

# The role of peroxisome proliferator-activated receptor gamma and adiponectin in children with Kawasaki disease

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## Abstract

**Objective:** To investigate the relationship between peroxisome proliferator-activated receptor gamma (PPAR $\gamma$ ) mRNA, serum adiponectin (ADP) and lipids in paediatric patients with Kawasaki disease (KD).

**Methods:** This prospective study enrolled paediatric patients with KD and grouped them according to the presence or absence of coronary artery lesions (CAL). A group of healthy age-matched children were recruited as the control group. The levels of PPAR $\gamma$  mRNA, serum ADP and lipids were compared between the groups. Receiver operating characteristic (ROC) curve analysis was undertaken to determine if the PPAR $\gamma$  mRNA level could be used as a predictive biomarker of CAL prognosis.

**Results:** The study enrolled 42 patients with KD (18 with CAL [CAL group] and 24 without CAL [NCAL group]) and 20 age-matched controls. PPAR $\gamma$  mRNA levels in patients with KD were significantly higher than those in the controls; but significantly lower in the CAL group than the NCAL group. ROC curve analysis demonstrated that the PPAR $\gamma$  mRNA level provided good predictive accuracy for the prognosis of CAL. There was no association between PPAR $\gamma$ , ADP and lipid levels.

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**Conclusion:** There was dyslipidaemia in children with KD, but there was no correlation with PPAR $\gamma$  and ADP. PPAR $\gamma$  may be a predictor of CAL in patients with KD with good predictive accuracy.

### Keywords

Kawasaki disease, peroxisome proliferator-activated receptors gamma (PPAR $\gamma$ ), adiponectin, blood lipid, coronary artery lesion

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## Introduction

Kawasaki disease (KD) is an acute vasculitis complicated by coronary artery abnormalities and it occurs mainly in infancy and early childhood.<sup>1</sup> In the acute phase, coronary artery lesions may cause coronary artery stenosis or myocardial infarction.<sup>2</sup> It is reported to be one of the major causes of heart disease in children in developed countries.<sup>3</sup> The long-term outcome of KD depends on resolution and ongoing cardiovascular pathology.<sup>4</sup> Recent studies have shown that endothelial injury and atherosclerosis may occur early in KD patients, even in the chronic phase.<sup>5,6</sup> KD is considered to be an early risk factor for atherosclerosis.<sup>7,8</sup> Some studies have reported that children with KD have lipid abnormalities,<sup>9,10</sup> which usually occur during the acute phase of KD. In some cases of KD, the lipid abnormalities can last for several years after an acute episode.<sup>11</sup>

The key adipocyte-derived hormone adiponectin (ADP) regulates lipid and glucose metabolism.<sup>12,13</sup> ADP is considered to be an anti-inflammatory adipokine that protects blood vessel walls.<sup>14</sup> Peroxisome proliferator-activated receptor gamma (PPAR $\gamma$ ) is a transcription factor that participates in the production of atheroma-associated pro-inflammatory cytokines

such as tumour necrosis factor (TNF- $\gamma$ ).<sup>15</sup> Furthermore, PPAR $\gamma$  has been reported to be involved in lipid metabolism.<sup>16</sup> Studies have confirmed that both PPAR $\gamma$  and ADP have anti-inflammatory and endothelial protective effects.<sup>17–20</sup> The reduction in the incidence of coronary artery lesions (CAL) due to intravenous immunoglobulin (IVIG) treatment, the preferred treatment for KD, may be due to its anti-inflammatory mechanisms.<sup>21</sup> PPAR $\gamma$  and ADP may be related to lipid abnormalities and the formation and development of CAL.<sup>17,18</sup>

This current study hypothesized that PPAR $\gamma$  and ADP may directly or indirectly influence the progression of KD and that they might be potential predictors of CAL in coronary artery disease. Therefore, the levels of PPAR $\gamma$  mRNA, serum ADP and lipids in children with KD were compared in order to investigate the relationship between PPAR $\gamma$  mRNA, serum ADP and CAL.

