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ORIGINAL ARTICLE

A new scoring system to predict Kawasaki disease with coronary artery lesions

Wang Hua[1] · Feiyue Ma[1] · Ying Wang[1] · Songling Fu[1] · Wei Wang[1] · Chunhong Xie[1] · Yiying Zhang[1] · Fangqi Gong[1]

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Abstract

Objectives To clarify the independent risk factors and construct a scoring system for Kawasaki disease (KD) with coronary artery lesions (CAL) at acute and subacute stages.

Method Data of KD inpatients at acute and subacute stages were reviewed in a tertiary care center from January 2009 to December 2014.

Results A total of 2305 acute and subacute KD cases were enrolled in this study with a CAL rate of 24.1%. The OR (95%CI) values of male, total fever duration ≥ 8 days, IVIG resistance (IVIGR), albumin (ALB) ≤ 35.9 g/L, eosionphils (EO) ≥ 2.2%, and monocytes (MO) ≥ 5.9% were 1.45 (1.15–1.82), 1.78 (1.43–2.22), 1.42 (1.09–1.85), 1.53 (1.23–1.91), 1.17 (0.94–1.45), and 1.37 (1.09–1.69), respectively. In patients ≤ 6 months old, the OR (95%CI) values for total fever duration ≥8 days, delayed diagnosis, and ALB ≤ 35.9 g/L were 3.61 (2.02–6.45), 3.49 (1.49–8.16), and 2.07 (1.14–3.74), respectively. ROC curve showed that the AUC value and sensitivity and specificity of predicting KD with CAL in patients ≤ 6 months old were 0.731, 64.7%, and 80.9%, respectively.

Conclusions The independent risk factors for acute and subacute KD combined with CAL, including being a boy, long fever duration, IVIGR, low ALB, elevated EO, and MO. Joint of parameters (total fever duration ≥ 8 days, delayed diagnosis, and ALB ≤ 35.9 g/L) can be used to predict the occurrence of CAL in KD patients ≤ 6 months old.

Keywords Coronary artery lesions · Kawasaki disease · Scoring systems

Introduction

Kawasaki disease (KD), formerly known as mucocutaneous lymph node syndrome, is an acute febrile illness first described by Dr. Tomisaku Kawasaki in Japan in 1967. It causes a severe vasculitis of all blood vessels but predominantly affecting the medium-sized arteries, with predilection for the coronary arteries. Great concerns have been raised about how to identify patients who were more likely to be combined with coronary artery lesions (CAL). Clarification of the risk factors and establishment of scoring systems for CAL are important for early diagnosis, active intervention, and formulation of follow-up strategies.

A meta-analysis of KD in Chinese patients [1] showed that elevated platelets, platelet hematocrit, neutrophils count (NE), platelet distribution width, mean platelet volume, and erythrocyte sedimentation rate (ESR), and decreased albumin (ALB) and hemoglobin were seen in the group with CAL. Honkanen et al. [2] analyzed 344 cases of KD (including 98 cases with CAL) and found that low ALB, young age, and long fever duration were independent risk factors for CAL, however, using the joint indicators resulted in poor prediction of CAL. Tremoulet et al. [3] reported a risk-scoring system for coronary artery aneurysms as follow: illness days at initial IVIG treatment ≤ 4 days, 1 point; age-adjusted hemoglobin concentrations ≤ − 2, 1 point; γ-glutamyl transpeptidase (GGT) ≥ 60 U/L, 1 point; and bands ≥ 20%, 2 points, which yielding a sensitivity of 0.722 and a specificity of 0.576 at a total score of 2. Sato et al. [4] reported a prediction model for CAL with a sensitivity of 0.69 and a specificity of 0.7, where break points and score points for each variable were as follow: serum

Wang Hua and Feiyue Ma contributed equally to this work.

✉ Fangqi Gong
gongfangqi@zju.edu.cn

[1] Department of Cardiology, Children's Hospital, Zhejiang University School of Medicine, No. 3333, Binsheng Road, Hangzhou 310052, People's Republic of China

interleukin (IL)-6 ≥ 70 pg/mL but < 140 pg/mL, 1 point; NE count ≥ 75%, 2 points; and serum IL-6 ≥ 140 pg/mL, 2 points. Because of IL-6, the proportion of bands and the age-adjusted hemoglobin has not been routinely examined, and the related models for CAL have not been verified and applied.

Therefore, scoring systems for CAL with well ability, easy application, and convenient communication are still urgently needed in clinical practices. In this study, data of KD inpatients from a tertiary care center were used to clarify the independent risk factors and construct a scoring system for KD with CAL at acute and subacute stages.

