

Bilateral Diffuse Bulbar Conjunctival Congestion is a Marker for the Diagnosis of Kawasaki Disease

Li JY^{1#}, Zhong XM[#], Lin CW^{1##} and Zhang JP¹

¹Pediatric Department, Shunde Women's and Children's Hospital of Guangdong Medical University, Foshan 528300, China

²Pediatric Department, Sanshui Women's and Children's Healthcare Hospital, Foshan 528100, China

*Corresponding author:

Chun-wang Lin,

Pediatric Department, Shunde Women's and Children's Hospital of Guangdong Medical University, 3 Baojian Street, Shunde, Foshan 528300, China

#Contributed equally to this work

ORCID Number: Jie-yan Li (0009-0003-0842-3550), Xiang-ming Zhong (0000-0002-7250-2822), Chun-wang Lin (0000-0003-4738-2395), Jian-ping Zhang (0009-0004-3675-1321)

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Abbreviations: KD: Kawasaki disease; BCG: Bacillus Calmette-Guérin; Ckd: Complete Kawasaki disease; iKD: Incomplete Kawasaki disease; CRP: C-reactive protein; WBC: white blood cell; NLR: Neutrophil/lymphocyte ratio; CK-MB: Creatine kinase-MB; cTnI: Cardiac troponin I; HDL-C: High-density lipoprotein cholesterol; ALT: liver transaminase; IVIG: Intravenous immunoglobulin; CAA: Coronary artery aneurysm.

1. Abstract

1.1. Background: Kawasaki disease (KD) is a systemic vasculitis, whose diagnosis can be quite challenging which can easily lead to misdiagnosis, and guidelines seem do not to find a solution to the problem.

1.2. Aim: In this study, we aimed to determine a most important single indicator for diagnosing KD.

1.3. Methods: This is a retrospective study, in which clinical and laboratory data of 210 children with KD was analyzed from January 2018 to December 2021. A single indicator with the highest sensitivity and specificity was selected as a marker for diagnosing KD. Statistical analysis included descriptive statistics and t- and chi-squared tests.

1.4. Results: The incidence of fever, bilateral diffuse bulbar conjunctival congestion, and congestion and cracking of lips among 210 children diagnosed with KD was 100%, 91% and 76.7%, respectively, with a statistically significant difference ($P < 0.01$). Diffuse bulbar conjunctival congestion affected almost all patients with KD, with no overlap with other diseases. Other clinical signs were omitted in the summary. Diffuse bulbar conjunctival

congestion, for diagnosis with KD, AUC was 0.882 (95% CI: 0.772–0.993); sensitivity and specificity were 0.925 and 0.837, respectively.

1.5. Conclusions: Bilateral diffuse bulbar conjunctival congestion affected almost all patients with KD, with no overlap with other diseases. It was found to be a single indicator with the highest sensitivity and specificity and may therefore serve as a marker for diagnosing KD.

1.6. Core Tip: Kawasaki disease (KD) is a systemic vasculitis, whose diagnosis can be quite challenging which can easily lead to misdiagnosis, and guidelines seem do not to find a solution to the problem. In this study, we aimed to determine a most important single indicator for diagnosing, bilateral diffuse bulbar conjunctival congestion affected almost all patients with KD, with no overlap with other diseases. It first was found to be a single indicator with the highest sensitivity and specificity and may therefore serve as a mark for diagnosing KD.

2. Introduction

Kawasaki disease (KD) is an acute childhood vasculitis syndrome that affects various systems due to changes in the immune system,

with unknown etiology [1-3]. This disorder is the most common cause of acquired heart disease in childhood [1, 3, 4]. KD is characterized by prolonged fever lasting more than 5 days, bilateral non-purulent conjunctivitis, diffuse mucosal inflammation (bulbar conjunctival congestion, and congestion and cracking of lips), polymorphous skin rashes, indurative angioedema of the hands and feet, and non-suppurative cervical lymphadenopathy with erythematous changes in the palm, among other symptoms.

