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Evaluation of Serum PAF, 1,25-(OH)2D3 and MMP-9 Levels in the Diagnosis of Kawasaki Disease and Prediction of the Risk of Coronary Artery Lesion

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ABSTRACT

The objective of this study was to investigate the serum platelet activating factor (PAF), 1,25-dihydroxyvitamin D3 (1,25-(OH)2D3) and matrix metalloproteinase-9 (MMP-9) levels in the diagnosis of Kawasaki disease (KD) and prediction of coronary artery lesion (CAL) value at risk. A total of 120 children with KD were selected as the KD group, and they were divided into acute stage group (n=64) and recovery stage group (n= 56), and another 60 healthy children were selected as the healthy control group. In addition, the KD group was divided into CAL group (n=48) and non-CAL group (n=72) according to the echocardiographic findings. The area under the receiver operating characteristic (ROC) curve (AUC) was used to compare the value of serum PAF, 1,25-(OH)2D3 and MMP-9 levels in diagnosing KD and predicting the risk of CAL. The levels of serum PAF and MMP-9 in the recovery group were raised than those in the healthy control group, and the levels of 1,25-(OH)2D3 were reduced than those in the healthy control group (P<0.05). Both were raised than the recovery period group and the healthy control group, and the level of 1,25-(OH)2D3 was reduced than the recovery period group and the healthy control group (P<0.05). The levels of serum PAF and MMP-9 in the CAL group were raised than those in the non-CAL group, and 1,25-(OH)2D3 level was reduced than that in the non-CAL group (P< 0.05). The AUC values of serum PAF, 1,25-(OH)2D3 and MMP-9 alone and in combination to diagnose KD were 0.807, 0.767, 0.834 and 0.867, respectively. The AUC values of serum PAF, 1,25-(OH)2D3 and MMP-9 alone and in combination to diagnose KD were 0.813, 0.758, 0.866 and 0.887, respectively. It was concluded that the changes of serum PAF, 1,25-(OH)2D3 and MMP-9 levels have a certain relationship with the degree of CAL in KD. It has high clinical application value in predicting the occurrence of CAL.

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Authors' Contribution
WL conceived the idea, supervised the study and wrote the manuscript. HX performed the experimental work. SL helped in collection of samples and literature review. JL performed all the statistical tests.

Key words
Platelet-activating factor, 1,25-dihydroxyvitamin D3, Matrix metalloproteinase-9, Kawasaki disease, Coronary artery lesion

INTRODUCTION

Kawasaki disease (KD) is an eruptive disease in children with febris acuta, manifested as vasculitis all over the body, which mainly involves coronary arteries (Huang *et al*., 2022). Early diagnosis and treatment of the disease along with administration of high-dose aspirin and gamma globulin can effectively avoid or reduce the complications of coronary artery lesion (CAL). However, studies have found that CAL is the most serious complication of KD, despite intravenous infusion of high dose gamma globulin within 10 days of onset, about 5% of children with KD still have transient coronary artery dilatation, and 1% of them developed giant coronary aneurysms (Gerling *et al*., 2022). Studies have shown that bone marrow megakaryocytes proliferate actively and platelet production function is enhanced in acute KD childre. Platelet activation, release, aggregation, and participation in vascular thrombosis are closely related to the complications of CAL in KD patients (Du and Lee, 2022). Serum platelet-activating factor (PAF), an endogenous lipid mediator, induces platelet aggregation, which has been confirmed to be closely associated with the progression of cardiovascular disease (CVD) (Yi *et al*., 2020). Previous studies have shown that changes in vitamin D (Vit D) levels are closely related to the occurrence and development of CVD 1,25-dihydroxy

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vitamin D3 (1,25-(OH)2D3), one of the important active forms of vitamin D3, is often used to evaluate the level of Vit D in the body (Murashima *et al*., 2022). Matrix metalloproteinase-9 (MMP-9), a proteolytic enzyme that is closely associated with inflammation and CAL (Wang *et al*., 2021). This study is to explore the value of serum PAF, MMP-9, 1,25-(OH)2D3 levels in the diagnosis of KD and the risk of CAL in order to provide new-sight for clinical diagnosis and treatment.

MATERIALS AND METHODS

Sunjects recruted for this study

120 KD children from January 2020 to June 2022 were included as KD group, and 60 healthy children were enrolled control group. KD group: 77 males and 43 females who aged from 6 to 80 months, average age was (23.56±8.43) months. Health control group: 38 males and 22 females who aged from 6 to 78 months, average age (22.34±9.24) months. The two groups general data was no significance (P>0.05), and it had comparability. Inclusion criteria for KD group: (1) Children with KD confirmed by clinical symptoms and signs on imaging examination (Molloy *et al*., 2022). (2) Those without history of CVD and related diseases. (3) Those with no other treatment received before the first diagnosis and treatment. (4) Those with complete clinical medical records. Exclusion criteria: (1) Patients complicated with other viral infectious diseases; (2) Those combined with other autoimmune diseases; (3) Those with severe heart, liver and kidney dysfunction; (4) Those combined with other bacterial infectious diseases.