## Patients and methods

### Patients

This prospective study consecutively recruited all children that were diagnosed KD that were admitted to the Department of Paediatrics, Affiliated Shenzhen

Maternity and Child Healthcare Hospital, Southern Medical University, Shenzhen, Guangdong Province, China between October 2016 and July 2017. All of patients met the fourth revised diagnostic criteria of the Kawasaki Disease Research Committee of Japan.<sup>22</sup> Any patients with metabolic diseases were excluded from the study. Patients that were lost to follow-up during the acute, subacute and convalescent phases were excluded from the final analyses. Age-matched healthy children that attended for physical examinations in the Department of Child Health, Affiliated Shenzhen Maternity and Child Healthcare Hospital were selected as controls.

All children of KD with CAL were diagnosed by echocardiography. A classification of CAL on the basis of the Z-score was adapted and recommended as follows:<sup>22</sup> (1) normal: always <2; (2) mild dilation: 2 to <2.5; or if initially <2, a decrease in Z score during follow-up  $\geq 1$ ; (3) small aneurysm:  $\geq 2.5$  to 5; (4) medium aneurysm:  $\geq 5$  to  $\leq 10$  and absolute dimension <8 mm; (5) large or giant aneurysm:  $\geq 10$  or absolute dimension  $\geq 8$  mm. Echocardiography was performed within 2 weeks of disease onset or before IVIG treatment. Patients with KD were divided into two groups: patients with CAL and patients without CAL. Acute KD patients were limited to the pre-IVIG phase to avoid treatment bias.

The study protocol was approved by the Ethics Committee of the Affiliated Shenzhen Maternity and Child Healthcare Hospital (no. W[2015]127). Written or verbal informed consent was obtained from the parents or legal guardians of all patients and healthy control subjects.

### Biochemical measurements

Venous blood samples were collected at the time of the clinical examinations during the acute phase (during the first 10 days of

the disease course), subacute phase (days 11–20) and convalescent phase (days 21–30). Venous blood samples (3 ml) were collected and centrifuged in a high-speed freezing centrifuge at 12 000 *g* for 15 min at 4 °C (Anhui USTC Zonkia Scientific Instruments, Hefei, Anhui, China). The serum was stored at –80 °C until use. The serum lipid levels, including triglycerides (TG), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), apolipoprotein A (Apo A), apolipoprotein B (Apo B) and lipoprotein A (LPA), were measured using an automated biochemical analyser (UniCel DxC 800 chemistry analyser; Beckman Coulter, Brea, CA, USA).

### Analysis of PPAR $\gamma$ mRNA levels

Total RNA was extracted using TRIzol<sup>®</sup> reagent (Thermo Fisher Scientific, Rockford, IL, USA) according to the manufacturer's instructions. A Thermo Scientific RevertAid H Minus First Strand cDNA Synthesis Kit (Thermo Fisher Scientific) was used to reverse transcribe 1  $\mu$ g of total RNA. Quantitative polymerase chain reaction (PCR) was performed on an Applied Biosystems<sup>™</sup> 7300 Real Time PCR instrument (Applied Biosystems, Foster City, CA, USA) and the levels of mRNA were automatically quantified using the in-built software based on automatic baseline and threshold values. The primer sequences for PPAR $\gamma$  were as follows: 5'-AACTCCCTCATGGCCATTGA-3' (sense) and 5'-CCTTGCATCCTTCA CAAGCA-3' (antisense). Primers for the internal control  $\beta$ -actin were as follows: 5'-GTGGGAATGGGTCAGAAGGA-3' (sense) and 5'-CTTCTCCATGTCGT CCCAGT-3' (antisense). The conditions of the PCR product synthesis were as follows: pre-denaturation at 95 °C for 3 min, followed by 40 cycles of denaturation at 95 °C for 3 s, annealing at 60 °C for 30 s,

elongation at 60°C for 30 s, and followed by a final elongation step at 40°C for 10 min. The same procedure was used to determine the transcriptional abundance of  $\beta$ -actin mRNA (Shanghai Generay Biotech, Shanghai, China). At the same time, the transcripts of  $\beta$ -actin mRNA were determined as internal standard to normalize the mRNA quantity of each transcript. PCR products were analysed using Sequence Detection Software, version ABI7300 (Thermo Fisher Scientific). The relative amount of PPAR $\gamma$  mRNA compared with that of  $\beta$ -actin was calculated using the equation  $2^{-\Delta\Delta C_t}$ .

