

# Study Progress of Coronary Artery Damage in Kawasaki Disease

## Abstract

Kawasaki Disease (KD) is a vasculitis of unknown etiology commonly seen in infants and children. Children with Kawasaki disease are at risk for serious cardiovascular sequelae, especially coronary artery abnormalities, which can lead to myocardial ischemia, myocardial infarction, and sudden death. Coronary artery lesions (CAL) caused by Kawasaki disease has become one of the common acquired heart diseases in children in some countries and regions. This article reviews the current research progress on the mechanism, risk factors and treatment of coronary artery damage in Kawasaki disease, aiming to improve the long-term prognosis of vascular health management in children with KD, in order to provide references for clinicians.

**Key words** Kawasaki disease; Coronary artery damage; Risk factors; Mechanism; heal

## Introduction

Kawasaki disease, also known as cutaneous mucosal lymph node syndrome, was first reported by Dr. Tomisaku Kawasaki in Japan in 1967. The etiology of Kawasaki disease is unknown, but it is generally believed that Kawasaki disease is an acute systemic immune vasculitis triggered by infectious factors, which may be complicated by coronary artery lesions (CAL). CAL caused by Kawasaki disease has become one of the common

acquired heart diseases in some countries and regions. Kawasaki disease tends to occur in children under 5 years of age, and can occur throughout the year, with a male to female incidence ratio of 1.7: 1. “The incidence is significantly higher in East Asia, and the incidence is increasing, while the incidence is lower in European and American countries. Data published in Beijing and Shanghai in recent years show that there are more than 100 new cases of Kawasaki disease every year in every 100,000 children aged 0 to 4 years” <sup>[1]</sup>. In recent years, many studies have shown that the pathogenesis of KD is significantly related to infection, genetic susceptibility and immune response <sup>[2]</sup>. The mechanism, risk factors and treatment of coronary artery damage in Kawasaki disease in recent years are reviewed.

## **1. Mechanism of Coronary Artery Damage**

### **1.1 Vascular endothelial Injury and Endothelial dysfunction**

In normal blood vessel walls, endothelial cells (ECs), which act as an endodermal barrier, come into direct contact with plasma and blood cell components and transmit these signals to the media. KD acute vascular injury, including rapid destruction of endothelial cells, elastic layer and medial smooth muscle cells. When endothelial cells are injured, they release a variety of vasoactive substances to the vascular wall, such as nitric oxide (NO) and endothelin. These vasoactive substances participate in the contraction or relaxation of the vascular wall, the adhesion of inflammatory cells to the vascular wall, vascular permeability, and the regulation of coagulation and fibrinolysis systems, ultimately causing endothelial cell dysfunction <sup>[3]</sup>. NO is a vasodilator synthesized by endothelial NO synthase (eNOS) and induced NO synthase (iNOS), which is expressed by neutrophils, monocytes and endothelial cells at different stages of KD acute phase. Among them, NO synthesized by iNOS in neutrophils plays an important role in the early initiation of endothelial dysfunction of KD <sup>[4]</sup>. In addition, in the acute KD stage, the platelet count is often elevated, which can lead to hyperplatelet function, platelet adhesion, deformation, aggregation and release of various cytokines

and inflammatory factors, forming a state of blood hypercoagulation, causing vascular endothelial damage, collagen exposure, triggering chemotaxis of various cytokines, and eventually forming vasculitic lesions <sup>[5]</sup>. The upregulation of neuropilinase 1 (NRP1) and vascular endothelial growth factor receptor 2 (VEGFR2) in endothelial cells (ECs) and the increase of vasoactive factor ANGPTL4 and vascular endothelial growth factor (VEGF) in serum also participate in the increase of endothelial cell permeability, resulting in vascular hyperosmosis in the context of KD <sup>[6]</sup>. It can be seen that vascular endothelial injury and endothelial dysfunction play an important role in the vascular lesions of KD.

### **1.2 Production of inflammatory factors and proteases**

“During KD acute phase, peripheral blood mononuclear macrophages were significantly activated. Activated macrophages play an important role in the development of KD coronary artery disease. Macrophages can produce tumor necrosis factor- $\alpha$ , vascular endothelial growth factor, interleukin-1 and other inflammatory factors, which will further amplify the inflammatory response and have a direct inflammatory effect on coronary artery endothelial cells. Macrophages also produce proteases, including matrix metalloproteinase-2 (MMP-2) and matrix metalloproteinase-9 (MMP-9), which degrade elastin fibers within artery walls, leading to coronary artery dilation and aneurysms” <sup>[1,7]</sup>. “In addition, tissue inhibitor of metalloproteinase-1 (TIMP-1) is an active inhibitor of MMP-9, which binds with MMP-9 in a ratio of 1:1 to form a complex, blocking the binding of MMP-9 to the substrate and inactivating it” <sup>[8,9]</sup>. “Under physiological conditions, MMP-9 and TIMP-1 are in a state of dynamic equilibrium. When KD occurs, a large amount of MMP-9 is produced, thus disrupting the dynamic balance between MMP-9 and TIMP-1 and degrading the matrix of the blood vessel wall, further causing the migration of inflammatory cells to deep blood vessels, thus leading to the reconstruction of blood vessel structure” <sup>[10]</sup>.

