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Clinical characteristics of Kawasaki disease in adolescents

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Abstract

Objective: Studies focusing on Kawasaki disease (KD) in adolescents are lacking in Southwest China. We systematically summarized the clinical characteristics of KD in adolescents to improve pediatricians' recognition of this condition.

Methods: The clinical data of patients with adolescent-onset KD in our center were retrospectively analyzed. The patients were divided into Group A (n = 7), whose first hospitalization was at our hospital, and Group B (n = 10), who were transferred from their local hospital or community health center.

Results: Seventeen patients with adolescent-onset KD were identified (constituent ratio of 0.8%). Seven patients had an intermittent fever for >10 days. The incidence of incomplete KD was 52.9%. These patients had a high incidence of other atypical clinical manifestations. Fifteen patients were initially misdiagnosed with other infectious diseases. Although the incidence of typical KD was higher in Group B, the overall misdiagnosis rate at the initial stages was higher and the average fever duration on arrival and before IVIG administration were much longer in Group B than A.

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Conclusions: KD in adolescents was frequently misdiagnosed, which might be associated with its atypical, diverse clinical features and pediatricians' poor recognition. Pediatricians must be aware of the possibility of KD in adolescents.

Keywords
Kawasaki disease, adolescent, misdiagnosis, infectious disease, fever, China

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Introduction

Kawasaki disease (KD) is an acute, self-limiting systemic vasculitis that predominately affects children aged 6 months to 5 years. It is characterized by fever, bilateral non-exudative conjunctivitis, erythema of the lips and oral mucosa, changes in the extremities such as erythema or desquamation, rash, and cervical lymphadenopathy.[1] Coronary artery lesions (CALs), severe sequelae of KD that develop in 20% to 25% of children without treatment, have surpassed acute rheumatic fever as the leading cause of acquired heart disease in children.[2] However, it has been proven that timely therapy with intravenous immunoglobulin (IVIG) can significantly reduce the incidence of CALs to about 4.5%.[3] Currently, the identification of KD mainly relies on the principle clinical manifestations after excluding other clinically similar entities with known etiologies. However, incomplete KD is difficult for pediatricians to recognize and is often misdiagnosed as other similar entities, particularly infectious diseases such as cervical lymphangitis, respiratory tract infection, and infectious diarrhea. This results in a delayed diagnosis of KD, impeding prompt IVIG treatment and thereby increasing the risk of CALs.

Prior studies have shown that incomplete KD is more frequently found in the extreme age spectrum, particularly in children aged <6 months and 5 to 10 years.[4] One study showed that more than 50% of general pediatricians and about 25% of infectious disease specialists did not consider the diagnosis of KD in patients younger than 6 months and older than 8 years.[5] However, pediatricians' recognition and awareness of KD in patients younger than 6 months and 5 to 10 years of age improved after a series of studies summarized the clinical manifestations of KD among patients in those age spectrums.[6–8] Nonetheless, adolescent-onset KD (defined as onset from 10 to 18 years of age), which has a much lower estimated incidence of 0.10 to 1.45 per 100,000 population,[9] has gained much less attention from clinicians. Only limited studies are available in the literature. Most pediatricians, particularly from undeveloped areas, do not consider the diagnosis of KD in adolescents, and they lack recognition and awareness of KD in this age group. The present study was therefore performed to retrospectively summarize the clinical characteristics of adolescent-onset KD in our center and review all available literature reporting KD in adolescents with an aim to improve the recognition and outcomes of KD in this extreme age spectrum.

Methods and materials

We retrospectively reviewed the data of all patients (n = 2118) who were diagnosed

with KD from January 2007 to July 2017 at the West China Second University Hospital of Sichuan University (WCSUH-SCU), the largest pediatric medical center in Southwest China. Among these 2118 patients, 17 adolescent patients aged 10 to 18 years were included in the present study. To explore the effect of pediatricians' awareness on the early diagnosis and prognosis of KD in this age group, these patients were divided into two groups based on their first hospitalization: Group A (n = 7), whose first hospitalization was at our hospital, and Group B (n=10), who were transferred from their local hospital or community health center to our hospital. The patients' clinical details, laboratory examination parameters, echocardiography data, treatment effectiveness, and follow-up results were systematically collected and analyzed. Informed written consent was obtained from the patients' parents after the nature of this study had been fully explained to them. The University Ethics Committee on Human Subjects at Sichuan University approved the study. Our study followed the relevant EQUATOR Network guidelines.[10]