Methods

Patients and clinical data

We retrospectively reviewed the data of KD inpatients at acute and subacute stages in our hospital (Children's hospital, Zhejiang University School of Medicine) for six consecutive year (from January 2009 to December 2014). At least one coronary ultrasonic was performed in the enrolled cases during hospitalization. All parameters were recorded including: (1) epidemiological and clinical indicators (gender, age, illness days at admission and at initial IVIG treatment, numbers of main diagnostic criteria at admission, total fever duration, length of hospitalization, effectiveness of the IVIG therapy, echocardiographic results); (2) complete blood count indicators pre-IVIG therapy; and (3) liver function panel (alanine aminotransferase (ALT), aspartate transaminase (AST), ALB, total bilirubin (TBil), and GGT) and serum electrolytes (sodium, potassium, chloride, and calcium), and measured pre-IVIG therapy. This study was approved by the research ethics service of our hospital. Our retrospective data did not include the use of glucocorticoid, and all patients were initially received the standard regimen after diagnosis of KD.

Definitions

The main symptoms for KD were as follow: fever, rash, bilateral non-exudative conjunctival injection, erythema of the lips and oral mucosa, changes in the extremities, and acute non-suppurative cervical lymphadenopathy. Those who meet at least 5 of the 6 main symptoms were diagnosed with complete KD [5] and those who have 4 or less clinical manifestations regardless of CAL and have no evidence suggested other diseases were diagnosed with incomplete KD [6, 7], both of whom were analyzed in this study. Other febrile diseases that could mimic KD were excluded (such as sepsis, scarlet, measles, acute lymphadenitis, adenovirus infection, infectious mononucleosis, exudative erythema multiforme, and juvenile idiopathic arthritis). The acute and subacute stages were defined as 0–10 days and 11–21 days after KD onset, respectively [8]. Delayed diagnosis of KD was defined as days of initial IVIG treatment longer than 10 days [9]. Resistance to IVIG was defined as persisting or reemerging fever > 37.3 °C 48 h to 2 weeks post-initial IVIG therapy accompanied by at least one of the main diagnostic criteria [10]. CAL were assessed by echocardiography and were defined by either (1) the internal lumen diameter ≥ 2.5 mm in patients aged 0–3, ≥ 3.0 mm in patients aged 3–9, and ≥ 3.5 mm in patients aged 9–14, (2) the internal diameter of a segment ≥ 1.5 times that of an adjacent segment, or (3) the demonstration of clearly irregular lumen [11]. The total samples were grouped according to the presence or absence of CAL, and patients younger than 6 months and older than 5 years were also divided by the same way.

Statistics

Data were given as median (P25-P75) for continuous variables or number of cases for categorical variables. All analyses were performed by the SPSS statistical software package (SPSS statistics 16.0). Comparisons of the intergroup medians and of the intergroup percentages were undertaken by non-parametric rank sum test and chi-square test, respectively. Significantly, different indicators were selected by the univariate analysis. Subsequently, independent risk factors for CAL were determined and the odds ratio (OR) and 95% confidence interval (CI) were calculated by the multivariate logistic regression analysis; $p < 0.05$ was considered to be statistically significant. Break points for each variable were determined using the receiver-operating-characteristics (ROC) curve, and the set of credit for each independent risk factor was based on the OR values. Goodness-of-fit of the regression model was tested with the Hosmer-Lemeshow method, with $p > 0.05$ considered to indicate lack of deviation between the model and the total samples. Area under the curve (AUC) and the sensitivity and specificity of scoring systems were assessed by the ROC curve.

Results

Data collection and basic characteristics

This study included a total of 2305 KD cases. The male:female ratio was 1.60:1 and patients with a complication of CAL at acute and subacute stages accounted for 24.1% (556/2305) of the total samples.

Univariate analysis

The non-parametric rank sum test and chi-square test were performed in groups with CAL and non-CAL (NCAL) at

acute and subacute stages, and it was found more than twenty variables that showed significant differences (Table 1). The same analysis were also performed in KD patients younger than 6 months and older than 5 years, and more than ten variables (Table 2), and only five variables (Table 3) with significant differences were obtained, respectively. These variables were then subjected to next multivariate logistic regression analysis.