### **1.3 CD36 and AIM2 activate the inflammasome pathway**

“Effective clearance of apoptotic cells by macrophages and dendritic cells is important for maintaining immune homeostasis and cultivating

peripheral tolerance. Macrophages help phagocytose apoptotic cells and cell debris and induce self-tolerance by expressing scavenger receptors (including SCARF1, CD305, CD11b, CD11c, and CD36)”<sup>[11]</sup>. “Patients in the acute phase of KD may have a higher burden of apoptotic cell debris, higher expression of CD36 (a scavenger receptor that helps clear apoptotic debris), and higher expression of interferon-induced protein AIM2 (an inflammasome receptor protein), which may lead to subsequent involvement of the inflammasome pathway. Apoptotic cells secrete plasma mitochondrial DNA, and particles including mitochondrial DNA can enter cells through endocytosis, bind to intracellular toll-like receptor 9 (TLR9), activate transcription factor NF- $\kappa$ B, and increase the transcription of pro-inflammatory genes pro-IL-1 $\beta$  and pro-IL-18, CD36 amplifies the immune response by helping to clear plasma mitochondrial DNA and activating the inflammasome pathway through interferon-induced protein AIM2 (an inflammasome receptor protein), thereby causing the occurrence and development of KD”<sup>[12,13]</sup>. It was found that both CD36 and AIM2 mRNA were decreased after IVIG treatment, and a larger decline in their percentages at 21 days after IVIG treatment also suggested that they were associated with the development of coronary artery disease<sup>[12]</sup>.

#### **1.4 Other mechanisms**

Some IgM antibodies are thought to be involved in the pathophysiology of coronary artery disease because of its regulatory role in vascular remodeling. The level of antiphosphorylated choline IgM decreased in patients with major acute cardiovascular events, and the study of Zheng et al. suggested that the decrease of IgM in KD patients 6 months after IVIG treatment was associated with the increase of coronary artery z score<sup>[14]</sup>. “It has also been found that one of the KD related molecules is the oxidized (hydroxylated) form of phosphatidylcholine. Oxidized phospholipids, including oxidized phosphatidylcholine (PCs), are involved in the regulation of inflammation, thrombosis, angiogenesis, endothelial barrier function, immune tolerance and other important processes. Oxidized phospholipids play a multidirectional role through receptor-mediated and receptor-independent biological mechanisms, and may play a role in the pathogenesis of atherosclerosis and its complications”<sup>[15,16]</sup>.

## 2. Risk Factors

“Coronary artery lesions (CAL) is a common complication of KD, which can lead to ischemic heart disease, myocardial infarction, sudden death and other serious consequences. Therefore, timely diagnosis and treatment are the key to reducing Kawasaki disease CAL. Mastering the risk factors of CAL and providing targeted treatment to children can minimize the risk of CAL”<sup>[17]</sup>. Early identification of risk factors to accurately predict CAL or aneurysm formation is still the focus of current research<sup>[18]</sup>. The author summarized the risk factors of CAL as follows.

### 2.1 Long-term fever, age and various biomarkers

Li have shown that “long-term fever before IVIG treatment is an independent risk factor for CAL in KD children younger than 6 months”<sup>[19]</sup>. Wang et al. also confirmed that “IVIG treatment over 10 days and hypersensitive CRP over 100mg/L are independent risk factors for CAL”<sup>[20]</sup>. “Studies have analyzed a variety of possible risk factors and found that children with long fever, younger than 1 year old, increased NT-proBNP and decreased Hb may be independent risk factors for the development of CAL in KD children”<sup>[17]</sup>. “Other studies have also found that matrix metalloproteinase-9 (MMP-9) is an independent risk factor for CALs after adjusting for other variables (male, fever duration, incomplete Kawasaki disease, platelet, albumin, CRP, ESR)<sup>[10]</sup>. Cao et al. found that decreased AST/ALT was a risk factor for CALs on admission, but not for progressive CALs”<sup>[21]</sup>. Nakashima et al. confirmed that “oxidized phosphatidylcholine (PCs) increased in the acute phase of KD, and oxidized phosphatidylcholine (PCs) is a widely accepted molecule that causes vascular inflammation, so oxidized PCS and its related products can be used as useful biomarkers for KD coronary arteritis in Japanese and non-Asian patients”<sup>[22]</sup>. “Studies have found that most children with KD have elevated serum IgE levels, and compared with non-CALS patients, the serum IgE level in patients with KD combined with CALs is elevated, so the serum IgE level may be an independent risk factor for CALs, which can provide reference for monitoring CALs”<sup>[23]</sup>. “Penetrin 3 (PTX3) is of high value in the diagnosis of KD and is an excellent biomarker to distinguish KD cases from non-KD cases (including subjects with high suspicion of KD). For example, PTX3