Biochemical anaysis of blood serum

Peripheral venous blood (3ml) from all subjects on an empty stomach were collected in the morning and was centrifuged for 10 min at a rate of 3500 r/min to isolate serum, and then was placed in a refrigerator at -80°C. Serum levels of PAF, MMP-9, 1,25-(OH)2D3 were checked using enzyme-linked immunosorbent assay (ELISA) and with Varioskan LUX Automatic Enzyme Labeling Instrument (Thermo Fisher Scientific, USA). The kit was purchased from Beijing Leadman Biochemistry Co., Ltd, and was used strictly in accordance with the instructions.

Diagnostic creteria of CAL

According to the results of echocardiography, we divided KD group into CAL group (n=48) and non-CAL group (n=72). Criteria for judging CAL: (1) Criteria for coronary artery dilatation: Patients are ≤ 3 years old with coronary artery diameter ≥ 2.5mm; three years old, ≥ 3.0mm; (2) Enhanced endometrial echo of coronary artery (Xie and Han, 2022).

Statistical analysis

SPSS 20.0 was used for analysis, the counting data were compared by $\chi 2$ test, the measurement data were expressed by mean ± standard deviation, t test and variance analysis were used for comparison between two groups and for that among various groups respectively, LSD test was performed for pairwise comparison among multiple groups, and area under ROC curve (AUC) was used to compare the diagnostic value of each parameter.

RESULTS

Table I demonstrates serum PAF, 1,25-(OH)2D3 and MMP-9 levels. Serum PAF and MMP-9 levels in convalescence group were increased than those in control group, meanwhile 1,25-(OH)2D3 was reduced (P<0.05). The levels of serum PAF and MMP-9 in acute phase were raised than those in control group, and 1,25-(OH)2D3 was reduced (P<0.05). It illustrates that the serum levels of PAF, 1,25 - (OH) 2D3, and MMP-9 in children with Kawasaki disease are different from those in normal children, but also from those in children with Kawasaki disease at different disease stages. This table also shows the level of serum PAF, 1,25-(OH)2D3 and MMP-9 levels in children with KD and different CAL. Compared with non-CAL group, the serum MMP-9 and PAF levels of CAL group patients were raised, and the 1,25-(OH)2D3 level was reduced (P<0.05). This illustrates that serum levels of PAF, 1,25 - (OH) 2D3, and MMP-9 during the acute phase differ among children with Kawasaki disease due to different coronary pathologies.

Table I. Serum PAF, MMP-9, and 1,25-(OH)2D3 levels in children with KD and different CAL.

Group	N	PAF (mU/mL)	1,25-(OH) 2D3 (ng/mL)	MMP-9 (ng/mL)
Acute stage	64	185.02±68.43	12.45±3.43	319.55±50.78
Recovery stage	56	125.54±28.52	25.13±7.28	150.45±43.43
Health control	60	112.34±24.85	46.94±10.50	38.38±37.12
CAL group	48	413.51±63.08	11.47±3.51	366.52±70.81
Non-CAL group	72	345.89±45.35	27.23±8.24	280.58±62.59
F		43.849	326.255	634.254
t		6.831	-12.503	6.989
P		0.000	0.000	0.000

PAF, platelet-activating factor; 1,25-(OH)2D3, 1,25-dihydroxy vitamin D3; MMP-9, matrix metalloproteinase-9; KD, Kawasaki disease; CAL, coronary artery lesion.

Table II and Figure 1A demonstrate the analysis on ROC curves of PAF, 1,25-(OH)2D3 and MMP-9 in diagnosing KD alone and jointly. In the two diagnostic methods, the AUC values of serum PAF, 1,25-(OH)2D3 and MMP-9 were 0.807, 0.767, 0.834, 0.867, respectively. Among them, the combined diagnosis had the best diagnostic efficacy, with a specificity and sensitivity of 88.24% and 79.61%, respectively.