Analysis of independent risk factors for KD with CAL and assessment of scoring systems via ROC curves

Table 4 shows that the independent risk factors for KD with CAL were gender, longer total fever duration, IVIGR, decreased ALB, and elevated EO and MO. Further analyses (Table 5) showed that the OR (95% CI) values for being a boy, total fever duration ≥ 8 days, IVIGR, ALB ≤ 35.9 g/L,

Table 1 Comparison of groups with CAL and NCAL at acute and subacute stages

Variables	NCAL		CAL		U/χ^2	*p*
	n	Median (p25-p75)/*n* (%)	*n*	Median (p25-p75)/*n* (%)		
Male-to-female ratio	1749	1.46:1	556	2.23:1	16.85	< 0.001
Age of onset, months	1749	23 (11–47)	556	19 (9–33)	− 3.696	< 0.001
Illness days at admission, days	1749	6 (5–7)	556	7 (5–9)	− 7.389	< 0.001
Number of major diagnostic criteria	1749	4 (3–5)	556	4 (3–5)	− 3.352	0.001
		4.1 ± 1.3		3.8 ± 1.5		
Total fever duration, days	1744	7 (6–9)	553	8 (7–11)	− 9.725	< 0.001
Length of hospitalization, days	1749	6 (5–8)	556	7 (6–10)	− 6.328	< 0.001
Incomplete KD, %	1749	1013 (57.9)	556	343 (61.7)	2.478	0.115
Delayed diagnosis, %	1672	93 (5.6)	510	74 (14.5)	44.267	< 0.001
IVIGR, %	1626	262 (16.1)	489	118 (24.1)	16.4	< 0.001
ESR, mm/h	1605	64 (44–88)	496	71 (47–96)	− 3.591	< 0.001
CRP, mg/L	1594	73 (33–125)	518	71 (28–130)	− 0.831	0.406
WBC, × 10^9/L	1606	12.4 (8.9–16.4)	523	12.9 (8.9–17.4)	− 1.225	0.221
NE, %	1606	62.9 (48.6–75.1)	523	58.2 (45.3–72.5)	− 3.531	< 0.001
Absolute NE, × 10^9/L	1606	7.6 (4.5–11.2)	523	7.2 (4.2–11.6)	− 0.912	0.362
LY, %	1606	27.5 (16.9–39.8)	523	29.9 (19.2–42.2)	− 2.55	0.011
Absolute LY, × 10^9/L	1606	3.1 (2.0–4.6)	523	3.5 (2.3–5.0)	− 3.425	0.001
NLR	1606	2.3 (1.2–4.3)	523	1.9 (1.1–3.8)	− 2.971	0.003
EO, %	1602	2.1 (0.9–4.1)	522	2.4 (1.0–4.6)	− 2.368	0.018
Absolute EO, × 10^9/L	1602	0.26 (0.10–0.47)	522	0.28 (0.12–0.58)	− 2.932	0.003
MO, %	1602	5.6 (3.3–8.1)	522	6.1 (3.7–9.0)	− 3.157	0.002
Absolute MO, × 10^9/L	1602	0.64 (0.39–1.00)	522	0.75 (0.43–1.13)	− 3.66	< 0.001
Hemoglobin, g/L	1604	108 (101–115)	523	104 (96–112)	− 6.033	< 0.001
Platelet, × 10^9/L	1604	366 (289–462)	523	384 (287–491)	− 2.28	0.023
ALT, U/L	1693	22 (12–50)	547	22 (13–43)	− 0.262	0.794
AST, U/L	1693	31 (23–45)	547	31 (23–45)	− 0.018	0.986
Albumin, g/L	1693	36.5 (33.8–39.1)	547	35.2 (31.8–38.4)	− 5.453	< 0.001
TBil, μmol/L	1692	4.5 (3.0–7.0)	547	4.1 (2.8–6.8)	− 1.62	0.105
GGT, U/L	1692	21 (10–73)	547	26 (12–71)	− 1.647	0.1
Sodium, mmol/L	1583	137 (134–139)	507	136 (134–139)	− 1.724	0.085
Chloride, mmol/L	1582	105 (103–108)	506	105 (102–108)	− 0.788	0.431
Potassium, mmol/L	1583	3.7 (3.4–4.1)	507	3.7 (3.4–4.1)	− 0.182	0.856
Calcium, mmol/L	1580	1.13 (1.06–1.19)	506	1.14 (1.07–1.20)	− 1.67	0.095

CALs, coronary artery lesions; *NCALs*, without coronary artery lesions; *KD*, Kawasaki disease; *IVIGR*, intravenous immunoglobin-resistant; *ESR*, erythrocyte sedimentation rate; *CRP*, C-reactive protein; *WBC*, white blood cell count; *NE*, neutrophils; *LY*, lymphocytes; *NLR*, neutrophil-to-lymphocyte ratio; *EO*, eosionphils, *MO*, monocytes; *ALT*, alanine aminotransferase; *AST*, aspartate transaminase; *TBil*, total bilirubin; *GGT*, gamma-glutamyl transferase

and MO ≥ 5.9% were 1.45 (1.15–1.82), 1.78 (1.43–2.22), 1.42 duration ≥ 8 days, delayed diagnosis, and ALB ≤ 35.9 g/L