Classic KD is diagnosed in patients who have had a fever for at least 5 days and exhibit at least four of the five principal clinical features.[11] Incomplete KD is suspected in patients with a prolonged unexplained fever, cervical lymphadenitis, or retropharyngeal/parapharyngeal phlegmon that is nonresponsive to antibiotics but whose condition does not fulfill the classic criteria. Laboratory testing and/or echocardiography are further performed in such cases. If the patients' laboratory results show an increased C-reactive protein concentration of $\geq$30 mg/L and/or an erythrocyte sedimentation rate of $\geq$40 mm/hour along with more than three additional laboratory criteria including an albumin concentration of $\leq$30 g/L, elevated alanine aminotransferase concentration, $\geq$10 white blood cells per high-power field in the urine, white blood cell count of $\geq 15 \times 10^9$/L, platelet count of $\geq 450 \times 10^9$/L after 7 days, anemia for age, or fewer than three additional laboratory criteria but with positive echocardiography, the diagnosis of incomplete KD is established with reference to the incomplete KD diagnostic algorithm proposed in the 2017 American Heart Association scientific statement for the diagnosis, treatment, and long-term management of KD.[1] The diagnoses of the patients in the present study were confirmed by two pediatricians (including a KD specialist).

All patients underwent the same treatment program after the diagnosis of KD was established. IVIG (2 g/kg) and aspirin (30–50 mg/kg/day) were administered during the acute phase of KD. After the patient defervesced, the aspirin dosage was decreased to 3 to 5 mg/kg/day and continued for 6 to 8 weeks. If the patient had CALs, the aspirin administration was continued until the patient showed no evidence of coronary changes. If the patient had a recurrent or persistent fever for $\geq$36 hours after the first IVIG administration, IVIG (1 g/kg) was administered a second time. Furthermore, methylprednisolone and/or prednisone were administered if the patient had a recurrent or persistent fever even after the second IVIG administration. IVIG resistance was defined as a persistent or recurrent fever (oral temperature of $\geq$38.0°C) or other clinical signs of KD for $\geq$36 hours but $\leq$7 days after the first IVIG infusion.[12]

CALs are defined based on a coronary artery branch internal lumen diameter that meets the following Japanese Ministry of Health criteria: any coronary artery branch internal lumen diameter of $\geq$3 mm for children <5 years of age or $\geq$4 mm for children >5 years of age, or the internal diameter of any branch being 1.5 times greater than that of any adjacent segment.[13]

According to our institutional protocol, patients with CALs underwent standardized echocardiography by two pediatric ultrasonologists during the acute phase and 6 to 8 weeks later during their cardiology clinic follow-up evaluations until resolution of the CALs.

Statistical analysis

All data analyses were conducted with IBM SPSS Statistics for Windows, Version 21.0 (IBM Corp., Armonk, NY, USA). Quantitative data are presented as mean and range or mean ± standard deviation, and qualitative data are expressed as n (%). The Shapiro–Wilk test and homogeneity test of variance were applied to confirm that the quantitative data from different groups came from a normal distribution and met the homogeneity of variance. Differences in quantitative data between Group A and Group B were determined by the independent-samples t-test or Mann–Whitney U test. Fisher's exact test was applied to compare proportions because the sample size was <40 (n = 17 patients). Statistical significance was defined as a two-tailed P value of <0.05.

Results

Seventeen adolescents were diagnosed with KD, including 13 male and 4 female patients (male:female ratio of 3.25:1.00). Their ages ranged from 10.1 to 13.5 years (median age, 11.8 years); 10 (58%) were 10 to 11 years of age, 3 (18%) were 12 to 13 years of age, and 4 (24%) were >13 years of age (Figure 1(a), (b)). On admission, the mean fever duration was 10.2 days (range, 2.0–35.0) (Figure 1(c)). Notably, seven patients had experienced an intermittent fever for >10 days before being transferred to our hospital. The longest fever duration of one child (Patient 10) was 35 days (Table 1).

Of the 17 patients, 9 (52.9%) were diagnosed with incomplete KD. All patients had a prolonged fever for >5 days. Sixteen (94.1%) patients had bilateral non-exudative conjunctivitis, 15 (88.2%) had