### Serum levels of ADP

The serum levels of ADP were assayed with an enzyme-linked immunosorbent assay kit (Reichel & Drews, Minneapolis, MN, USA). Samples were prepared at the appropriate dilutions and paired samples were assayed together according to the manufacturer's instructions. The minimum detectable concentration of ADP was 25 ng/ml. The intra- and inter assay coefficients of variation for ADP were: 4.7% and 6.9%, respectively.

### Statistical analyses

All statistical analyses were performed using the SPSS® statistical package, version 13.0 (SPSS Inc., Chicago, IL, USA) for Windows®. Continuous data with a normal distribution are expressed as mean  $\pm$  SD. Categorical data were compared using  $\chi^2$  test. Differences in continuous data among groups were assessed using Independent-Samples T test and repeated measures analysis of variance. Pearson's correlation analysis was used to test the correlation between sequential parameters. A  $P$ -value  $< 0.05$  was considered statistically significant. A receiver operating characteristic (ROC) curve was constructed using the R language "pROC"

package (SPSS Inc.) and the area under the curve (AUC) under the 95% confidence interval was calculated. The PPAR $\gamma$  cut-off value was determined by the point of optimal specificity and sensitivity.

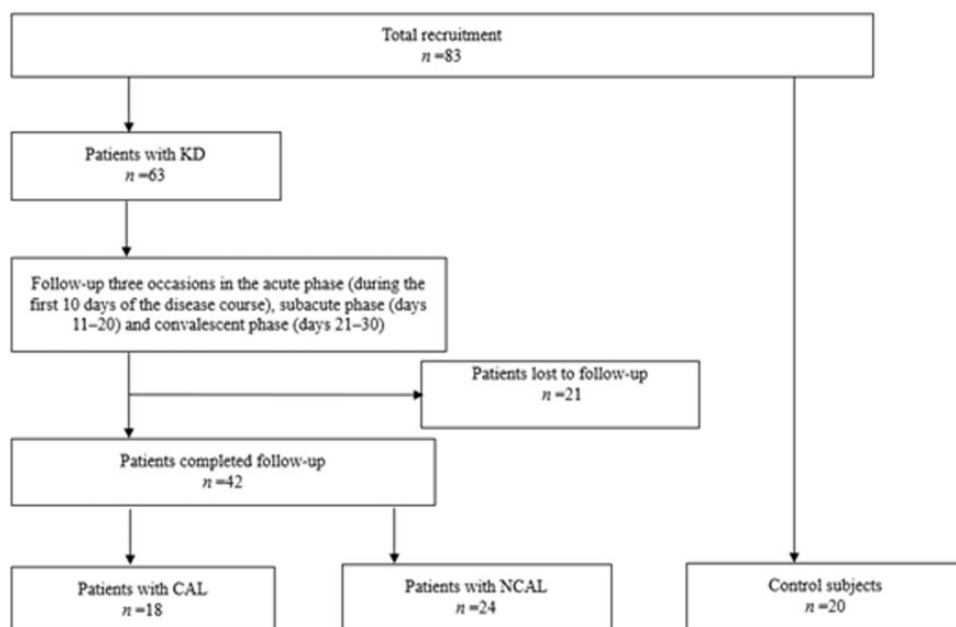
## Results

This study enrolled 62 paediatric patients; 42 patients with KD and 20 age-matched healthy control subjects. The flow of paediatric patients and control subjects is presented Figure 1. Patients with KD were divided into two groups: 18 patients with CAL and 24 patients without CAL. There were no significant differences in age, sex distribution and body weight between the three groups (Table 1).

The PPAR $\gamma$  mRNA levels are presented in Figure 2. The levels of PPAR $\gamma$  mRNA in patients with KD in either the acute, sub-acute or convalescent phases were significantly higher than that of the control group ( $P < 0.05$  for all comparisons). The level of PPAR $\gamma$  mRNA was highest in the acute phase in patients with KD.

The 42 children with KD included 18 patients with CAL (CAL group) and 24 patients without CAL (NCAL group). As shown in Figure 3, regardless of the phase of KD, the levels of PPAR $\gamma$  mRNA in the CAL group were significantly lower compared with the NCAL group ( $P < 0.05$  for all comparisons).