The presence of fever for more than 5 days together with 2 or 3 main clinical findings, or fever for more than 7 days with no known cause are essential criteria for the diagnosis of KD [5, 6]. In 2020, erythema at Bacillus Calmette-Guérin (BCG) inoculation sites was included as diagnostic criteria for KD in guidelines developed by the Japanese Circulation Society and the Japanese Society for Cardiovascular Surgery [7]. For classification purposes, cases that meet the diagnostic criteria are defined as complete KD (cKD), and when diagnostic criteria for KD are not met, cases are defined as incomplete KD (iKD) [5, 7].

However, the diagnosis of KD still remains to be a challenge, especially in the early course of the disease, due to the lack of a gold standard for diagnosis and sensitive and specific biological markers [8-10]. Moreover, both delayed diagnosis and treatment can increase the risk of serious complications, especially coronary artery lesions [4, 8, 11]. Therefore, in the present study we investigated the incidence of clinical features of KD with the aim of determining an important single indicator for diagnosing the disease. The present retrospective study was conducted to calculate the incidence of clinical characteristics of KD with the aim of determining an important single indicator to serve as window for the diagnosis of this disorder.

3. Materials and Methods

3.1. Ethics

This study was approved by the Ethics Committee of Shunde Women's and Children's Hospital of Guangdong Medical University (ethics approval number: 2022106; date of approval: May 16, 2022). All patients and their guardians provided written informed consent before the start of the study.

3.2. Study Groups and Inclusion Criteria

This retrospective study included pediatric patients with KD who were seen between January 2018 to December 2021 at Shunde Women's and Children's Hospital of Guangdong Medical University and Foshan Sanshui Women's and Children's Healthcare Hospital. KD was diagnosed based on the scientific statement from the American Heart Association [5, 12].

- Complete Kawasaki disease (cKD): cases characterized by prolonged fever (lasting more than 5 days), bilateral non-purulent conjunctivitis, diffuse mucosal inflammation (congestion and cracking of lips), polymorphous skin rashes, indurative angioedema of the hands and feet, and non-suppurative cervical lymphadenopathy.

nopathy.

- Incomplete Kawasaki disease (iKD): cases in which the above criteria are not completely met.
- Exclusion criteria: 1. Under 18 years old; and 2. There is only fever but none of the above clinical signs of KD.

A total of 210 children (aged 13 years or younger) with KD were included and divided into two groups: cKD and iKD. Patient data were obtained from the medical records using PL/SQL Developer Version 11.0 (Oracle Inc. California, USA).

3.3. Laboratory Assays

Pediatric patients with sepsis had a blood sample taken at hospital admission. For all samples, 5 ml of venous blood was collected in a tube containing ethylenediaminetetraacetic acid-K2. The laboratory project was used blindly.

C-reactive protein, white blood cell and platelet count, erythrocyte sedimentation rate, creatine kinase-MB, cardiac troponin I, bilirubin, liver alanine transaminase, serum sodium, high-density lipoprotein cholesterol, albumin and immunoglobulin levels were measured with a biochemical analyzer (No. p800, Roche Diagnostics, Basel, Switzerland).

3.4. Statistical Analysis

Social Sciences Statistics Package version 20.0 statistical software (SPSS, Chicago, IL, USA) was used for all statistical analyses. Continuous data were presented as mean \pm standard deviation. Laboratory findings, including C-reactive protein, white blood cell and platelet count, neutrophil-to-lymphocyte ratio (NLR), hemoglobin, creatinine kinase-MB, cardiac troponin I, serum sodium, high-density lipoprotein cholesterol, bilirubin, alanine transaminase, albumin, and immunoglobulin levels were analyzed using the t-test. ROC curve statistical analysis was performed to determine the area under the curve (AUC), 95% CI, sensitivity, and specificity in paediatric patients with KD for diagnostic accuracy of diffuse bulbar conjunctival congestion, congestion and cracking of lips, polymorphous skin rashes, and non-suppurative cervical lymphadenopathy. Median age and sex were analyzed using the chi-squared test. A P-value < 0.05 was considered significant.

4. Results

4.1. Clinical Characteristics of Study Participants

We included 210 pediatric patients with KD, 141 males (67.1%) and 69 females (32.9%), with a median age of 1.4 years (range: 0.17-13 years). There was no significant statistical difference between the ages of children in the cKD and iKD groups ($P > 0.05$). On the other hand, we found significant statistical differences in the comparison between males and females ($P < 0.01$). Gender and age-matched healthy subjects corresponded to 118 healthy children, of which 78 were males and 40 were females.