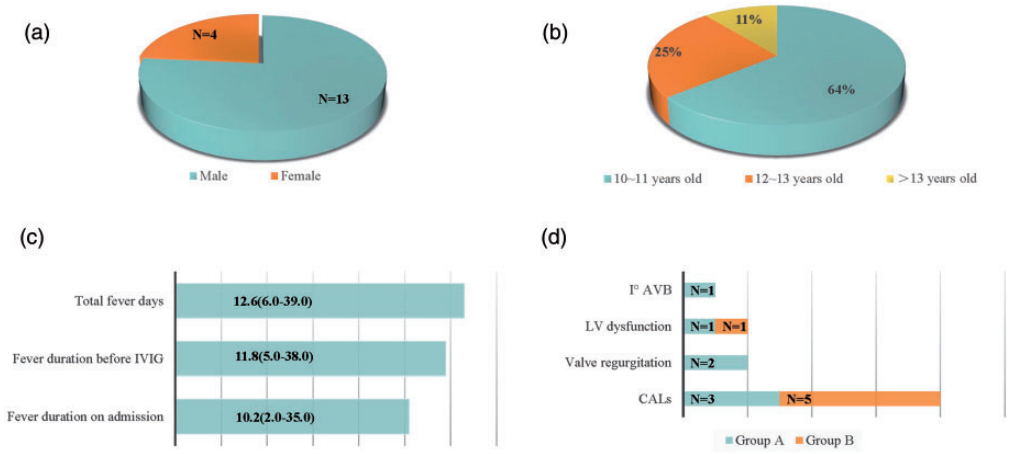

Figure 1. Sex, age distribution, fever duration, and cardiac complications of adolescents with KD. (a) Sex distribution of adolescents with KD. (b) Age distribution of adolescents with KD. (c) Fever duration in adolescents with KD. (d) Cardiac complications in adolescents with KD. KD, Kawasaki disease; IVIG, intravenous immunoglobulin; I° AVB, primary atrioventricular block; LV, left ventricular; CALs, coronary artery lesions.

Table 1. Clinical features, treatment, cardiac complications, and follow-up of adolescents with KD.

Patient No.	Age (years)/ sex	Fever duration, days: On admission	Before IVIG	After IVIG	Primary misdiagnosis	Principle clinical features[c]	Other clinical findings	IVIG resistance	Aspirin/ sec-IVIG/ steroid	Cardiac complications	Follow-up
Group A[a]TR											
1	11.0/M	5	6	1	Cervical lymphadenitis	1,2,3,6	Cough, dizziness, left knee arthritis, SOM	−	+/−/−	CAD (LCA 3.8 mm, RCA 3.5 mm)	Normal 1 week later
2	10.1/M	5	6	3	Amygdalitis	1,2,3,5,6	Diarrhea, vomiting	+	+/+/+	TR, MR	Normal 3 weeks later
3	11.8/M	3	5	1	Cervical lymphadenitis	1,2,5,6	Cough, diarrhea, dizziness	−	+/−/−	CAA (LCA 5.0 mm), LVEF↓	Normal 6 weeks later
4	13.1/M	7	10	3	Bronchitis, infectious diarrhea, pyohemia	1,2,3,5	Cough, diarrhea, vomiting, fatigue, dizziness, tinnitus, proteinuria, sterile pyuria, pleural effusion	+	+/+/+	CAD (RCA 3.3 mm), TR, I°AVB	Normal 2 months later
5	10.8/M	2	7	0	Cervical lymphadenitis	1,2,3,4,6	–	−	+/−/−	NA	N
6	12.1/M	7	9	0	Suspected KD	1,2,3,5	Vomiting, headache, proteinuria, sterile pyuria	−	+/−/−	NA	N
7	11.3/M	6	7	0	Suspected KD	1,2,3,5	Cough, arthritis, arthralgia of limbs	−	+/−/−	NA	N
Group B[b]											
8	11.1/M	15	15	4	RTI	1,3,4,5	Cough, pharyngalgia, diarrhea, fatigue, drowsiness, proteinuria	+	+/+/−	CAD (LCA 3.6 mm)	Normal 4 weeks later
9	11.8/M	6	IVIG allergy	/	RTI, infectious diarrhea	1,2,3,5	Diarrhea, vomiting, abdominal pain	IVIG allergy	+/−/−	CAD (LAD 3.4 mm)	Normal 1 week later
10	12.8/M	35	38	1	Mesenteric lymphadenitis, infective skin rashes	1,2,3,5,6	Cough, vomiting, abdominal pain, ankle joint edema, swelling of right epididymis	−	+/−/−	CAA (LCA 8.2 mm)	CAA still present 11 months later
11	10.9/F	14	15	0	Pneumonia	1,2,3,4,5	Cough, vomiting, arthritis, arthralgia	−	+/−/−	CAA (RCA 5.7 mm)	CAA still present at 1 year later

(continued)

Table 1. Continued.