plasma values are increased more in patients with acute early CAL than in patients without acute early CAL. Pre-ivig PTX3 levels are a strong and sensitive predictor of IVIG non-responsiveness and subsequent CAL formation, and may help identify high-risk patients who require additional second-line therapy, not just repeated IVIG therapy” [24]. Watanabe et al. found that “serum soluble lipoprotein receptor 11 (sLR11) was elevated in patients who did not respond to IVIG treatment and was a potential biomarker for evaluating vascular disease, including atherosclerosis and coronary artery disease. The serum sLR11 level of KD patients with CALs was significantly higher than that of patients without CALs and healthy controls. Therefore, sLR11 may be a novel biomarker for post-KD vascular disease” [25].

## **2.2 IVIG Resistant patients**

“Patient age, Pro-BNP, CRP, ESR, total bilirubin, AST, ALT and other biomarkers were positively correlated with IVIG resistance. Subgroup analysis showed that the incidence of CAL in IVIG resistance group was still higher than that in IVIG response group under different regions, different diagnostic criteria for IVIG resistance, different CAL diagnostic criteria and different study types. This indicates that under various conditions, IVIG-resistant groups have a higher CAL risk than IVIG-responsive groups” [26].

## **2.3 Standard deviation of Red blood cell Distribution Width (RDW-SD) and Coefficient of Variation of Red Blood Cell Distribution Width (RDW-CV)**

“High RDW-SD is independent marker of CALs in patients with complete KD, and this association is independent of multiple potential confounding factors. They included age, sex, IVIG resistance, hemoglobin, RDW-CV, glutamyltranspeptidase, procalcitonin, AST/ALT, albumin and serum sodium. In patients with incomplete KD, high RDW-CV was an independent marker of CALs after adjusting for age, sex, mean red cell volume, and total bilirubin. Therefore, in patients with complete KD, RDW-SD may be superior to RDW-CV as a predictor of CALs. RDW-SD is an independent predictor of CALs in patients with complete KD, while RDWCV is only an independent risk factor for CALs in patients with incomplete KD” [27].

## **2.4 Brachial artery flow-mediated dilation (FMD)**

FMD= (internal diameter after brachial artery filling-basic internal diameter of brachial

artery)/basic internal diameter of brachial artery  $\times 100\%$ , the normal value of brachial artery FMD  $> 10\%$ <sup>[28]</sup>. FMD can sensitively reflect the pathological process of acute coronary artery dilatation by showing incipient arterial endothelial dysfunction in KD, especially in aneurysms smaller than 3.44%. Therefore, FMD  $\leq 3.44\%$  can be regarded as the signal of KD acute coronary artery disease<sup>[29]</sup>. The percentage change of flow-mediated vasodilation (%FMD) reflects endothelial nitric oxide dependent vasodilation, the decrease of FMD% reflects endothelial cell dysfunction, and the significant decrease of FMD% indicates endothelial injury and the risk of atherosclerosis<sup>[30]</sup>.

### **2.5 Integrin $\alpha 2$ (ITGA2)**

ITGA2 gene polymorphism is one of the important factors affecting CAL in children with KD combined with CAL, and the risk of KD combined with CAL associated with ITGA2rs1126643 genotype is significantly increased. Stratified analysis showed that ITGA2rs1126643 could inhibit the formation of coronary artery small aneurysms (SCAL) and coronary artery medium aneurysms (MCAL) induced by KD, among which, compared with rs1126643CC genotype, the harmful effects of CT/TT variant genotype were more obvious in children  $\leq 60$  months and men<sup>[31]</sup>.

### **2.6 Others**

For KD patients with no history of antibiotic use, the increase of immature granulocyte percentage (neutrophil percentage, lymphocyte percentage) and total protein is an independent risk factor for the development of CAL, and the use of antibiotics can affect the physiological indicators and predictive diagnosis of KD patients with CAL<sup>[32]</sup>. Suzuki et al. found that water retention in the acute phase of Kawasaki disease may be a risk factor for CAL, and water retention may lead to changes in ion concentration of patients<sup>[33]</sup>. Wang et al. showed that breastfeeding and longer duration of breastfeeding did not reduce CALs in patients with KD<sup>[34]</sup>.

## **3. Treatment**

The most important aspect of the treatment of KD in the acute phase is the prevention of CAL, and effective treatment of CAL prevention can not only reduce the risk of subsequent coronary complications, but also prevent the development of systemic

vascular atherosclerosis <sup>[35]</sup>.