Of the 210 patients, 74 had cKD (35.2%), while 136 had iKD (64.8%). Moreover, in the cKD patient group, two of them had

shock, two had pericardial effusion, and one had a coronary aneurysm that ruptured leading to death. The demographic and clinical characteristics of the children in the two groups are shown in (Table 1 and Figure 1).

The incidence of almost all clinical signs was found to have a significant difference ($P < 0.01$), with the exception of erythema at BCG inoculation sites, congestion and cracking of lips, and bilateral diffuse bulbar conjunctival congestion ($P > 0.05$). Fever was not analyzed with statistical tests.

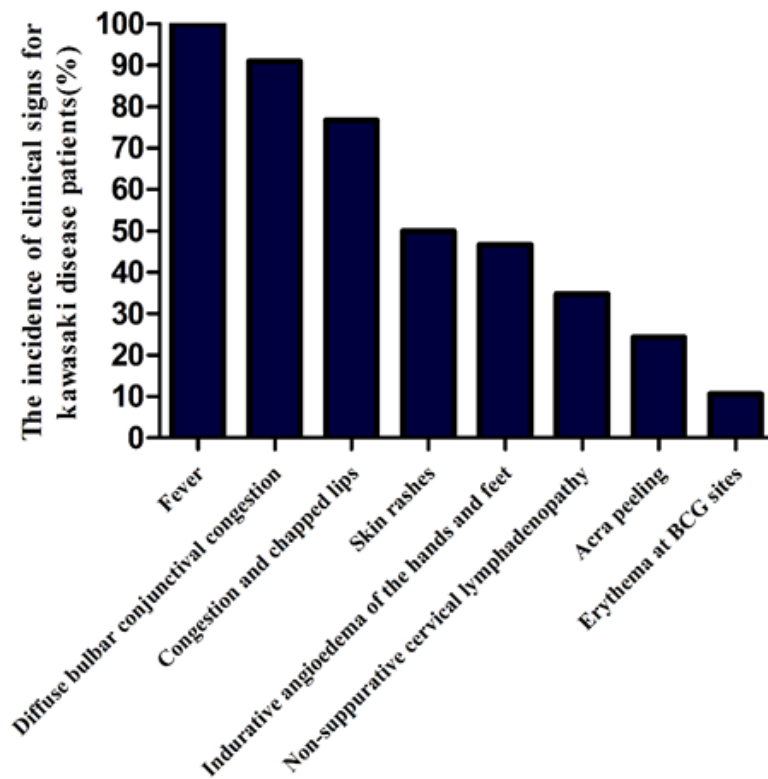


Figure 1: Incidence of fever and other clinical signs in 210 KD patients, these signs included bilateral diffuse bulbar conjunctival congestion, congestion and cracking of lips, acral peeling, skin rashes, indurative angioedema of the hands and feet, non-suppurative cervical lymphadenopathy, and erythema at BCG inoculation sites.

Table 1: Clinical characteristics of patients with KD (cKD and iKD)

Characteristics	KD (n = 210), n (%)	cKD (n = 74), n (%)	iKD (n = 136), n (%)	X2	P
Age (median, years) (range)	1.4 (0.17-13)	1.3 (0.17-13)	1.5 (0.25-13)	1.15	> 0.05
Male	141 (67.1)	49 (66.2)	88 (64.7)	0.69	> 0.05
Female	69 (32.9)	25 (33.8)	48 (35.3)	0.75	> 0.05
Male/Female	141/69 (67.1/32.9)	49/25 (66.2/33.8)	88/48 (64.7/35.3)	4.86	< 0.01
Fever (range, days)	210 (100) (3-22)	74 (100) (3-22)	136 (100) (3-20)	-	-
Bilateral diffuse bulbar conjunctival congestion	191 (91)	68 (91.9)	123 (90.4)	0.41	> 0.05
Congestion and cracking of lips	161 (76.7)	58 (78.4)	103 (75.7)	0.75	> 0.05
Non-suppurative cervical lymphadenopathy	73 (34.8)	55 (74.3)	18 (13.2)	5.66	< 0.01
Erythema at BCG inoculation sites	22 (10.5)	9 (12.2)	13 (9.6)	1.37	> 0.05
Polymorphous skin rashes	105 (50)	51 (68.9)	54 (39.7)	3.45	< 0.01
Indurative angioedema of the hands and feet	98 (46.7)	50 (67.7)	48 (35.3)	3.77	< 0.01
Acral peeling	51 (24.3)	29 (39.2)	22 (16.2)	4.28	< 0.01
Shock	2 (0.95)	2 (0.95)	-	-	-
Pericardial effusion	2 (0.95)	2 (0.95)	-	-	-