Patient No.	Age (years)/ sex	Fever duration, days: On admission	Before IVIG	After IVIG	Primary misdiagnosis	Principle clinical features[c]	Other clinical findings	IVIG resistance	Aspirin/ sec-IVIG/ steroid	Cardiac complications	Follow-up
12	11.2/F	10	11	0	Suppurative tonsillitis, scarlatina	1,2,4,5	–	–	+/–/–	CAD (LCA 3.1 mm)	Normal 5 days later
13	13.0/M	17	17	7	Tonsillitis	1,2,3,4,5	–	+	+/+/–	NA	N
14	13.5/M	10	10	0	Cervical lymphadenitis	1,2,3	Fatigue, sterile pyuria	–	+/–/–	NA	N
15	11.8/F	10	10	0	Bronchitis	1,2,3,4,5	Cough	–	+/–/–	NA	N
16	13.3/F	11	11	0	Intracranial infection	1,2,3,4,5	Cough, diarrhea, vomiting, sterile pyuria	–	+/–/–	NA	N
17	13.3/M	10	11	0	Pyohemia	1,2,3,5,6	Cough, abdominal pain	–	+/–/–	LVEF↓	Normal 2 weeks later

[a]Group A: first hospitalization was at our hospital.

[b]Group B: transferred from their local hospital or community health center.

[c]Principal clinical features of KD: 1. Fever for at least 5 days, 2. Bilateral non-exudative conjunctival injection, 3. Erythema of lips/oral mucosa, 4. Extremity changes, 5. Polymorphous skin rash, 6. Cervical lymphadenopathy.

CAA, coronary artery aneurysm; CAD, coronary artery dilation; IVIG, intravenous immunoglobulin; I°AVB, first-degree atrioventricular block; F, female; KD, Kawasaki disease; LCA, left coronary artery; LVEF, left ventricular ejection fraction; M, male; MR, mitral regurgitation; NA, not available; RCA, right coronary artery; RTI, respiratory tract infection; TR, tricuspid regurgitation; Sec-IVIG, second intravenous immunoglobulin; SOM, secretory otitis media.

erythema of the lips and oral mucosa, 14 (82.4%) had a polymorphous skin rash, 7 (41.2%) had changes in the extremities, and 6 (35.3%) had cervical lymphadenopathy (Figure 2(a)). Remarkably, other atypical clinical findings were observed. The gastrointestinal system was the most commonly affected; gastrointestinal symptoms were found in 10 (58.8%) patients, presenting as vomiting (n = 7), diarrhea (n = 6), and abdominal pain (n = 3). Ten (58.8%) patients had respiratory symptoms, namely cough (n = 10) and pharyngalgia (n = 1). Neurological symptoms were also observed in six (35.3%) patients and included dizziness (n = 3), fatigue (n = 3), tinnitus (n = 1), headache (n = 1), and drowsiness (n = 1). The genitourinary system was affected in six (35.3%) patients, manifesting as sterile pyuria (n = 4), proteinuria (n = 3), and swelling of the right epididymis (n = 1). Additionally, four (23.5%) patients had musculoskeletal system involvement, including arthritis (n = 3), arthralgia (n = 2), and ankle joint edema (n = 1) (Figure 2(b)). The diagnosis of KD was only proposed in two patients at the initial stage of illness. The remaining patients were misdiagnosed as having other similar entities, including cervical lymphangitis (n = 4), tonsillitis (n = 2), respiratory tract infection (n = 2), infectious diarrhea (n = 2), bronchitis (n = 2), pyohemia (n = 1), pneumonia (n = 1), and intracranial infection (n = 1) (Table 1). Generally, the time interval from fever onset to the diagnosis of KD was 11.8 days.

One patient developed anaphylaxis after IVIG administration; the remaining 16 (94.1%) patients received IVIG (2 g/kg) and aspirin (30–50 mg/kg) after the diagnosis of KD. However, seven of these patients received the IVIG therapy at >10 days from fever onset. Four children presented with initial IVIG resistance, and two of them defervesced after additional IVIG infusion (1 g/kg). The other two children had a normal body temperature until receiving methylprednisolone pulse infusion (10 mg/kg/day for 3 days).