The serum levels of ADP, TC, HDL-C, LDL-C and Apo A during the acute phase in patients with KD were significantly lower compared with the control group ( $P < 0.05$  for all comparisons) (Table 2). During the subacute phase, the levels of ADP and HDL-C in patients with KD were significantly lower compared with the control group ( $P < 0.05$  for both comparisons); and the TG level was significantly increased compared with the control group ( $P < 0.05$ ). During the convalescent phase, the levels of ADP and LDL-C in patients



**Figure 1.** Flow chart of the selection and recruitment of patients with Kawasaki disease (KD) and the healthy age-matched control paediatric subjects. CAL, coronary artery lesions; NCAL, no coronary artery lesions.

**Table 1.** Clinical and demographic characteristics of patients with Kawasaki disease stratified according to the presence or absence of coronary artery lesions compared with healthy control subjects.

Characteristic	Patients with CAL <i>n</i> = 18	Patients with NCAL <i>n</i> = 24	Control subjects <i>n</i> = 20
Age, years	1.89 ± 1.53	1.58 ± 1.06	1.75 ± 1.16
Sex			
Male	14 (77.8%)	14 (58.3%)	14 (70.0%)
Female	4 (22.2%)	10 (41.7%)	6 (30.0%)
Body weight, kg	11.79 ± 3.81	11.75 ± 3.01	12.29 ± 3.67

Data presented as mean ± SD or *n* of patients (%).

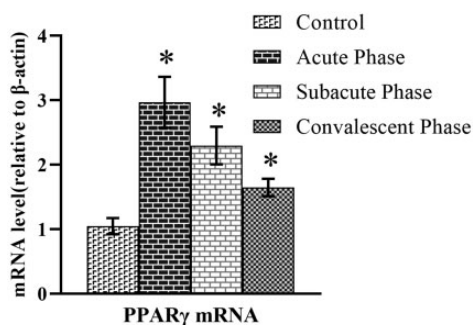
No significant between-group differences ( $P \geq 0.05$ ).

CAL, coronary artery lesions; NCAL, no coronary artery lesions.

with KD were significantly lower compared with the control group ( $P < 0.05$  for both comparisons); and the Apo A level was significantly increased compared with the control group ( $P < 0.05$ ). The levels of LPA during the acute and subacute phases were significantly increased in patients with KD

compared with the control group ( $P < 0.05$  for both comparisons).

When comparing patients in the acute phase, patients with KD in the NCAL group had significantly lower levels of ADP and significantly higher levels of HDL-C than those with CAL (CAL

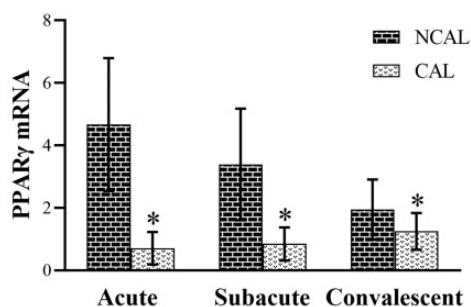


\*  $P < 0.05$

**Figure 2.** Levels of peroxisome proliferator-activated receptor gamma (PPAR $\gamma$ ) mRNA in patients with Kawasaki disease (KD) stratified according to the phase of the disease compared with the healthy age-matched control paediatric subjects. Data presented as mean  $\pm$  SD. \* $P < 0.05$ , compared with the control group; Independent-Samples T test.

group) ( $P < 0.05$  for both comparisons) (Table 3). During the subacute phase, the NCAL group had significantly higher levels of TG compared with those in the CAL group ( $P < 0.05$ ). During the convalescent phase, the NCAL group had significantly lower levels of ADP and significantly higher levels of TG compared with the CAL group ( $P < 0.05$  for both comparisons).