Coronary artery dilation	50 (23.8)	28 (37.8)	22 (16.2)	4.87	< 0.01
Coronary artery narrow	25 (11.9%)	11 (14.9%)	14 (10.3%)	3.28	< 0.01
Coronary aneurysm rupture	1 (0.48)	1 (0.48)	0	-	-
WBC ($\times 10^9/l$) \pm SD	15.18 \pm 2.26	17.05 \pm 1.85	15.11 \pm 2.68	0.89	> 0.05
Neutrophil-to-lymphocyte ratio \pm SD	3.21 \pm 0.16	3.22 \pm 0.15	3.20 \pm 0.17	0.44	> 0.05
Thrombocyte (\uparrow) (Normal range: 100-300 $\times 10^9/L$)	166 (79.1)	60 (81.1)	106 (77.9)	0.57	> 0.05
Hemoglobin (\downarrow) (Normal range: 110-160g/L)	154 (73.3)	59 (79.7)	95 (69.9)	1.15	> 0.05
Erythrocyte sedimentation rate (\uparrow) (Normal range: 0-10mm/h)	152 (72.4)	64 (86.5)	88 (64.7)	2.98	< 0.05
CRP (\uparrow) (Normal range: 0-5mg/L)	201 (95.7)	73 (98.7)	128 (94.1)	0.65	> 0.05
CK-MB (\uparrow) (Normal range: 0~20U/L)	148 (70.5)	55 (74.3)	93 (68.4)	0.92	> 0.05
cTnI (\uparrow) (Normal range: 0-0.13ug/L)	36 (17.1)	11 (14.9)	25 (18.4)	1.3	> 0.05
Na (\downarrow) (Normal range: 135-145mmol/L)	71 (33.8)	38 (51.4)	33 (24.3)	3.91	< 0.01
HDL-C (\downarrow) (Normal range: 1.04-1.55)	17 (8.1)	7 (9.5)	10 (7.4)	1.65	> 0.05
Bilirubin (\uparrow) (Normal range: 3.4-20 μ mol/L)	16 (7.6)	5 (6.8)	11 (8.1)	1.17	> 0.05
ALT (\uparrow) (Normal range: 7-40U/L)	81 (38.6)	31 (41.9)	50 (36.8)	0.97	> 0.05
Albumin (\downarrow) (Normal range: 35~50g/L)	49 (23.3)	19 (25.7)	30 (22.1)	0.85	> 0.05
Immunoglobulin (\uparrow) (Normal range: 9.5~12.5mg/ml)	32 (15.2)	13 (17.6)	19 (14.0)	1.09	> 0.05

4.2. Bilateral Diffuse Bulbar Conjunctival Congestion

Among the 210 patients, there were 191 with bilateral diffuse bulbar conjunctival congestion, of which 32 (16.8%) had diffuse bulbar conjunctival congestion on the 3rd day of fever, while 159 (83.2%) had diffuse bulbar conjunctival congestion on the 4th or 5th day of fever. The mean duration of diffuse bulbar conjunctival congestion was 5.5 ± 2.25 days and such clinical findings were

not recorded in all patients. However, we observed that bilateral diffuse bulbar conjunctival congestion was more frequent in cKD patients, with onset at the initial stage of KD, which is 3-5 days (Figure 2). Among the 118 healthy children, there was no record of cases involving bilateral diffuse bulbar conjunctival congestion, with a statistically significant difference between KD and healthy children ($P < 0.01$).