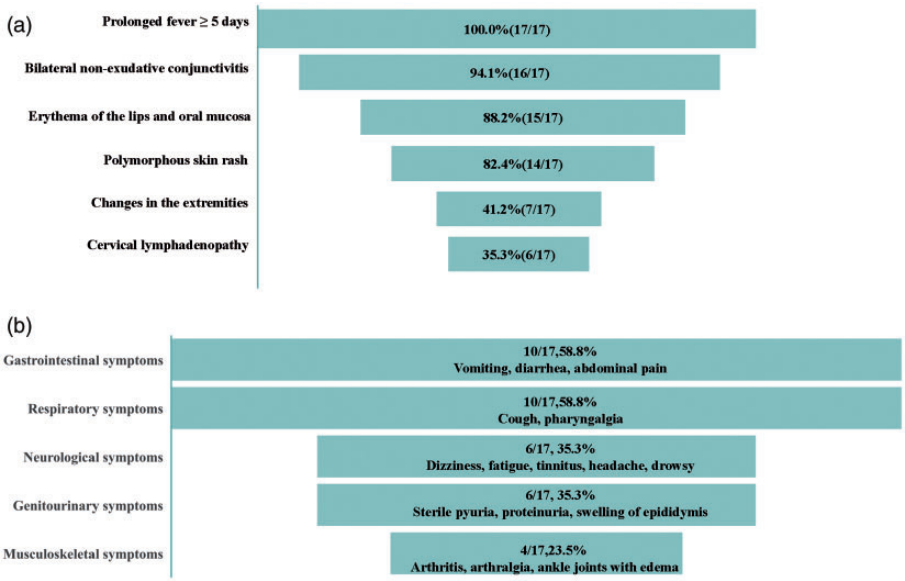

Figure 2. Typical and atypical clinical manifestations of KD in adolescents. (a) Typical clinical manifestations of KD in adolescents. (b) Atypical clinical findings of KD in adolescents. KD, Kawasaki disease.

Ten patients had cardiac complications, including CALs (n = 8), valve regurgitation (n = 2), left ventricular dysfunction (n = 2), and first-degree atrioventricular block (n = 1) (Figure 1(d)). No cardiac enlargement or pericardial effusion was found. All cases of valve regurgitation, left ventricular dysfunction, and first-degree atrioventricular block resolved 2 months later. After a mean follow-up of 2 years, six of the eight children with CALs completely recovered to normal. One patient (Patient 11) developed right coronary artery dilation (5.7 mm) at the initial stage of illness, and the dilation further progressed to 7.9 mm and segmental stenosis at the latest follow-up. The left coronary artery of another patient (Patient 10) was found to be dilated (8.2 mm) on admission but gradually decreased to 6.7 mm 11 months later.

There was no significant difference in the baseline clinical and laboratory data between Group A and Group B. More patients in Group B came from rural areas (90.0% vs. 14.3%, $P = 0.004$), where the population's medical condition was relatively poor and pediatricians were more unlikely to be aware of the possibility of KD in adolescents. Indeed, although the incidence of typical KD was higher in Group B than Group A (60.0% vs. 29.6%), Group B had a higher overall misdiagnosis rate at the initial stage (100.0% vs. 71.4%) as well as a longer average fever duration on arrival (13.8 days; range, 6.0–35.0 days vs. 5.0 days; range, 2.0–7.0 days; $P = 0.013$) and before IVIG administration (15.3 days; range, 10.0–38.0 days vs. 7.1 days; range, 5.0–10.0 days; $P = 0.032$). All patients in Group A were treated with IVIG within 10 days from fever onset, whereas only 3 of 10 patients in Group B received IVIG therapy in a timely manner. The rate of IVIG resistance and steroid use did not differ between the two groups. Cardiac complications including CALs, valve regurgitation, left ventricular dysfunction, and arrhythmia were more common in Group B (60.0% vs. 57.1%) (Table 2). Only the CALs of two children in Group B (Patients 10 and 11) did not resolve and even became more severe during follow-up.

Discussion

The estimated incidence of KD in adolescents is reportedly significantly lower (0.10–1.45 per 100,000 population) than that of KD in patients of other ages,[9] which is consistent with the findings in our study (with a low constituent ratio of 0.8%). Therefore, most pediatricians, particularly from undeveloped areas, lack recognition and awareness of KD in this age group and may not even consider the diagnosis of KD in adolescents. A study of physicians' practices in diagnosing KD in the United States showed that ≥50% of general pediatricians and 25% of infectious disease specialists always ignore the possibility of KD in children >8 years of age.[5] The present study is the largest series of adolescent-onset KD in China to date and has summarized all available literature reporting KD in adolescents. As shown in Table 3, the four largest series of adolescent-onset KD merely reported 46, 28, 17, and 10 cases from India,[14] the United States,[15] Indonesia,[16] and Canada,[17] respectively. Another 18 cases were documented in other case reports.[18–33] Among the 136 reported cases, including ours, the oldest patient was 17 years old,[27,32] suggesting that KD can affect patients of any age because adult-onset KD in patients from 18 to 68 years of age has also been previously identified. KD in adolescents is more likely to affect male patients. The incidence of incomplete KD was 52.9% in our study cohort and 46% to 59% in previous studies,[15,16] which is much higher than that in the general KD population.[34] Most patients were misdiagnosed as having other conditions, such as

Table 2. Demographic data and clinical characteristics of adolescents with Kawasaki disease.