Table 2 Comparison of groups with CAL at acute and subacute stages in patients ≤ 6 months old

Variables	NCAL		CAL		U/χ^2	*p*
	n	Median (p25-p75)/*n* (%)	*n*	Median (p25-p75)/*n* (%)		
Male-to-female ratio	243	1.70:1	95	1.57:1	0.106	0.419
Illness days at admission, days	243	5 (4–6)	95	6 (5–10)	− 4.555	< 0.001
Number of major diagnostic criteria	243	4 (2–4)	95	3 (2–4)	− 2.269	0.023
Total fever duration, days	242	6 (6–8)	94	9 (7–12)	− 7.112	< 0.001
Length of hospitalization, days	243	7 (5–9)	95	7 (6–12)	− 3.105	0.002
Incomplete KD, %	243	193 (79.4)	95	77 (81.1)	0.113	0.432
Delayed diagnosis, %	237	11 (4.6)	87	21 (24.1)	27.18	< 0.001
IVIGR, %	232	25 (10.8)	84	18 (21.4)	5.953	0.024
ESR, mm/h	219	58 (42–78)	78	69 (46–95)	− 2.21	0.027
CRP, mg/L	225	90 (49–138)	86	86 (47–146)	− 0.417	0.677
WBC, × 10^9/L	226	14.0 (10.1–18.6)	86	14.4 (11.5–20.1)	− 1.128	0.259
NE, %	226	55.4 (40.9–67.7)	86	53.4 (40.4–66.8)	− 0.327	0.743
Absolute NE, × 10^9/L	226	7.8 (4.7–11.0)	86	8.3 (4.6–11.4)	− 0.631	0.528
LY, %	226	34.7 (25.2–45.2)	86	32.5 (23.9–44.4)	− 0.742	0.458
Absolute LY, × 10^9/L	226	4.5 (3.3–6.2)	86	5.2 (3.5–6.3)	− 1.11	0.267
NLR	226	1.6 (0.9–2.7)	86	1.7 (0.9–2.7)	− 0.364	0.716
EO, %	225	3.0 (1.1–4.9)	86	3.5 (1.6–6.4)	− 1.813	0.07
Absolute EO, × 10^9/L	225	0.40 (0.17–0.65)	86	0.51 (0.21–1.00)	− 2.307	0.021
MO, %	225	5.6 (3.6–8.7)	86	6.9 (4.5–9.5)	− 1.893	0.058
Absolute MO, × 10^9/L	225	0.73 (0.45–1.25)	86	0.98 (0.53–1.68)	− 2.307	0.021
Hemoglobin, g/L	226	97 (91–103)	86	94 (88–100)	− 2.184	0.029
Platelet, × 10^9/L	226	450 (363–536)	86	459 (300–684)	− 1.067	0.286
ALT, U/L	236	26 (16–43)	93	22 (15–42)	− 0.445	0.656
AST, U/L	236	33 (24–45)	93	33 (24–54)	− 0.693	0.489
Albumin, g/L	236	35.6 (32.9–37.7)	93	32.9 (30.6–36.1)	− 4.243	< 0.001
TBil, μmol/L	236	5.2 (3.4–8.4)	93	5.1 (3.4–10.0)	− 0.595	0.552
GGT, U/L	236	46 (20–109)	93	44 (27–103)	− 0.924	0.356
Sodium, mmol/L	222	136 (134–138)	87	136 (133–138)	− 0.937	0.349
Chloride, mmol/L	222	106 (103–108)	87	104 (102–107)	− 1.727	0.084
Potassium, mmol/L	222	3.9 (3.6–4.2)	87	4.0 (3.7–4.3)	− 1.141	0.254
Calcium, mmol/L	222	1.16 (1.09–1.22)	87	1.17 (1.13–1.23)	− 1.324	0.186

CALs, coronary artery lesions; *NCALs*, without coronary artery lesions; *KD*, Kawasaki disease; *IVIGR*, intravenous immunoglobin-resistant; *ESR*, erythrocyte sedimentation rate; *CRP*, C-reactive protein; *WBC*, white blood cell count; *NE*, neutrophils; *LY*, lymphocytes; *NLR*, neutrophil-to-lymphocyte ratio; *EO*, eosionphils; *MO*, monocytes; *ALT*, alanine aminotransferase; *AST*, aspartate transaminase; *TBil*, total bilirubin; *GGT*, gamma-glutamyl transferase

(1.09–1.85), 1.53 (1.23–1.91), and 1.36 (1.09–1.69), respectively. Based on these values, a scoring system was developed (Table 6). ROC curve shows a total score of 3 produces a sensitivity of 51.4% and a specificity of 68.2%, with an AUC of 0.634.