### **3.1 Intravenous Immunoglobulin (IVIG)**

The successful management of intravenous immunoglobulin (IVIG) in the acute phase of KD is very important for the prevention of CAL. IVIG has become a first-line drug with good safety in the treatment of Kawasaki disease and can effectively reduce the incidence of cardiovascular complications. It is extremely important to standardize the use of IVIG for CAL caused by Kawasaki disease. For complete Kawasaki disease, the dose of IVIG is 2g/kg, a single intravenous infusion within 12 to 24 hours, and oral aspirin; The incidence of CAL in children with incomplete Kawasaki disease is higher than that of complete Kawasaki disease, and IVIG should be given in time to reduce the occurrence of CAL. The recommended dose of IVIG is 2g/kg, and the recommended dose is a single intravenous infusion within 12 to 24 hours, combined with aspirin orally. The dose of IVIG for recurrent Kawasaki disease was 2g/kg, a single intravenous infusion within 12 to 24 hours, combined with oral aspirin; For non-reactive Kawasaki disease (IVIg-resistant Kawasaki disease), it is recommended to re-apply IVIG as soon as possible, the dose is still 2g/kg, a single intravenous infusion within 12 to 24 hours, and there are still fever, and glucocorticoids can be combined with IVIG <sup>[36]</sup>. In addition, the appropriate timing of IVIG standard therapy is also crucial for limiting **coronary artery lesions** (CALs) <sup>[37]</sup>. The best time is 5 to 10 days after onset, and the best time is within 7 days. Use within 5 days after onset may lead to increased incidence of IVIG resistance; Patients with severe conditions, such as hypotension, shock, hemodynamic instability of myocarditis, paralytic ileus, etc. should still be used in time. The children of more than 10 d, rule out other causes of persistent fever accompanied by a red blood cell sedimentation rate (erythrocyte sedimentation rate, ESR) or elevated c-reactive protein (C-reactive protein, CRP), or elevated inflammatory indicators combined with CAL, IVIG therapy is still required [36]. IVIG treatment within 7 days of onset was found to be sufficient to prevent coronary artery abnormalities in KD patients. Early IVIG treatment on day 4 may not increase the higher incidence of coronary artery abnormalities and IVIG resistance <sup>[38]</sup>.

### **3.2 Aspirin (Asp)**

**Aspirin** is a common antipyretic and analgesic drug. After taking **Aspirin** in children, it can act on the body temperature regulation center of hypothalamus, thereby causing peripheral vascular dilation, so as to increase the skin blood flow, sweat and heat dissipation of children. Asp can also acetylate serine residues at position 530 of the active part of the cyclooxygenase-1 polypeptide chain in children, completely inactivating cyclooxygenase, blocking the conversion of arachidonic acid to thromboxane A<sub>2</sub>, and playing an anti-platelet aggregation effect, thus effectively avoiding embolism in the children and affecting blood circulation. Therefore, **Aspirin** in the treatment of KD children will play a role in antipyretic analgesia, prevent thrombosis and other curative effects, is a more effective drug. Standardized use of Asp has important clinical significance for prevention and treatment of cardiovascular sequelae caused by KD<sup>[39-41]</sup>. Because Asp is the standard treatment for acute treatment, if KD is diagnosed and fever is present, an oral moderate dose of aspirin [30 to 50mg/(kg·d), 3 times daily] should be initiated. After fever reduction, aspirin is reduced to a low dose [3 to 5mg/(kg·d), once daily, orally], which is continued even in the absence of coronary aneurysm (CAA) until 2 to 3 months after onset, and if CAA is present, to resolution<sup>[42]</sup>.

### **3.3 Combination Therapy**

Asp combined with IVIG in the treatment of KD has become a safe and reliable first-line therapy, which can effectively reduce the incidence of cardiovascular complications<sup>[41]</sup>. 23% to 43% of patients taking Asp alone developed CAL later in life, compared to 8% to 15% of patients with IVIG+Asp<sup>[43,44]</sup>. Yu et al. found that compared with IVIG responders, IVIG-resistant KD patients had a higher risk of CAL<sup>[4]</sup>. For high-risk patients with IVIG resistance, the efficacy of adding prednisolone or cyclosporine to the standard treatment (IVIG+Asp) as first-line treatment has been confirmed by randomized controlled trials<sup>[35,45]</sup>. Studies have also shown that **traditional herbal medicine** combined with conventional western medicine is more effective in reducing the prevalence rate of CAL in KD patients and improving the cure rate and total effective rate of CAL, and the clinical efficacy is higher than that of conventional Western medicine<sup>[46]</sup>. It can be seen that the efficacy of drug combination

therapy for KD is better than that of single drug therapy, and it is a high clinical value therapy.