	Group A[a]	Group B[b]	*P* value
Clinical characteristics			
Patients, n	7	10	–
Sex, male:female	7:0	6:4 (1.5:1.0)	0.103
Age, years	11.5 (10.1–13.1)	12.3 (10.9–13.5)	0.120
From urban areas/rural areas	6/1	1/9	0.004*
Total fever duration, days	9.0 (6.0–13.0)	15.6 (6.0–39.0)	0.044*
Fever duration on admission, days	5.0 (2.0–7.0)	13.8 (6.0–35.0)	0.013*
Fever duration before IVIG, days	7.1 (5.0–10.0)	15.3 (10.0–38.0)	0.032*
$\geq$10 days from fever onset to IVIG therapy	1 (14.3)	7 (70.0)	0.060
IVIG therapy	7 (100.0)	9 (90.0)	<0.001*
Failure to respond to initial IVIG therapy	2 (28.6)	2 (22.2)	1.000
Intravenous and/or oral steroid treatment	2 (28.6)	1 (11.1)	0.550
Incomplete Kawasaki disease	5 (71.4)	4 (40.0)	0.335
Cardiac complication	4 (57.1)	6 (60.0)	1.000
Coronary artery lesions	3 (42.9)	5 (50.0)	1.000
Valve regurgitation	2 (28.6)	0 (0.0)	0.154
Left ventricular dysfunction	1 (14.3)	1 (10.0)	1.000
Laboratory features			
C-reactive protein, mg/L	136.6 (18.0–298.0)	89.2 (5.0–179.0)	0.204
White blood cell count, $\times 10^9$/L	15.8 (10.7–25.4)	13.2 (4.6–29.7)	0.485
Erythrocyte sediment rate, mm/hour	39.1 (22.0–100.0)	60.4 (21.0–111.0)	0.207
Platelet, $\times 10^9$/L	216.7 (112.0–272.0)	282.0 (152.0–495.0)	0.157
Hemoglobin, g/L	124.4 (113.0–136.0)	113.1 (96.0–134.0)	0.077
Alanine transaminase, U/L	58.4 (20.0–100.0)	52.0 (17.0–96.0)	0.655
Aspartate transaminase, U/L	35.6 (14.0–50.0)	41.6 (15.0–78.0)	0.526
Albumin, g/L	30.0 (22.9–34.0)	33.6 (23.6–39.7)	0.956
Total bilirubin, μmol/L	9.6 (6.6–13.1)	7.5 (3.1–18.1)	0.308
LDH, U/L	351.4 (152.0–562.0)	359.2 (129.0–728.0)	0.933
Na^+, mmol/L	137.9 (130.0–151.0)	136.4 (128.0–143.7)	0.286

Data are presented as n, n (%), or mean (range).
Differences in quantitative data between Group A and Group B were determined by an independent-samples t-test. Fisher's exact test was applied for comparison. *$P < 0.05$.
[a]Group A: first hospitalization was at our hospital.
[b]Group B: transferred from their local hospital or community health center.
IVIG, intravenous immunoglobulin; LDH, lactate dehydrogenase; Na^+, serum sodium.

cervical lymphangitis, and the mean duration from disease onset to diagnosis of KD was 10.8 days (range, 4–38 days). Accordingly, IVIG infusion was delayed (>10 days from fever onset) in most patients (30%–61%).[15,16] Notably, 47.1% to 77.8% of patients had coronary artery abnormalities,[17] which most likely resulted from the delayed diagnosis and treatment. These findings strongly suggest that the recognition and awareness of KD in adolescents are extremely limited worldwide, and further studies are needed to clarify the clinical profiles of these patients.

There are two possible reasons for KD in adolescents being usually diagnosed and treated later than in patients of other ages. First, some reports have indicated that older children, who are more likely to present with atypical clinical manifestations,

Table 3. Summary of patients with adolescent-onset KD reported in the literature.