Table 4 shows that the independent risk factors for KD with CAL in patients ≤ 6 months old were longer total fever duration, delayed diagnosis, and decreased ALB. Further analyses (Table 5) showed that the OR (95% CI) values for total fever were 3.61 (2.02–6.45), 3.49 (1.49–8.16), and 2.07 (1.14–3.74), respectively. A scoring system was developed with an AUC of 0.731 on the basis of these indicators (Table 6). When the cutoff values of total scores was 3; the system to predict CAL yielded a sensitivity of 64.7% and a specificity of 80.9%.

The indicators that show significant differences by the univariate analysis in KD with CAL in patients > 5 years old include fever duration, ALB, blood sodium, and hemoglobin (Table 4). However, all *p* values are > 0.05 after multivariable

Table 3 Comparison of groups with and without CAL at acute and subacute stages in patients > 5 years old

Variables	NCAL		CAL		U/χ^2	*p*
	n	Median (p25-p75)/*n* (%)	*n*	Median (p25-p75)/*n* (%)		
Male-to-female ratio	252	1.52:1	70	2.68:1	3.697	0.068
Illness days at admission, days	252	6 (5–8)	70	7 (6–9)	− 1.9	0.057
Number of major diagnostic criteria	252	4 (3–5)	70	4 (3–5)	− 0.04	0.971
Total fever duration, days	249	8 (6–10)	70	9 (7–10.3)	− 2.98	0.003
Days of hospitalization, days	252	6 (5–8)	70	7 (5–9)	− 2.32	0.021
Incomplete KD, %	252	144 (57.1)	70	38 (54.3)	0.182	0.385
Delayed diagnosis, %	232	26 (11.2)	65	6 (9.2)	0.206	0.423
IVIGR, %	225	35 (15.6)	64	17 (26.6)	4.091	0.064
ESR, mm/h	232	56 (29–85)	67	64 (40–91)	− 1.47	0.141
CRP, mg/L	231	51 (20–110)	66	65 (9–152)	− 0.46	0.646
WBC, × 10^9/L	232	11.1 (7.4–15.2)	67	10.0 (6.8–15.4)	− 0.5	0.62
NE, %	232	73.2 (59.3–83.3)	67	71.2 (54.7–83.5)	− 0.52	0.602
Absolute NE, × 10^9/L	232	8.0 (4.3–11.9)	67	7.0 (3.8–12.7)	− 0.49	0.625
LY, %	232	16.7 (10.4–29.9)	67	19.7 (10.5–31.9)	− 0.46	0.643
Absolute LY, × 10^9/L	232	1.9 (1.2–2.5)	67	1.8 (1.1–2.6)	− 0.14	0.892
NLR	232	4.3 (2.0–8.0)	67	3.7 (1.7–7.7)	− 0.5	0.618
EO, %	232	1.5 (0.7–3.1)	67	1.6 (0.8–3.3)	− 0.61	0.54
Absolute EO, × 10^9/L	232	0.17 (0.07–0.31)	67	0.17 (0.10–0.36)	− 0.92	0.358
MO, %	232	5.9 (3.4–8.1)	67	6 (3.2–9.4)	− 0.25	0.807
Absolute MO, × 10^9/L	232	0.58 (0.35–0.92)	67	0.51 (0.34–0.92)	− 0.33	0.739
Hemoglobin, g/L	232	116 (110–122)	67	113 (105–119)	− 2.33	0.02
Platelet, × 10^9/L	232	313 (235–395)	67	351 (247–440)	− 1.52	0.128
ALT, U/L	240	14 (10–38)	70	19 (11–36)	− 1.44	0.149
AST, U/L	240	25 (20–37)	70	28 (21–40)	− 0.97	0.331
Albumin, g/L	240	37.3 (34.3–40.0)	70	35.9 (32.7–38.7)	− 2.14	0.032
TBil, μmol/L	239	4.7 (3.2–6.9)	70	4.3 (3.1–7.0)	− 0.97	0.331
GGT, U/L	239	11 (8–34)	70	15 (9–37)	− 1.33	0.184
Sodium, mmol/L	217	138 (135–140)	63	136 (134–138)	− 2.89	0.004
Chloride, mmol/L	217	104 (101–107)	63	103 (101–106)	− 0.87	0.382
Potassium, mmol/L	217	3.5 (3.2–3.7)	63	3.5 (3.2–3.7)	− 0.46	0.645
Calcium, mmol/L	217	1.09 (1.02–1.15)	63	1.11 (1.05–1.14)	− 1.07	0.283