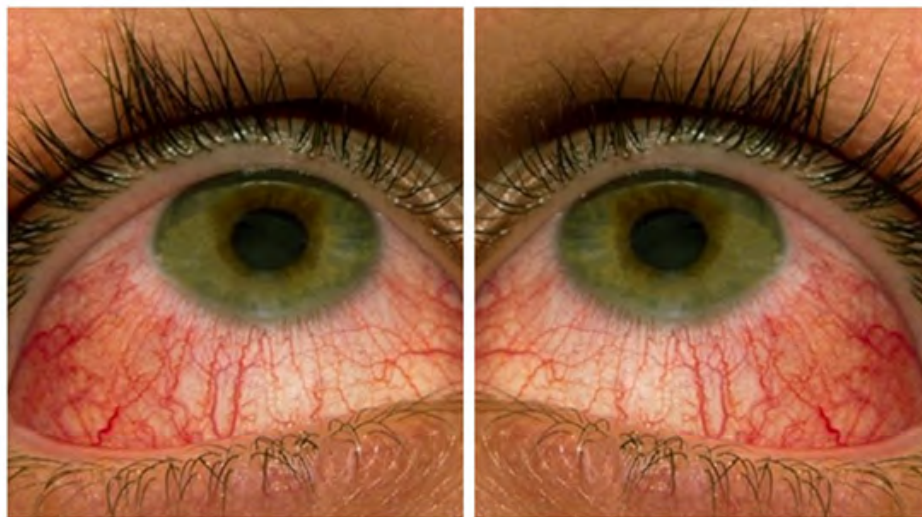


Figure 2: Image of ocular surface shows bilateral diffuse bulbar conjunctival congestion in a pediatric KD patient on the fifth day of fever.

4.3. Erythema at BCG Inoculation Sites

Among the 210 patients, 22 (10.5%) had erythema at BCG inoculation sites, of which 9 patients (12.2%) had cKD and 13 (9.6%) had iKD. Among the 118 healthy children, 8 patients (6.8%, all patients younger than 6 months) had erythema at BCG inoculation sites. However, we found no statistically significant difference for the occurrence of erythema at BCG inoculation sites in the comparison between cKD, iKD and healthy children groups ($P < 0.05$). Comparison of AUC, sensitivity and specificity of diffuse bulbar

conjunctival congestion, congestion and cracking of lips, polymorphous skin rashes, and non-suppurative cervical lymphadenopathy for patients diagnosed with KD. For those diagnosed with KD, the AUC for Diffuse bulbar conjunctival congestion, cracking of lips, polymorphous skin rashes, and non-suppurative cervical lymphadenopathy, were 0.882 (95% CI: 0.772–0.993), 0.855 (95% CI: 0.714–0.955), 0.863 (95% CI: 0.757–0.998), and 0.661 (95% CI: 0.474–0.848), respectively. The sensitivity and specificity were 0.925 and 0.837, 0.863 and 0.765, 0.875 and 0.778, and 0.558 and 0.529, respectively (Figure 3).