### **3.4 Other treatments**

In the activated T nuclear factor (NFAT) gene family, NFAT2 has been determined to play an important role in the Ca<sup>+</sup>/NFAT pathway. Forkhead like transcription factor O4 (FOXO4) acts as a transcription suppressor to inhibit vasculitis and maintain endothelial cell homeostasis through negative regulation of NFAT2, thereby controlling vasculitis in KD. Therefore, the FOXO4/NFAT2 signaling pathway can be used as a new therapeutic target, and its related intrinsic inhibition mechanism can be used to develop new therapies to prevent and treat KD<sup>[47]</sup>. Previous studies have also reported that NFAT inhibitors, such as cyclosporine, can prevent the progression of arterial wall inflammation by preventing cytotoxic CD8<sup>+</sup>T cells from infiltrating into the artery wall<sup>[48]</sup>.

### **Conclusion**

KD is a kind of acute self-limited febrile disease, CAL is its common complication, CAL can lead to ischemic heart disease, myocardial infarction, sudden death and other serious consequences. The prevalence of KD in children has increased in recent years, which is more important for the identification and diagnosis of CAL. This article reviews the pathogenesis, risk factors and treatment of KD, which provides a new clinical idea for the cardiovascular prevention and treatment of KD in children. However, due to the limited research on KD, the relevant mechanism and treatment need to be further studied. It is believed that with the development of medical technology, there will be more effective clinical methods for the pathogenesis and prevention of KD CAL.

### **References**

- [1] Chinese Journal of Pediatrics , 2022,60(1) : 6-13 DOI : 10.3760/cma.j.cn11214-0-20211018-00879.
- [2] Fan X, Zhou Y, Guo X, Xu M. Utilizing single-cell RNA sequencing for analyzing the characteristics of PBMC in patients with Kawasaki disease. BMC P

ediatr. 2021 Jun 14;21(1):277. doi: 10.1186/s12887-021-02754-5. PMID: 34126969; PMCID: PMC8201934.

[3] Seki M, Minami T. Kawasaki Disease: Pathology, Risks, and Management. *Vasc Health Risk Manag.* 2022 Jun 10;18:407-416. doi: 10.2147/VHRM.S291762. PMID: 35711626; PMCID: PMC9196282.

[4] Yu X, Hirono KI, Ichida F, et al. Enhanced iNOS expression in leukocytes and circulating endothelial cells is associated with the progression of coronary artery lesions in acute Kawasaki disease. *Pediatr Res.* 2004;55:688–694. doi:10.1203/01.PDR.0000113464.93042.A4.

[5] Kim HJ, Choi EH, Lim YJ, Kil HR. The usefulness of platelet-derived microparticle as biomarker of antiplatelet therapy in Kawasaki disease. *J Korean Med Sci.* 2017;32:147–53.

[6] Huang J, Zhang S. Overexpressed Neuropilin-1 in Endothelial Cells Promotes Endothelial Permeability through Interaction with ANGPTL4 and VEGF in Kawasaki Disease. *Mediators Inflamm.* 2021 Aug 13;2021:9914071. doi: 10.1155/2021/9914071. PMID: 34434074; PMCID: PMC8380503.

[7] Rowley, A., Baker, S., Orenstein, J. et al. Searching for the cause of Kawasaki disease—cytoplasmic inclusion bodies provide new insight. *Nat Rev Microbiol* 6, 394–401 (2008).

[8] Korematsu S, Ohta Y, Tamai N, et al. Cell distribution differences of matrix metalloproteinase-9 and tissue inhibitor of matrix metalloproteinase-1 in patients with Kawasaki disease. *Pediatr Infect Dis J* 2012;31:973–4.

[9] Saito S, Trovato MJ, You R, et al. Role of matrix metalloproteinases 1, 2, and 9 and tissue inhibitor of matrix metalloproteinase-1 in chronic venous insufficiency. *J Vasc Surg* 2001;34:930–8.

[10] Wang L, Yang Y, Cui Q, Cui Y, Li Q, Che X, Wang C, Quan P, Hu X. Evaluating the added predictive ability of MMP-9 in serum for Kawasaki disease with coronary artery lesions. *J Investig Med.* 2021 Jan;69(1):13-19. doi: 10.1136/jim-2020-001281. Epub 2020 Oct 1. PMID: 33004469.

[11] Trahtemberg U, Mevorach D. Apoptotic Cells Induced Signaling for Immun

e Homeostasis in Macrophages and Dendritic Cells. *Front Immunol* (2017) 8:1356. doi: 10.3389/fimmu.2017.01356.

[12]Guo MM, Huang YH, Wang FS, Chang LS, Chen KD, Kuo HC. CD36 is Associated With the Development of Coronary Artery Lesions in Patients With Kawasaki Disease. *Front Immunol*. 2022 Jan 27;13:790095. doi: 10.3389/fimmu.2022.790095. PMID: 35154107; PMCID: PMC8828496.