CALs, coronary artery lesions; *NCALs*, without coronary artery lesions; *KD*, Kawasaki disease; *IVIGR*, intravenous immunoglobin-resistant; *ESR*, erythrocyte sedimentation rate; *CRP*, C-reactive protein; *WBC*, white blood cell count; *NE*, neutrophils; *LY*, lymphocytes; *NLR*, neutrophil-to-lymphocyte ratio; *EO*, eosionphils; MO, monocytes; *ALT*, alanine aminotransferase; *AST*, aspartate transaminase; *TBil*, total bilirubin; *GGT*, gamma-glutamyl transferase

regression analysis. Therefore, these indicators are not the independent risk factors for KD with CAL in patients > 5 years old and further investigation is not carried out.

Discussions

CAL is the most common and most important clinical complication of KD. The 20th National Survey of Japan data [12] in 2007–2008 showed that the coronary complication rate of KD was 10.03%. The 21st National Survey of Japan data [13] in 2009–2010 showed that the coronary complication rate of KD was 8.57%. The incidences of CAL in the USA from 1994 to 2003 [14], South Korea from 2009 to 2011 [15], Beijing from 2000 to 2004 [16], and Shanghai from 2003 to 2007 [17] were 12.9%, 18.3%, 20.6%, and 19.8%, respectively. In this study, the CAL incidence was 24.1%, which is similar to its incidence in other cities in China but higher than its incidence in other countries.

Table 4 Multivariable logistic regression analysis of risk factors for CAL

	Variables	B	S.E.	Wald	df	*p*	Exp. (B)	95% CI for Exp. (B)	
								Lower	Upper
All cases	Gender	− 0.338	0.124	7.463	1	0.006	0.713	0.560	0.909
	Age of onset	− 0.002	0.002	0.739	1	0.390	0.998	0.994	1.003
	Illness day at admission	0.014	0.039	0.138	1	0.710	1.014	0.941	1.094
	Number of major symptoms	− 0.051	0.046	1.216	1	0.270	0.951	0.869	1.040
	Total fever duration	0.080	0.035	5.163	1	0.023	1.083	1.011	1.160
	Delayed diagnosis	0.398	0.293	1.846	1	0.174	1.489	0.838	2.646
	IVIGR	0.400	0.151	6.986	1	0.008	1.492	1.109	2.008
	Albumin	− 0.056	0.014	14.868	1	< 0.001	0.946	0.919	0.973
	ESR	0.003	0.002	2.755	1	0.097	1.003	0.999	1.008
	NLR	0.001	0.009	0.010	1	0.919	1.001	0.984	1.018
	EO	0.047	0.020	5.685	1	0.017	1.048	1.008	1.089
	MO	0.045	0.017	7.518	1	0.006	1.046	1.013	1.081
Cases ≤ 6 months old	Illness days at admission	− 0.147	0.117	1.576	1	0.209	0.864	0.687	1.086
	Number of major symptoms	0.012	0.142	0.007	1	0.934	1.012	0.765	1.338
	Total fever duration	0.220	0.112	3.858	1	0.050	1.246	1.000	1.551
	Delayer diagnosis	1.762	0.772	5.212	1	0.022	5.824	1.283	26.437
	IVIGR	0.501	0.478	1.101	1	0.294	1.651	0.647	4.210
	Albumin	− 0.175	0.057	9.493	1	0.002	0.839	0.750	0.938
	ESR	0.009	0.006	2.260	1	0.133	1.009	0.997	1.020
	EO	0.207	0.303	0.470	1	0.493	1.230	0.680	2.227
	MO	0.302	0.232	1.689	1	0.194	1.352	0.858	2.132
	Hemoglobin	0.016	0.021	0.576	1	0.448	1.016	0.975	1.059
Cases > 5 years old	Total fever duration	0.051	0.038	1.768	1	0.184	1.052	0.976	1.135
	Albumin	− 0.015	0.037	0.177	1	0.674	0.985	0.916	1.058
	Serum sodium	− 0.032	0.032	0.999	1	0.318	0.969	0.910	1.031
	Hemoglobin	− 0.028	0.017	2.538	1	0.111	0.973	0.940	1.006