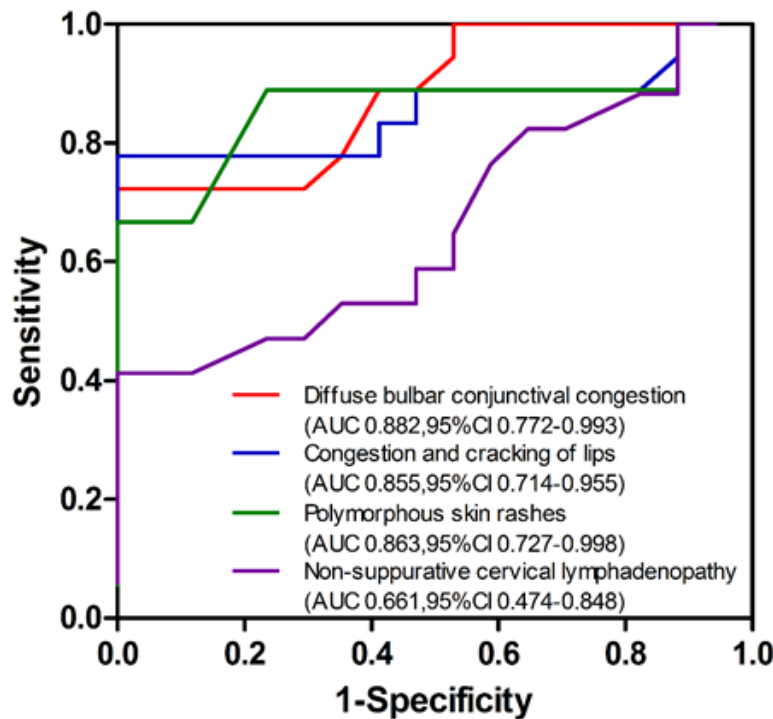


Figure 3: Comparison of AUC, sensitivity and specificity of ROC curves of diffuse bulbar conjunctival congestion, congestion and cracking of lips, polymorphous skin rashes and non-suppurative cervical lymphadenopathy for patients diagnosed with KD.

4.4. Neutrophil-to-Lymphocyte Ratio

In the KD, cKD and iKD groups, the mean neutrophil counts ($\times 10^3/\text{mm}^3$) were 7.56 ± 0.16 , 7.65 ± 0.15 and 7.25 ± 0.19 , respectively; the mean lymphocyte counts ($\times 10^3/\text{mm}^3$) were 2.35 ± 0.15 , 2.37 ± 0.17 and 2.27 ± 0.12 , respectively; and the NLR mean was 3.21 ± 0.16 , 3.22 ± 0.15 and 3.20 ± 0.17 , respectively,

with no significant statistical difference between the groups ($P > 0.05$). For the healthy children group, the mean neutrophil count ($\times 10^3/\text{mm}^3$) was 3.81 ± 0.18 , the mean lymphocyte count ($\times 10^3/\text{mm}^3$) was 6.12 ± 0.12 , and the NLR mean was 1.65 ± 0.11 , with a statistically significant difference between cKD, iKD and healthy children ($P < 0.01$) (Figure 4A, 4B and 4C). This finding indicates higher NLR levels in the cKD and iKD groups.

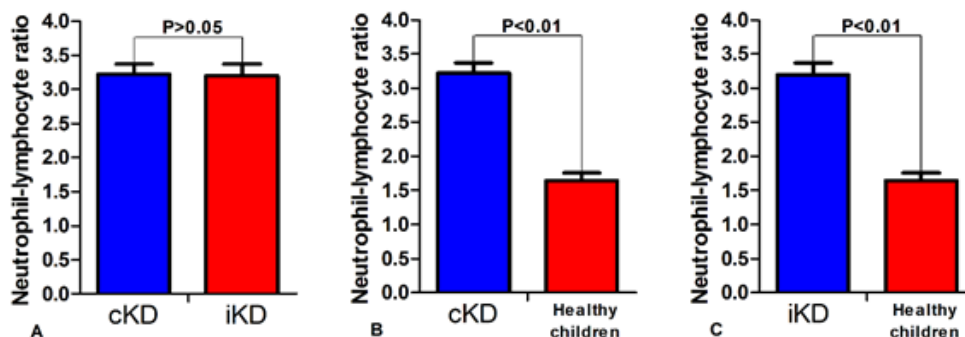


Figure 4A, 4B and 4C: In cKD and iKD patients, the neutrophil-to-lymphocyte ratio (NLR) mean were 3.22 ± 0.15 and 3.20 ± 0.17 , respectively, with no significant difference between the groups ($P > 0.05$). In the healthy children group, the NLR mean was 1.65 ± 0.11 , with a statistically significant difference between the cKD, iKD, and healthy children ($P < 0.01$).

4.5. Coronary Artery Lesions

Among all patients, 55 of them (23.8%) had coronary artery dilatation, of which 28 patients (37.8%) had cKD and 22 (16.2%) had iKD. In addition, 25 patients (11.9%) had coronary artery stenosis, of which 11 patients (14.9%) had cKD and 14 (10.3%) had iKD.