As there was a significant difference in the levels of PPAR $\gamma$  mRNA between the CAL and NCAL groups (Figure 3), the study investigated whether the PPAR $\gamma$  mRNA level could be used as a predictive biomarker of CAL prognosis. A ROC curve analysis demonstrated that the PPAR $\gamma$  mRNA level provided good predictive accuracy for the prognosis of CAL, particularly in the acute and subacute phases (Figure 4). The sensitivity was 94.7% and the specificity was 91.3% at a cut-off value of 1.8 during the acute phase. The sensitivity was 89.5% and the specificity was 87.0% at a cut-off value of 1.6 during the subacute phase.



\*  $P < 0.05$

**Figure 3.** Levels of peroxisome proliferator-activated receptor gamma (PPAR $\gamma$ ) mRNA in patients with Kawasaki disease (KD) stratified according to the presence or absence of coronary artery lesions. CAL, coronary artery lesions; NCAL, no coronary artery lesions. Data presented as mean  $\pm$  SD. \* $P < 0.05$ , compared with the NCAL group; Independent-Samples T test.

Pearson's correlation analysis demonstrated that there was no significant association between the levels of serum lipids, ADP and PPAR $\gamma$  mRNA (Table 4).

## Discussion

This current study demonstrated that the levels of PPAR $\gamma$  mRNA in patients with KD were significantly increased in the acute, subacute and convalescent phases compared with the control group. After further subgroup analysis, the level of PPAR $\gamma$  mRNA in patients with CAL was significantly lower than in patients with NCAL regardless of the phase of KD. ROC curve analysis was undertaken to determine whether the level of PPAR $\gamma$  mRNA could help to predict the prognosis of CAL. The results showed high predictive accuracy in the acute and subacute phases. The levels of serum ADP in the patients in the three phases of KD were significantly lower than that of the control group. Subgroup analyses based on the presence of CAL demonstrated that the serum ADP levels



**Table 2.** Serum lipid and adiponectin (ADP) levels of patients with Kawasaki disease stratified according to the phase of the disease compared with healthy control subjects.

Biochemical parameter	Phase of Kawasaki disease			Control subjects n = 20	Statistical analysis <sup>a</sup>
	Acute n = 42	Subacute n = 42	Convalescent n = 42		
ADP, $\mu\text{g/ml}$	$5.26 \pm 2.33^*$	$5.81 \pm 2.33^*$	$7.78 \pm 2.32^*$	$9.05 \pm 2.01$	$P < 0.001$
Total cholesterol, $\text{mmol/l}$	$3.21 \pm 0.75^*$	$4.25 \pm 1.17$	$4.11 \pm 0.93$	$4.18 \pm 0.28$	$P = 0.004$
Triglycerides, $\text{mmol/l}$	$1.13 \pm 0.47$	$1.45 \pm 0.61^*$	$0.90 \pm 0.45$	$1.03 \pm 0.15$	$P = 0.001$
HDL-C, $\text{mmol/l}$	$0.58 \pm 0.31^*$	$0.79 \pm 0.30^*$	$1.09 \pm 0.38$	$1.03 \pm 0.13$	$P = 0.002$
LDL-C, $\text{mmol/l}$	$2.03 \pm 0.77^*$	$2.77 \pm 0.78$	$2.40 \pm 0.69^*$	$2.69 \pm 0.34$	$P < 0.001$
Apo A, $\text{g/l}$	$0.83 \pm 0.45^*$	$1.22 \pm 0.47$	$1.41 \pm 0.46^*$	$1.22 \pm 0.08$	$P = 0.002$
Apo B, $\text{g/l}$	$0.84 \pm 0.31$	$0.95 \pm 0.27$	$0.80 \pm 0.30$	$0.97 \pm 0.10$	NS
LPA, $\text{mg/dl}$	$18.27 \pm 6.01^*$	$13.6 \pm 5.8^*$	$12.7 \pm 4.5$	$12.4 \pm 5.3$	$P = 0.001$

Data presented as mean  $\pm$  SD.

\* $P < 0.05$  versus the control group; differences were assessed using repeated measures analysis of variance.

<sup>a</sup>Differences in continuous data among groups were assessed using repeated measures analysis of variance.

HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; Apo, apolipoprotein; LPA, lipoprotein A; NS, no significant between-group difference ( $P \geq 0.05$ ).

in the CAL group were significantly higher than those of the NCAL group in the acute and convalescent phases. The levels of ADP in the subacute phase in the CAL group was higher than the NCAL group, but it did not reach statistical significance, possibly due to the small sample size. These results suggest that PPAR $\gamma$  and ADP may play important roles in the progression of KD.