First author, year	Age (years)/ Sex	Fever duration, days[a]	Primary diagnosis	iKD	Treatment	IVIG resistance	Coronary artery lesions	Prognosis
Bello,[24] 1995	15/M	6/8	Pneumonia	No	IVIG, aspirin, dipyridamole	No	Diffuse CAD 2 weeks later	–
Davies,[28] 1996	13/M	10/14	TSS	No	IVIG, aspirin	No	CAD (RCA 4 mm, LCA 5 mm, LAD 3 mm)	–
Von Xylander,[22] 1997	14/M	18/21	*Streptococcus* infection	Yes	Prednisone, salicylate	–	CAA (LAD 8 mm, LCA 8 mm, RCA 7 mm) at 3 weeks	Persistent aneurysm of LCA 3 years later
Callaway,[18] 2002	15/M	2/12	Anterior uveitis	No	IVIG, aspirin	No	Left ventricular systolic dysfunction	Normal
Marchetto,[26] 2004	15/M	5/9	–[c]	Yes	IVIG, aspirin	No	Normal	Recurrent KD 9 days later
Yang,[20] 2006	11.75/M	7/7	–	Yes	IVIG, aspirin, intravenous methylprednisolone	No	CAD (LCA 4.5 mm, RCA 2.8 mm)	CAA 2 weeks later
Guven,[23] 2010	12/F	4/4	–	No	IVIG, aspirin, dexamethasone		CAD (LCA 5.6–5.8 mm)	Normal 4 weeks later
Hadid,[29] 2011	13/M	9/–	Cytomegalovirus hepatitis	Yes	No treatment	–	CAA 1 year later	CABG performed and ICD inserted
Hyams,[30] 2012	15/M	9/21	Vasculitis, infection	Yes	IVIG, aspirin, prednisolone	Yes	CAD (RCA 4.6 mm, LCA 4.7 mm, LAD 4.2 mm, LCX 4.2 mm)	–
Yamauchi,[21] 2012	16/F	4/12	Acute myocarditis	Yes	IVIG, aspirin	No	CAA (LAD 10 mm)	Aneurysm and occlusion of CAA 1 year later
Fradin,[19] 2013	16/M	6/9	–	Yes	IVIG, aspirin	No	CAD (Z-score 2.9) at 9 days after fever onset	CAD (Z-score 3.0)

(continued)

Table 3. Continued.

First author, year	Age (years)/ Sex	Fever duration, days[a]	Primary diagnosis	iKD	Treatment	IVIG resistance	Coronary artery lesions	Prognosis
Sileikiene,[27] 2013	17/M	12/13	Pneumonia, pleurisy	No	IVIG, aspirin, steroid, infliximab, warfarin	Yes	CAA (LCA 8 mm, RCA 7 mm)	LCA 7.8 mm, LAD 14.4 mm, RCA 8.6 mm 6 months later
Sinhabahu,[25] 2016	12/F	3/8	Septic shock	Yes	IVIG, aspirin	No	CAD (LAD 3.5 mm)	Dilated LAD 2 months later
Momenah,[17] 1998	≥9/(M:F, 5:5)	–	–	0	IVIG, aspirin	2/10	CAD (6/10), CAA (2/10)	–
Stockheim,[15] 2000	≥8/(M:F, 20:8)[b]	9/10.5	–	46%	IVIG, aspirin	1/28	CAA (6/28, all were male)	Remaining CAA in two patients
Advani,[16] 2019	≥10/(M:F, 14:3)	–	–	59%	IVIG, aspirin	–	CAD (8/17)	–
Jindal,[14] 2020	≥10/(M:F, 26:20)	10/–	–		IVIG, aspirin	5/46	CAA (6/46)	–
Silveira,[31] 2021	16/F	7/14	Influenza B infection	No	IVIG, aspirin	Yes	Normal	Normal
El Haddar[33], 2021	11/M	10/17	Typhoid fever	Yes	IVIG, aspirin	No	CAD	Normal 3 months later
Sakai[32], 2021	17/F	7/–	Acute tonsillitis	No	Infliximab	–	CAA	Normal
	17/F	2/6	Viral infection	Yes	IVIG	No	Normal	Normal
	16/M	2/–	–	No	IVIG	No	Normal	Normal

[a]Fever durations on admission and before IVIG.
[b]There were 28 patients with KD aged ≥8 years in that study, including 13 patients aged >10 years (range, 10–15 years).
[c]Not mentioned in the study.
KD, Kawasaki disease; iKD, incomplete Kawasaki disease; IVIG, intravenous immunoglobulin; ICD, implantable cardioverter defibrillator; M, male; F, female; CAD, coronary artery dilation; CAA, coronary artery aneurysm; LCA, left coronary artery; LCX, left circumflex artery; LAD, left anterior descending artery; RCA, right coronary artery; CABG, coronary artery bypass grafting; TSS, toxic shock syndrome.

have a higher incidence of incomplete KD. In older patients, the typical clinical presentations are often dispersed throughout the course of KD, in contrast to the close clustering of presentations seen in younger patients. In our cohort, nine (52.9%) patients did not fulfill the diagnostic criteria of classic KD. Their clinical presentations were dispersed throughout the course of KD; the criteria may have been met only fleetingly and therefore missed. In contrast, the primary clinical manifestations were variable and nonspecific in our adolescent patients with KD (i.e., cough, vomiting, abdominal pain, diarrhea, fatigue, and drowsiness), similar to previous studies.[4,17,19,24,35–37] This has commonly led to misdiagnosis of KD as other infectious diseases such as tonsillitis, respiratory tract infection, lymphadenitis, pneumonia, infectious diarrhea, and intracranial infection.