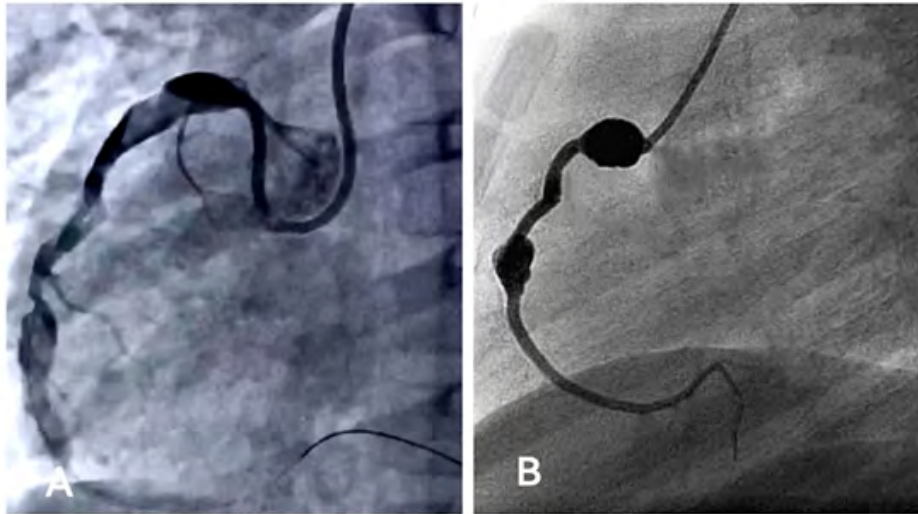


Figure 5A: Coronary angiography (CAG) shows multiple dilatations and stenosis in the middle of the right coronary artery in a pediatric cKD patient. **B.** CAG shows multiple coronary aneurysms in the proximal and middle portions of the right coronary artery in a pediatric cKD patient.

5. Discussion

The conjunctiva is a transparent mucous tissue that covers part of the surfaces of the eyeball and eyelid, which can be divided into the bulbar conjunctiva and palpebral conjunctiva. The bulbar conjunctiva covers the porcelain white sclera, which is transparent and elastic. There are rich blood vessels on the surface of the bulbar conjunctiva, which are clearly visible to the naked eye when they become congested. The main feature of bulbar conjunctival congestion is the inflammatory dilation of vessels on the surface of the sclera observed in KD patients.

A notable finding in the present study was that bilateral diffuse bulbar conjunctival congestion had the highest incidence among all clinical signs of KD (91%), with early onset (after three to five days of fever). However, the avascular area around the iris is usually uninvolved. Although fever is present in all KD patients, it is not a specific clinical sign of the disease.

Moreover, while bulbar conjunctival congestion can have different causes, including drunkenness and insomnia, neither of these two causes seems to occur in children. In these situations, conjunctivitis is usually characterized by palpebral conjunctival congestion and/or associated with mild peripheral bulbar conjunctival congestion, but not with diffuse bulbar conjunctival congestion. Conjunctivitis caused by pathogens such as viral, bacterial, chlamydial etc. does not have the characteristics of bilateral diffuse bulbar conjunctival congestion, making the two easily distinguishable. Therefore, our study suggests that diffuse bulbar conjunctival congestion is a highly specific finding in KD patients, serving as an important clinical sign for the differential diagnosis of suspected cases of the

In both cases there were significant statistical differences between males and females (all $P < 0.01$, Figure 5A and 5B). One patient died due to a ruptured coronary aneurysm, which was confirmed by a pathological examination.

disease.

KD is defined as an acute vasculitis syndrome [1-3]. The surface blood vessel of the bulbar conjunctiva is the only exposed blood vessel in the entire body, and the occurrence of inflamed blood vessels throughout the body can be identified by observing the presence of bulbar conjunctival congestion. Thus, diffuse bulbar conjunctival congestion may serve as a window for the early diagnosis of KD.

The results of the present study also showed that the incidence of congestion and cracking of lips was high (76.7%). However, this is not a characteristic clinical sign of KD, given that stomatitis and cheilitis are commonly found among the population. Furthermore, the incidence of acral membranous peeling (74%) was similarly high, with onset in the final stage of the disease due to delay in the early diagnosis of KD. These findings corroborate different guidelines and expert consensus in the United States and Japan [5, 7].