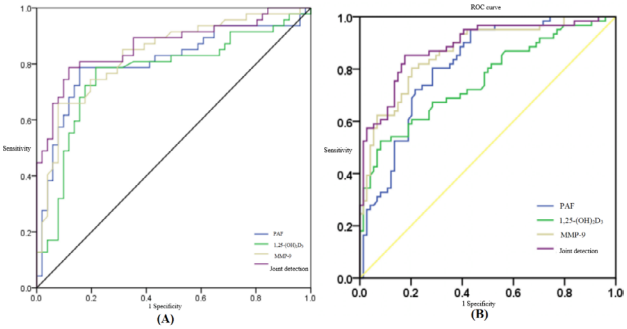

Fig. 1. Receiver operating characteristic (ROC) curves of platelet activating factor (PAF), 1,25-(OH)2D3 and matrix metalloproteinase-9 (MMP-9). (A), Diagnosing Kawasaki disease (KD) alone and jointly; (B), Predicting the risk of coronary artery lesion (CAL).

Table II. Analysis of ROC curves of PAF, 1,25-(OH)2D3 and MMP-9 in diagnosing KD and predicting the risk of CAL in patients with KD.

Inspection method	95%CI	AUC	Specificity (%)	Sensibility (%)
Diagnosing KD				
PAF	0.715-0.880	0.807	84.31	78.72
$1,25\text{-}(OH)_2D_3$	0.671-0.847	0.767	78.43	78.72
MMP-9	0.745-0.901	0.834	92.16	65.96
Joint diagnosis	0.783-0.927	0.867	88.24	78.72
Predicting the risk of CAL in patients with KD				
PAF	0.741~0.884	0.813	0.784	0.721
$1,25\text{-}(OH)_2D_3$	0.675~0.840	0.758	0.716	0.672
MMP-9	0.805~0.927	0.866	0.797	0.803
Joint diagnosis	0.829~0.944	0.887	0.824	0.852

For abbreviations, see Table I and Figure 1.

Table II and Figure 1B demonstrate the analysis on ROC curves of PAF, 1,25-(OH)2D3 and MMP-9 in diagnosing KD alone and jointly. In the two diagnostic methods, the AUC values of serum PAF, 1,25-(OH)2D3 and MMP-9 in the diagnosis of KD were 0.813, 0.758, 0.866, 0.887, respectively. Among them, the combined diagnosis had the best diagnostic efficacy, with a specificity and sensitivity of 82.44% and 85.24%, respectively.

DISCUSSION

KD is an acute febrile childhood disease with systemic vasculitis as the main lesion, it frequently occurs in infants under 5 years of age, clinically manifested as fever and skin rash of unknown cause (Ohnishi *et al*., 2022). KD is pathologically characterized by systemic and nonspecific vasculitis involving small and medium arteries, especially heart coronary arteries (Asadbeygi *et al*., 2022). Coronary artery endothelial cells are presented with swelling and necrosis in KD children, with separated smooth muscle cells of the vessel wall and fibrinous thrombus formation the vessel. Thrombosis, myocardial infarction, or secondary rupture of coronary aneurysms may occur in the late stage of CAL if a patient is not treated in time (Liu *et al*., 2022). Therefore, early prediction and diagnosis of CAL in patients with KD is of great clinical significance to detect the changes of the disease and to provide timely treatment, so as to avoid further aggravation of the disease and improve the prognosis. With the unceasing progress of clinical medicine, laboratory technology and molecular biotechnology, more and more medical researchers are turning to serum biochemistry for the early diagnosis and prognosis of KD in order to explore biochemical markers with high specificity and sensitivity to provide theoretical basis for early diagnosis of CAL in Kawasaki disease.

It was found that abnormal platelet metabolism and vascular endothelial dysfunction were closely related to CAL in KD (Yoo, 2022). PAF, a bioactive phospholipid, is produced by the action of acetyltransferase and phospholipase A2 on glycerol choline glycerophosphate in cell membrane, it is widely distributed in various tissues, when stimulated by mononuclear macrophages, vascular endothelial cells, neutrophils and platelets, PAF is largely synthesized and released into blood (Sato *et al*., 2022). PAF is not only the most effective platelet aggregation inducer that has biological effects such as platelet deformation, aggregation and release, thus causing thrombosis, but also is an important inflammatory factor which participates in the activation, chemotaxis, adhesion, aggregation and secretion of neutrophils, and has great role in the pathogenesis of vascular inflammatory diseases (Schönborn *et al*., 2022). The study showed that serum PAF level in convalescence group was raised than that in control group. Serum PAF level in acute phase group were raised than that in convalescence group and control group, and that in KD patients were raised in acute and recovery phases than that of non-coronary lesion group, suggesting that PAF level was highly expressed in KD

children, which is related to the degree of CAL in KD. The level can be used to diagnose KD and predict the risk of CAL. It was found that KD children were prone to large synthesis and release of PAF due to immune activation and vascular endothelial injury. PAF, as a powerful platelet activator, was synthesized and released in large quantities, and then could form a positive feedback mechanism, promote platelet activation, aggregation and release, and release a lot of inflammatory mediators, which can not only lead to blood hypercoagulable state, but also increase vascular permeability and vascular endothelial cell injury, consequently causing vasculitis. Severe damage to the vascular endothelium, vasculitis and platelet aggregation can cause severe impairment in the entire coronary artery and damage to the integrity of the artery wall, and then leads to the development of coronary artery dilatation or coronary aneurysm (Yi *et al*., 2020).