Hosmer and Lemeshow test: $p = 0.946$ (all cases); $p = 0.437$ (cases ≤ 6 months old); $p = 0.03$ (cases > 5 years old). *IVIGR*, intravenous immunoglobin resistance; *ESR*, erythrocyte sedimentation rate; *NLR*, neutrophil-to-lymphocyte ratio; *EO*, eosionphils; *MO*, monocytes

Many scholars have investigated the risk factors for KD combined with CAL, including delayed diagnosis, lack of medical insurance, and language barriers reported by Wilder et al. [18]; incomplete KD, IVIGR, fever duration ≥ 7 days, and the rs7604693 mutation (CC/AC) in the PELI1 gene reported by Kim et al. [19]; longer fever duration before and after re-administration of IVIG, longer illness days at initial IVIG therapy, elevated WBC before and after re-administration of IVIG, and CRP before re-administration of IVIG reported by Miura et al. [20]; and elevated WBC and CRP after IVIG therapy reported by Mori et al. [21]. The present study enhanced the understanding of the risk factors for CAL. However, it should be noted that the post-treatment parameters were inferior to the pre-treatment parameters in the predictive role, and scoring system for CAL prediction remained unavailable.

As the major targeted tissue in KD-related vasculitis, the coronary artery has attracted extensive attention from pediatricians. Early identification of risk factors for and accurate prediction of CAL is still the focus of the current studies. Clinical practice shows that the application of joint parameters that is routinely used, fast and easy to detect can result in stable predictions, thereby making it easier to communicate the clinical results and promote their use. In this study, univariate analysis was performed on the clinical indicators, blood count indicators, and blood biochemical indicators of all the KD samples and the risk factors were screened. Multivariate analysis was then performed to identify the independent risk factors, and based on these results, scoring systems for CAL were developed.

In a comparison of group with CAL and NCAL, it was found that the KD combined with CAL group had a higher male-to-female ratio, younger age of onset, longer illness days at admission, fewer number of main diagnostic criteria, longer fever duration, higher delayed diagnosis rate, and higher proportion of IVIGR cases, indicating that boys, younger

Table 5 Scoring system to predict CAL

	Variables	B	S.E.	Wald	df	*p*	Exp. (B)	95% CI for Exp. (B)		Score points
								Lower	Upper	
All cases	Male	0.369	0.116	10.019	1	0.002	1.446	1.151	1.817	1
	Total fever duration ≥ 8 days	0.576	0.113	26.033	1	< 0.001	1.778	1.425	2.218	1
	IVIGR	0.351	0.135	6.773	1	0.009	1.420	1.090	1.849	1
	Albumin ≤ 35.9 g/L	0.427	0.112	14.605	1	< 0.001	1.533	1.231	1.908	1
	EO ≥ 2.2%	0.156	0.111	1.954	1	0.162	1.169	0.939	1.454	
	MO ≥ 5.9%	0.305	0.111	7.480	1	0.006	1.356	1.090	1.687	1
	Total score									5
Cases ≤ 6 months old	Total fever duration ≥ 8 days	1.283	0.296	18.735	1	< 0.001	3.607	2.018	6.448	2
	Delayed diagnosis	1.249	0.434	8.301	1	0.004	3.488	1.491	8.161	2
	Albumin ≤ 35.9 g/L	0.727	0.303	5.757	1	0.016	2.068	1.142	3.743	1
	Total score									5

Hosmer and Lemeshow test: $p = 0.923$ (all cases); $p = 0.170$ (cases ≤ 6 months old). *IVIGR*, intravenous immunoglobin resistance; *EO*, eosionphils; MO: monocytes

patients, delayed visit to physicians, and atypical clinical manifestations tended to cause CAL in KD patients. Delayed treatment and IVIG resistance could also lead to CAL. Comparison of the complete blood count indicators showed that ESR, EO, MO, and platelets were higher; NLR was lower in cases with CAL, indicating that EO- and MO-induced inflammation were involved in the complications of coronary arteries. Decreased albumin in cases with CAL indicated that the permeability of the inflamed vascular walls was increased, leading to endothelial cell injury and leakage of albumin.