Another important point for discussion is the erythema at BCG inoculation sites, which corresponds to acute inflammation at the site of the original BCG vaccination with an incidence ranging from 9.4%-49.9% [13]. In Japan, the positive rate of erythema at BCG inoculation sites is as high as 69.7%, [14] which is higher than the incidence of lymph node enlargement. According to the findings of a relevant study conducted in Japan in 2010, erythema at BCG inoculation sites may be considered a useful diagnostic sign for KD [14]. In contrast, Xie et al. found a lower incidence of erythema at BCG inoculation sites (4.3%) in their research, while the BCG reaction occurred more frequently in children under 1-year-old (10.0%) [13].

In our study, the incidence of erythema at BCG inoculation sites was 10.5%, which was a value similar to that reported by Xie et al. Moreover, we observed 8 patients (6.8%) out of 118 healthy children with erythema at BCG inoculation sites who developed a peptic ulcer. Although the statistical difference was significant between KD and healthy children ($P < 0.05$), the presence of erythema at BCG inoculation sites cannot be considered a highly specific clinical sign for KD. Despite this, the above results suggest that erythema at BCG inoculation sites may be different in different countries, and further clinical studies are needed to confirm its relationship with the occurrence of KD.

This study shows that diffuse bulbar conjunctival congestion has the largest AUC and highest sensitivity and specificity for diagnosis with KD. Other several important clinical signs in order of importance (from high to low) were cracking of lips, polymorphous skin rashes, and non-suppurative cervical lymphadenopathy.

A further notable finding was that an $NLR > 3.0$ may be a useful parameter for the diagnosis of KD, with a statistically significant difference between cKD, iKD, and healthy children ($P < 0.01$). Ling-Sai et al. reported that an $NLR > 3.5$ may be an important predictor of the occurrence of coronary artery lesions associated with KD [11]. Other studies found that an $NLR \geq 3.83$ may predict intravenous immunoglobulin (IVIG) resistance in KD patients [15]. Based on all these previous investigations and the results of the present study, the NLR value may be essential for the proper diagnosis of KD.

It is also worth noting in this context that coronary artery dilatation can lead to coronary artery aneurysm (CAA), whose rupture is the leading cause of death for patients with KD [16]. Delayed diagnosis and delay in IVIG treatment may increase the risk of CAA [8, 11, 15-17]. We used the z -value to assess coronary artery lesions, which improved the reliability of the results [18, 19].

In this study, a child with multiple dilated coronary arteries, stenosis and a small CAA (due to a delayed diagnosis) was cured after percutaneous coronary intervention (Figure 3A). However, another case of CAA rupture led to the patient's death due to delays in diagnosis and treatment (Figure 3B). This strongly suggests that early diagnosis of coronary artery disease and timely IVIG treatment is very important to perform in KD patients. Although coronary artery lesions were found in this study to be more common in cKD patients compared to iKD patients ($P < 0.01$), the rationale for this is unclear.

Furthermore, our findings also demonstrate that among the 210 patients with KD, only 74 (35.2%) had cKD, while 136 (64.8%) had iKD, which can make the diagnosis of KD even more challenging, especially for pediatricians with little clinical experience. This concern is consistent with the report of different researchers [4, 5, 10, 20]. Unfortunately, guidelines do not yet exist regarding the dilemma of KD misdiagnosis.

In conclusion, although KD has certain clinical features, its early diagnosis is very difficult, and a delay in early treatment may increase the risk of coronary artery lesions. Diffuse bulbar conjunctival congestion has proven to be a single indicator with high sensitivity and specificity that may serve as a marker for the early diagnosis of KD. The study was the first to find cases involving only fever and diffuse bulbar conjunctival congestion may suggest a diagnostic hypothesis of KD.

6. Acknowledgment

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7. Funding Information

This research received no external funding.

8. Conflict of Interest statement

We have no financial relationships to disclose.

9. Informed Consent Statement

All patients and their guardians provided written informed consent before the start of the study.

10. Author Contributions

JL and CL contributed to the conception and design of the study. JL and XZ collected data. JZ, JL and XZ analyzed data. JL and CL prepared the manuscript. All authors read and approved the final manuscript.

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