[13]West AP, Shadel GS. Mitochondrial DNA in Innate Immune Responses and Inflammatory Pathology. *Nat Rev Immunol* (2017) 17(6):363–75. doi: 10.1038/nri.2017.21.

[14]Chang LS, Chen YJ, Huang PY, Chen KD, Lo MH, Huang YH, Guo MM, Kuo HC. Significantly Lower Immunoglobulin M Levels 6 Months After Disease Onset in Patients With Kawasaki Disease With Coronary Artery Lesions. *J Am Heart Assoc*. 2021 Jun 15;10(12):e020505. doi: 10.1161/JAHA.120.020505. Epub 2021 Jun 5. PMID: 34096327; PMCID: PMC8477878.

[15]Bochkov V, Gesslbauer B, Mauerhofer C, Philippova M, Erne P, Oskolkova OV. Pleiotropic effects of oxidized phospholipids. *Free Radic Biol Med* 2017;111:6–24.

[16]Que X, Hung MY, Yeang C, Gonen A, Prohaska TA, Sun X, Diehl C, Matta A, Gaddis DE, Bowden K, Pattison J, MacDonald JG, Yla-Herttuala S, Mellon PL, Hedrick CC, Ley K, Miller YI, Glass CK, Peterson KL, Binder CJ, Tsimikas S, Witztum JL. Oxidized phospholipids are proinflammatory and proatherogenic in hypercholesterolaemic mice. *Nature* 2018;558:301–306.

[17]Cai WJ, Ding SG. Retrospective analysis of clinical characteristics and related influencing factors of Kawasaki disease. *Medicine (Baltimore)*. 2022 Dec 30;101(52):e32430. doi: 10.1097/MD.00000000000032430. PMID: 36596080; PMCID: PMC9803503.

[18]Maggio MC, Corsello G, Prinzi E, Cimaz R. Kawasaki disease in Sicily: clinical description and markers of disease severity. *Ital J Pediatr*. (2016) 42:92. doi: 10.1186/s13052-016-0306-z.

[19]Li XQ, Wang JT, Wang XL, et al. Analysis of the characteristics and risk

factors of coronary artery lesions in children with Kawasaki disease under 6 months of age. *Lab Med Clin.* 2022;19:2177–80.

[20]Wang YF , Li PL, Tian YJ, et al. Analysis of risk factors for duration of small or medium-sized coronary artery aneurysms in children with Kawasaki disease. *Chin J Appl Clin Pediatr .* 2022;37:816–20.

[21]Cao L, Tang YJ, Gang M, Ma J, Qian WG, Xu QQ, Lv HT. AST-to-ALT ratio and coronary artery lesions among patients with Kawasaki disease. *World J Pediatr.* 2021 Dec;17(6):659-668. doi: 10.1007/s12519-021-00479-0. Epub 2021 Nov 18. PMID: 34792780.

[22]Nakashima Y, Sakai Y, Mizuno Y, Furuno K, Hirono K, Takatsuki S, Suzuki H, Onouchi Y, Kobayashi T, Tanabe K, Hamase K, Miyamoto T, Aoyagi R, Arita M, Yamamura K, Tanaka T, Nishio H, Takada H, Ohga S, Hara T. Lipidomics links oxidized phosphatidylcholines and coronary arteritis in Kawasaki disease. *Cardiovasc Res.* 2021 Jan 1;117(1):96-108. doi: 10.1093/cvr/cvz305. PMID: 31782770.

[23]Wang Z, Liu X, Duan Z, Peng Y. High Serum Total IgE at Admission Is Associated with Coronary Artery Lesions in Children with Kawasaki Disease. *J Trop Pediatr.* 2022 Jan 7;68(1):fmab113. doi: 10.1093/tropej/fmab113. PMID: 35043965.

[24]Kitoh T, Ohara T, Muto T, Okumura A, Baba R, Koizumi Y, Yamagishi Y, Mikamo H, Daigo K, Hamakubo T. Increased Pentraxin 3 Levels Correlate With IVIG Responsiveness and Coronary Artery Aneurysm Formation in Kawasaki Disease. *Front Immunol.* 2021 Apr 12;12:624802. doi: 10.3389/fimmu.2021.624802. PMID: 33912155; PMCID: PMC8072470.

[25]Watanabe K, Suzuki H, Jiang M, Tsukano S, Kataoka S, Ito S, Sakai T, Hirokawa T, Haniu H, Numano F, Hoshina S, Hasegawa S, Matsunaga M, Chiba K, Saito N, Yoshida H, Takami S, Okubo S, Hirano H, Saitoh A, Bujo H. Soluble LR11 as a Novel Biomarker in Acute Kawasaki Disease. *Circ J.* 2022 May 25;86(6):977-983. doi: 10.1253/circj.CJ-20-1271. Epub 2021 Sep 16. PMID: 34526431.