The second possible reason why KD in adolescents is usually diagnosed and treated later than in patients of other ages is that many pediatricians are subjectively unfamiliar with the clinical features of KD in adolescents and are reluctant to consider KD, particularly those from underdeveloped areas. General pediatricians, especially primary care physicians, mainly focus on only one or two signs of illness, even in patients with typical clinical features of KD; namely, a diagnosis of cervical lymphadenopathy causing fever. The present study suggests that even with the similar baseline information and laboratory data between patients in Groups A and B, patients from Group B (who were transferred from a local hospital or community health center) had a longer fever duration on admission and before IVIG treatment despite them being more likely to present with typical KD than patients in Group A. Seven (41.2%) patients had received IVIG therapy at >10 days from fever onset, and all seven of these patients were transferred from their local hospital or community health center, where pediatricians were more likely to be familiar with common diseases and rarely deal with KD, especially in older children. Notably, one patient from Group B was considered to have an infectious disease and was finally diagnosed with KD only after a fever duration of 38 days, even with classic clinical manifestations of KD at the initial stage of illness.

A new syndrome known as multisystem inflammatory syndrome in children (MIS-C), characterized by a systemic inflammatory status that seems to be related to SARS-CoV-2 infection, was recently identified.[33,38,39] It is essential to distinguish adolescent-onset KD from MIS-C during the COVID-19 pandemic because several common symptoms are common to both KD and MIS-C, and MIS-C predominantly affects older children.[40] Moreover, the prognosis of MIS-C is worse than that of KD. The mortality rate of MIS-C is 1.7% in the United States and 1.4% in Europe,[41] which is much higher than the mortality rate of 0.01% reported in children with KD.[40] Although MIS-C seems to significantly overlap with KD, these two syndromes appear to have some distinct differences, including racial and ethnic disparities, clinical manifestations, cardiac involvement, and inflammatory markers. First, the incidence of KD is significantly higher in East Asia[34,42] but lower in the United States and Europe.[1] In contrast to KD, MIS-C has mostly been reported in Europe and the United States.[40] Intriguingly, many fewer cases have been reported in Asian countries.[34,42] To date, no cases of MIS-C have been reported in China or Japan.[40] Underlying genetic discrepancies are considered to be a factor resulting in these epidemiologic differences. Second, the underlying mechanisms of hyperinflammation differ between KD and MIS-C. In KD, interleukin-1 (IL-1) has

direct inflammatory effects on coronary endothelial cells,[1] whereas in MIS-C, the myocardial dysfunction and higher severity of SAR-CoV-2 infection are predominantly driven by IL-6 and IL-10.[43] Third, compared with KD, patients with MIS-C likely develop a higher incidence of gastrointestinal symptoms, multisystem organ involvement, lower levels of platelet and lymphocytes, and higher ferritin and procalcitonin levels.[43]

The symptoms of MIS-C have greater resemblance to those of macrophage activation syndrome. Finally, unlike in classic KD, myocardial dysfunction is common in MIS-C. A recent study showed that 80% of patients with MIS-C who developed acute left ventricular failure required inotropic support, and 28% received extracorporeal membrane oxygenation support.[39] In contrast, coronary artery involvement, which is the cardiac hallmark of KD, is less common in MIS-C. In a case series of 503 patients with MIS-C, the incidence of coronary artery aneurysms was only 13%, and 93% of these aneurysms were mild; no large or giant aneurysm were observed.[44] Overall, altough it is challenging to distinguish these two syndromes because of their overlapping clinical presentations and the lack of a specific diagnostic test for either MIS-C or KD,[40] the aforementioned points provide some references for clinical management. Pediatricians should bear in mind that MIS-C must be regarded as a differential diagnosis for adolescent-onset KD, particularly for children with an epidemiological history of COVID-19.

This study must be viewed in light of some potential limitations inherent in its retrospective design. Additionally, the prevalence of adolescent-onset KD in our study compared with other series may naturally reflect some selection bias. Because our hospital is the largest children's medical center in Southwest China, we encounter a greater proportion of complicated cases of KD, and the nature of KD in adolescents suggests that these patients would be transferred to our hospital.

Conclusions

The constituent ratio of KD in adolescents was relatively low. Their clinical features were atypical, diverse, and frequently misdiagnosed. The high incidence of misdiagnosis might be associated with atypical clinical manifestations and pediatricians' poor recognition, leading to a subsequent delay of therapy or administration of nonstandardized IVIG treatment and a higher occurrence of CALs in this age spectrum. For adolescents with a prolonged fever of >5 days, the diagnosis of KD should still be highly suspected. Primary care physicians must be aware of the occurrence of KD in adolescents.

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The authors declare that there is no conflict of interest.

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