Vit D is an important steroid hormone in the body. The study found that the vitamin is important in the progression of CAL in KD by influencing platelet function and inflammatory factors (Hatano *et al*., 2020). 1,25-(OH)2D3 is one of the important active forms of vitamin D3 in the body, which can inhibit inflammation and antioxidation, regulate immune function and improve absorption of calcium and phosphorus by binding with Vit D receptor (Suzuki *et al*., 2012). The results showed that 1,25-(OH)2D3 level in convalescence group was reduced than that in control group, in acute phase group were evidently lower than that in convalescence group and control group, and in KD children were reduced than that in non-CAL group. suggesting that 1,25-(OH)2D3 level was highly expressed in children with KD, which is related to the degree of CAL. The level can be used to diagnose KD and predict the risk of CAL. Recent studies have shown that Vit D can reduce the secretion of tumor necrosis factor and interleukin factor by regulating T, B cells, dendritic cells and macrophages (Qi *et al*., 2017), and the 1,25-(OH)2D3 deficiency in the body may be more likely to lead to vascular endothelial dysfunction, therefore, the decreased level of 1,25-(OH)2D3 leads to the decline of its inhibitory effect on macrophage inflammation, and many inflammatory factors are produced, resulting in vasculitis. In addition, a decrease in 1,25-(OH)2D3 levels results in vascular endothelial dysfunction, thus causing CAL of children with KD (Tominaga *et al*., 2021).

MMP-9, a member of the matrix metalloproteinase family, is a protein involved in the extracellular mechanism of degradation of tissue throughout the body, secreted by a variety of inflammatory cells, it regulates a variety of biological behaviors such as neuroinflammation, tissue remodeling, apoptosis, atherosclerotic lesions, vascular remodeling and so on. The expression of MMP-9 is low in normal people peripheral blood and increased significantly in various physiological and pathological processes such as tumor invasion and metastasis, angiogenesis, oxidative stress and inflammation. The study showed that serum MMP-9 level in convalescence group was raised than that in control group, in acute phase group was raised than that in convalescence group and control group, and in KD patients was increased in acute and recovery phases than that of non-CAL group, suggesting that MMP-9 level was highly expressed in KD children, which is concerned to the degree of KD CAL. The level can be used to diagnose KD and predict the risk of CAL. It was found that children with KD were susceptible to the synthesis and release of MMP-9 due to immune activation and vascular endothelial injury. MMP-9 could degrade elastase and collagenase, which was beneficial to deep infiltration of monocytes or macrophages and neutrophils into vascular wall, and played an important role in vascular wall remodeling and vascular wall cell injury, consequently, the vascular wall structure was destroyed and coronary artery injury was induced in KD children (Suzuki *et al*., 2021; Tian *et al*., 2022; Kuo *et al*., 2017). In addition, this study also found that the AUC values of serum PAF, 1,25-(OH)2D3 and mmp-9 in the diagnosis of KD were 0.807, 0.767, 0.834 and 0.867, respectively. The serum PAF, 1,25-(OH)2D3 and MMP-9 in the diagnosis of KD were 0.813, 0.758, 0.866 and 0.887, respectively. suggesting that serum PAF, 1,25-(OH)2D3 and MMP-9 have high clinical value in diagnosing KD and predicting the occurrence of CAL.

CONCLUSION

The level of serum PAF and MMP-9 levels are high and that of 1,25-(OH)2D3 in children with KD. The levels of PAF, 1,25-(OH)2D3 and MMP-9 are correlated with the degree of CAL in KD. The detection of serum PAF, 1,25-(OH)2D3 and MMP-9 are clinically valuable in the diagnosis of KD and the prediction of CAL.

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IRB approval

This research was carried out with the approval of Research Guidance Workshop Committee (Chenzhou First People's Hospital).

Ethical statement

The study was carried out in compliance with guidelines issued by ethical review board and institutional biosafety committee of Chenzhou First People's Hospital. The official letter would be available on fair request to corresponding author.

Statement of conflict of interest

The authors have declared no conflict of interest.

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