[26]Zheng X, Li J, Yue P, Liu L, Li J, Zhou K, Hua Y, Li Y. Is there an association between intravenous immunoglobulin resistance and coronary artery lesion in Kawasaki disease?-Current evidence based on a meta-analysis. PLoS One. 2021 Mar 25;16(3):e0248812. doi: 10.1371/journal.pone.0248812. PMID: 33764989; PMCID: PMC7993784.

[27]Ming L, Cao HL, Li Q, Yu G. Red Blood Cell Distribution Width as a Predictive Marker for Coronary Artery Lesions in Patients with Kawasaki Disease. *Pediatr Cardiol.* 2021 Oct;42(7):1496-1503. doi: 10.1007/s00246-021-02633-x. Epub 2021 May 25. Erratum in: *Pediatr Cardiol.* 2021 Jul 9;: PMID: 34036412; PMCID: PMC8463334.

[28]Chen Zhongze, Hong Yongqiang, Yang Rurong, Wu Xiuqin, Chen Xinhua. The Monocyte to High-Density Lipoprotein Cholesterol Ratio in Predicting the Reduction of Brachial Artery Flow Mediated Dilatation[J]. *Chinese Journal of Ultrasound in Medicine*,2023,39(03):321-324.

[29]Wen Y, Wang X, Guo Y, Jin M, Xi J, Chen T, Shi K, Lu Y. Predictive value of brachial artery flow-mediated dilation on coronary artery abnormality in acute stage of Kawasaki disease. *Sci Rep.* 2021 Apr 14;11(1):8162. doi: 10.1038/s41598-021-87704-y. PMID: 33854198; PMCID: PMC8046814.

[30]Cheung YF, Woo OK. Oxidative stress in children late after Kawasaki disease: relationship with carotid atherosclerosis and stiffness. *BMC Pediatr.* 2008;8:20. doi:10.1186/1471-2431-8-20.

[31]Yuan J, Jiang Z, Li M, Li W, Gu X, Wang Z, Pi L, Xu Y, Zhou H, Zhang B, Deng Q, Wang Y, Huang P, Zhang L, Gu X. Integrin  $\alpha 2$  gene polymorphism is a risk factor of coronary artery lesions in Chinese children with Kawasaki disease. *Pediatr Rheumatol Online J.* 2021 Feb 8;19(1):12. doi: 10.1186/s12969-021-00494-5. PMID: 33557870; PMCID: PMC7869497.

[32]Lao S, Zhou T, Kuo HC, Zhong G, Zeng W. Risk Factors for Coronary Artery Lesions in Kawasaki Disease Independent of Antibiotic Use in Chinese Children. *Front Public Health.* 2022 May 5;10:817613. doi: 10.3389/fpubh.2022.817613. PMID: 35602151; PMCID: PMC9118346.

[33]Suzuki H, Takeuchi T, Minami T, Shibuta S, Uemura S, Yoshikawa N. Water retention in the acute phase of Kawasaki disease: relationship between oedema and the development of coronary arterial lesions. *Eur J Pediatr.* (2003) 162: 856–9. doi: 10.1007/s00431-003-1326-4.

[34]Wang H, Tang Y, Yan W, Xu Q, Li X, Qian W. Breastfeeding has no protective effects on the development of coronary artery lesions in Kawasaki disease: a retrospective cohort study. *BMC Pediatr.* 2022 Jun 20;22(1):353. doi: 10.1186/s12887-022-03422-y. PMID: 35725463; PMCID: PMC9208131.

[35]Takahashi K, Oharaseki T, Yokouchi Y, Hiruta N, Naoe S. Kawasaki disease as a systemic vasculitis in childhood. *Ann Vasc Dis.* 2010;3:173–181. doi: 10.3400/avd.sasvp01003.

[36]Shaanxi Province Diagnosis and Treatment Center of Kawasaki Disease, Shaanxi Provincial Clinical Medical Research Center for Pediatric Medical Diseases, Children's Hospital of Shaanxi Provincial People's Hospital, Editorial Board of Chinese Journal of Contemporary Pediatrics, Expert Committee of Advanced Training for Pediatrician, China Maternal and Children's Health Association, General Pediatric Group of Pediatrician Branch of Chinese Medical Doctor Association. PMCID : PMC8480171 *Chinese Journal of Contemporary Pediatrics*, 2021, 23(9) : 867-876 DOI:10.7499/j.issn.1008-8830.2107110 <http://www.zgdek.com/fileup/HTML/2021-9-867.htm>

[37]Fabi M, Filice E, Andreozzi L, Mattesini BE, Rizzello A, Palleri D, Dajti E, Zagari RM, Lanari M. Combination of fecal calprotectin and initial coronary dimensions to predict coronary artery lesions persistence in Kawasaki disease. *Sci Rep.* 2022 May 23;12(1):8640. doi: 10.1038/s41598-022-12702-7. PMID: 35606405; PMCID: PMC9127106.

