Normal	Pneumonia	Pleural thickening	Interlobular thickening	fissures	Normal	Normal	Pneumonia
SARS-CoV-2 nasopharyngeal PCR	Negative	Negative	Negative	Negative	Negative	Negative	Negative	Negative	
SARS-CoV-2 serology	Negative	Negative	Negative	Negative	Negative	Negative	Negative	Negative	
Type of Kawasaki disease	Incomplete	Classic	Classic	Classic	Incomplete	Classic	Classic	Classic	
Kobayashi score	5	2	1	0	1	5	5	4	
MAS	No	No	No	No	No	No	No	No	
KDSS	No	No	No	No	No	No	No	No	
Coronary artery dilatation	No	No	Yes	No	Yes	No	No	No	
Mitral regurgitation	Yes	No	No	No	No	No	No	No	
Tricuspid regurgitation	Yes	No	Yes	No	No	No	No	Yes	
Pericardial effusion	Yes	No	No	No	No	No	Yes	No	
Treatment	IVIG plus aspirin	IVIG aspirin plus	IVIG aspirin plus	IVIG plus aspirin	IVIG plus aspirin	IVIG aspirin plus	IVIG aspirin plus	IVIG aspirin plus	
Response to treatment	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	

NA = not available. MAS = macrophagic activation syndrome. KDSS = Kawasaki disease shock syndrome. IVIG = intravenous immunoglobulin.

Table 2. Comparison between the current cohort and the historical cohort

	Current cohort (N=15)	Historical cohort (N=89)	P value
Incidence	2.14 per month	1.48 per month	<0.001
Median age (month, IQR)	11 (IQR 4 to 17)	15 (IQR 7.5 to 30.5)	0.201
Gender (male/female)	10/5	54/35	0.778
Clinical features:n(%)			
Skin rash	14/15 (93%)	80/89 (90%)	1.000
Conjunctivitis	15/15 (100%)	78/89 (88%)	0.359
Dry cracked lips	12/15 (80%)	80/89 (90%)	0.374
Hands and feet erythema /oedema	7/15 (47%)	58/89 (65%)	0.248
Cervical lymphadenopathy	11/15 (73%)	62/89 (70%)	1.000
Complete kawasaki disease: n (%)	13/15 (87%)	79/89 (89%)	0.732
Abnormal chest x-ray or CT	9/15 (60%)	18/89 (20%)	0.003
Biological results: median(IQR)			
CRP (mg/L)	66.29 (IQR 37.25 to 108.77)	70.11 (IQR 30.20 to 107.46)	0.757
Hemoglobin (g/L)	107 (IQR 94 to 114)	105 (IQR 94 to 115)	0.756
Platelets (10 ⁹ /L)	301 (IQR 251 to 413)	336 (IQR 289 to 410)	0.456
Neutrophils (10 ⁹ /L)	8.02 (IQR 5.78 to 12.86)	8.83 (IQR 6.47 to 11.60)	0.985
Lymphocytes (10 ⁹ /L)	4.52 (IQR 2.95 to 5.02)	3.53 (IQR 2.46 to 4.77)	0.449
sodium (mmol/L)	133 (IQR 128 to 139)	129 (IQR 125 to 138)	0.150
Albumin (g/L)	35.3 (IQR 32.7 to 40.3)	36.5 (IQR 32.7 to 40.0)	0.598
AST (U/L)	31.8 (IQR 23.4 to 82.2)	34.7 (IQR 24.4 to 53.9)	0.068
ALT (U/L)	23.5 (IQR 19.8 to 38.6)	26.9 (IQR 15.5 to 52.1)	0.167
Echocardiography abnormalities: n (%)			
Coronary dilations	4 /15 (27%)	33/89 (37%)	0.565
Pericardial effusion	2/15 (13%)	3/89 (3%)	0.150
Mitral regurgitation	1/15 (7%)	12/89 (13%)	0.687
Tricuspid regurgitation	5/15 (33%)	20/89 (22%)	0.348
MAS	0/15 (0%)	1/89 (1%)	1.000
KDSS	0/15 (0%)	1/89 (1%)	1.000
Adjunctive steroid treatment	0/15 (0%)	6/89 (7%)	0.590
Resistance to treatment	15/15 (100%)	89/89 (100%)	1.000

CRP = C-reactive protein. AST = aspartate transaminase. ALT = alanine transaminase. MAS = macrophagic activation syndrome. KDSS = Kawasaki disease shock syndrome.

Figures

Figure 1

The typical chest CT findings in the historical cohort (red arrow). A, Bilateral pleural thickening. B, Subpleural nodules. C, Fibrous strips.

Figure 1

The typical chest CT findings in the historical cohort (red arrow). A, Bilateral pleural thickening. B, Subpleural nodules. C, Fibrous strips.

Figure 2

The total number of Kawasaki disease cases in different months in the historical cohort.

Figure 2

The total number of Kawasaki disease cases in different months in the historical cohort.