Univariate analysis on 113 KD cases (10 cases with CAL) from Iran's Fars province [22] showed that persistent fever and thrombocytosis were risk factors for CAL. Ruan et al. [23] analyzed 1370 cases of acute KD (484 cases with CAL) and showed that males, younger age, IVIG dose, delayed diagnosis, and elevated platelets and ESR were often associated with CAL. Honkanen et al. [2] analyzed 344 cases of KD (98 cases with CAL) and showed that low albumin, younger age, and long fever duration tended to result in CAL. Yeo et al. [24] carried out a univariate analysis on 136 cases of infant KD (16 cases with CAL) and found that group with CAL had a longer fever duration, lower number of major diagnostic criteria, higher WBC, and higher platelet. The results of their analyses were consistent with our findings. The 16th National Survey of Japan data [25] found that hyponatremia was more frequent in 3–5 days of onset and revealed that serum sodium < 135 mmol/L was the risk factor for CAL with an OR of 1.79. Suzuki et al. [26] monitored serum sodium and albumin levels of 127 cases of KD until 4 weeks after illness onset and found that in the second week, the blood sodium was lower in the CAL group than in the NCAL group, and for four consecutive weeks, the albumin levels in the CAL group were lower than those in the NCAL group. Our data showed that the hypoalbuminemia was also seen in cases in group with CAL group, but showed no difference in serum sodium, maybe due to the differently detective days of onset of illness.

Due to lack of specific markers, timely diagnosis of KD before all the main symptoms appearing were still a big challenge for clinicians and delayed treatment put these patients under high risk being CAL. In view of atypical characteristics of patients with KD younger than 6 months old and older than 5 years old, cases at the extremes of age in the total samples were further investigated.

In patients ≤ 6 months old, no differences were observed between groups with CAL and NCAL with regard to the parameters including the sex ratio, NE, LY, EO, MO, and platelets. In patients >5 years old, only two indicators were elevated (total fever duration and days of hospitalization); three indicators were increased (hemoglobin, albumin, serum sodium) in group with CAL. The analyses of the subgroups stratified by age indicated the clinical features of patients with KD at the extreme age were very different from the total samples and could be further subjected to multivariate logistic regression analysis.

Multivariate analysis showed that the independent risk factors for KD combined with CAL were being a boy, long total fever duration, IVIGR, decreased albumin, and elevated EO and MO; and the independent risk factors for KD patients ≤ 6 months old combined with CAL were long total fever duration, delayed diagnosis, and decreased albumin. We noted that pre-IVIG treatment NLR and platelet-to-lymphocyte ratios could be used to predict IVIGRKD reported by Kawamura et al. [27]. However, in our present data, NLR was a risk factor but not an independent risk factors for KD with CAL, indicating that NLR failed to predict KD with CAL. Independent risk factors for KD patients > 5 years old combined with CAL

Table 6 Ability of scoring system to predict CAL

	Area	S.E.	95% CI for area		Cutoff	Sensitivity	Specificity
			Lower	Upper			
All cases	0.634	0.015	0.605	0.663	2	0.831	0.339
					3	0.514	0.682
					4	0.226	0.900
Cases ≤ 6 months old	0.731	0.035	0.663	0.800	2	0.682	0.700
					3	0.647	0.809
					4	0.247	0.961

could not be generated in the present samples. Scoring systems were established for the independent risk factors, and the AUC value and sensitivity and specificity of predicting KD combined with CAL were 0.634, 51.4%, and 68.2%, respectively. However, our model was still not ideal in terms of its sensitivity and specificity, indicating the need for further optimization. Further studies showed that the AUC value and sensitivity and specificity of predicting KD combined with CAL in patients ≤ 6 months old were 0.731, 64.7%, and 80.9%, respectively, indicating a significant optimization had been achieved. Few studies about scoring systems for KD with CAL are available except two models reported by Tremoulet et al. [3] and Sato et al. [4]. Due to the indicators of the percentage of band and serum IL-6 were not routinely examined in the present data, the two models could not use to evaluate our data and compare with our new scoring system.

This study does have several weaknesses that we should illustrate. This study was a retrospective review of clinical data, raising the possibility of a bias in interpreting the results. For certain items of the data missing, it was impossible to perform multivariate logistic regression analysis. Because the data were collected over 6 consecutive years, the cases with large sample sizes were able to enhance the stability of the data, which compensates for the aforementioned limitations to a certain extent.

Conclusions

The independent risk factors for acute and subacute KD combined with CAL, including being a boy, long fever duration, IVIGR, low ALB, and elevated EO and MO. Joint of parameters (total fever duration ≥ 8 days, delayed diagnosis, and ALB ≤ 35.9 g/L) can be used to predict the occurrence of CAL in KD patients ≤ 6 months old.

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Compliance with ethical standards

Ethical approval The retrospective studies have been approved by the ethics committee in our hospital and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

Disclosure None.

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