[38]Li W, He X, Zhang L, Wang Z, Wang Y, Lin H, Yuan J, Xie X, Qin Y, Huang P. A Retrospective Cohort Study of Intravenous Immunoglobulin Therapy in the Acute Phase of Kawasaki Disease: The Earlier, the Better Cardiovascular Ther. 2021 Jun 18;2021:6660407. doi: 10.1155/2021/6660407. PMID: 34239607;

PMCID: PMC8233071.

[39] LIU Yi-Ling, WANG Xian-Min, CHEN Ting-Ting, SHI Kun, LU Ya-Heng, GUO Yong-Hong, LI Yan. D.Clinical effect and safety of clopidogrel combined with aspirin in antithrombotic therapy for children with Kawasaki disease complicated by small/medium-sized coronary artery aneurysms[J].Chinese Journal of Contemporary Pediatrics, 2019, 21(8): 801-805. PMID: 31416506.PMCID: PMC7389908. DOI: 10.7499/j.issn.1008-8830.2019.08.012.

[40] Loomba RS. Comment on the paper by Su et al. entitled 'safety and efficacy of warfarin plus aspirin combination therapy for giant coronary artery aneurysm secondary to Kawasaki disease: a meta-analysis'[J]. Cardiology, 2015, 130(3): 164-165. PMID: 25676566. DOI: 10.1159/000369879.

[41] Shaanxi Province Diagnosis and Treatment Center of Kawasaki Disease/Children's Hospital of Shaanxi Provincial People's Hospital; Children's Hospital of Shanghai Jiao Tong University; Beijing Children's Hospital of Capital Medical University; Shengjing Hospital of China Medical University; Affiliated Hospital of Yan'an University; Expert Committee of Advanced Training for Pediatrician, China Maternal and Children's Health Association; General Pediatric Group of Pediatrician Branch of Chinese Medical Doctor Association; Shanghai Cooperation Organization Hospital Cooperation Alliance; Pediatric International Exchange and Cooperation Center; Editorial Board of Chinese Journal of Contemporary Pediatrics. 阿司匹林在川崎病治疗中的儿科专家共识 [Pediatric expert consensus on the application of aspirin in Kawasaki disease]. Zhongguo Dang Dai Er Ke Za Zhi. 2022 Jun 15;24(6):597-603. Chinese. doi: 10.7499/j.issn.1008-8830.2023190. PMID: 35652428; PMCID: PMC9250407.

[42] Mu ZhiLong, FuYong Jiao, Xie KaiSheng.PMCID: PMC7969191 Chin J Contemp Pediatr, 2021, 23(3): 213-220DOI: 10.7499/j.issn.1008-8830.2010134 <http://www.zgdek.com/CN/abstract/html/2021-3-213.htm>

[43] Furusho K, Kamiya T, Nakano H, et al. High-dose intravenous gammaglobulin for Kawasaki disease. Lancet. 1984;2:1055-1058. doi:10.1016/S0140-6736

(84)91504-6.

[44]Newburger JW, Takahashi M, Burns JC, et al. The treatment of Kawasaki syndrome with intravenous gamma globulin. *N Engl J Med*.1986;315:341–347. doi:10.1056/NEJM198608073150601.

[45]Kobayashi T, Saji T, Otani T, et al. Efficacy of immunoglobulin plus prednisolone for prevention of coronary artery abnormalities in severe Kawasaki disease (RAISE study): a randomised, open-label, blinded-endpoints trial. *Lancet*. 2012;379:1613–1620. doi:10.1016/S0140-6736(11)61930-2.

[46]Choi, Jungyoon KMDa; Chang, Seokjoo KMDa; Kim, Eunjin KMD, PhDb; Min, Sang Yeon KMD, PhDa,c,\* . Integrative treatment of herbal medicine with western medicine on coronary artery lesions in children with Kawasaki disease. *Medicine* 101(7):p e28802, February 18, 2022. | DOI: 10.1097/MD.00000000000028802.

[47]Huang H, Dong J, Jiang J, Yang F, Zheng Y, Wang S, Wang N, Ma J, Hou M, Ding Y, Meng L, Zhuo W, Yang D, Qian W, Chen Q, You G, Qian G, Gu L, Lv H. The role of FOXO4/NFAT2 signaling pathway in dysfunction of human coronary endothelial cells and inflammatory infiltration of vasculitis in Kawasaki disease. *Front Immunol*. 2023 Jan 9;13:1090056. doi:10.3389/fimmu.2022.1090056. PMID: 36700213; PMCID: PMC9869249.

[48]Burns JC. Cyclosporine and coronary outcomes in Kawasaki disease. *J Pediatr* (2019) 210:239–42. doi: 10.1016/j.jpeds.2019.04.044.