Kawasaki disease is an acute, self-limiting febrile illness. Although the aetiology is unknown, KD is generally recognized to be complex due to the activation of inflammatory responses.<sup>3,23</sup> IVIG is the most common and important treatment for KD and it may reduce the incidence of CAL due to its anti-inflammatory effects.<sup>21</sup> PPAR $\gamma$  is a transcription factor that has been shown to be associated with anti-inflammatory responses and lipogenesis.<sup>24</sup> In this current study, the levels of PPAR $\gamma$  mRNA in the acute, subacute and convalescent phases in the NCAL group were upregulated compared with those of the CAL group. The ROC curve analysis demonstrated that the levels of PPAR $\gamma$  mRNA

had good predictive accuracy for CAL prognosis. A recent study found that PPAR $\gamma$  may play an important role in the early onset of atherosclerosis in KD patients.<sup>17</sup> PPAR $\gamma$  agonists (e.g. pioglitazone) may disturb monocyte collection, smooth muscle cell multiplication and cholesterol efflux from macrophages.<sup>24</sup> In the PERISCOPE trial, compared with glimepiride, pioglitazone significantly reduced the progression rate of coronary atherosclerosis in patients with type 2 diabetes.<sup>25,26</sup> A previous study reported that PPAR $\gamma$  agonist can inhibit the production of monocyte inflammatory cytokines.<sup>27</sup> In our opinion, PPAR $\gamma$  may be a protective factor and has an anti-inflammatory effect in KD.

A previous study reported that the changes in cholesterol and lipoprotein profiles in the late stages of KD were similar to the formation of atherosclerosis.<sup>28</sup> Atherosclerosis is the most common lesion resulting in coronary heart disease and it is affected by many factors, such as high plasma LDL-C concentration, blood sugar level, inflammation and oxidative stress, all

**Table 3.** Serum lipid and adiponectin (ADP) levels of patients with Kawasaki disease stratified according to the phase of the disease and the presence or absence of coronary artery lesions compared with healthy control subjects.

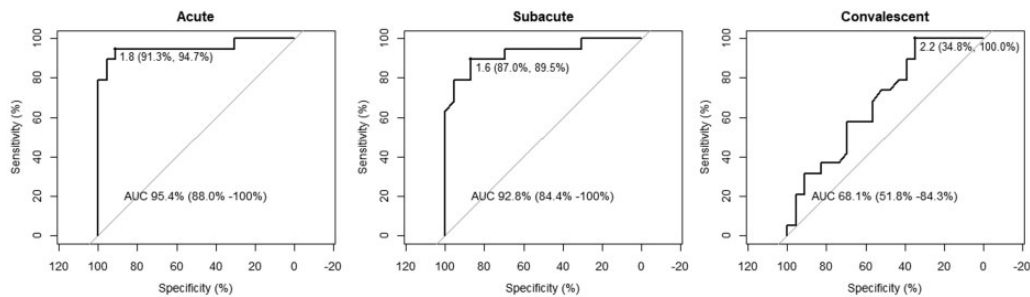
Biochemical parameter	Phase of Kawasaki disease							
	Acute			Subacute			Convalescent	
	Patients with NCAL n = 24	Patients with CAL n = 18	Statistical analysis <sup>a</sup>	Patients with NCAL n = 24	Patients with CAL n = 18	Statistical analysis <sup>a</sup>	Patients with NCAL n = 24	Patients with CAL n = 18
ADP, µg/ml	4.53 ± 1.83	6.22 ± 2.61	P = 0.018	5.44 ± 2.20	6.31 ± 2.47	NS	7.11 ± 2.36	8.67 ± 1.98
Total cholesterol, mmol/l	3.20 ± 0.72	3.23 ± 0.81	NS	4.32 ± 1.20	4.14 ± 1.17	NS	4.04 ± 1.03	4.21 ± 0.80
Triglycerides, mmol/l	1.09 ± 0.47	1.19 ± 0.48	NS	1.65 ± 0.63	1.19 ± 0.48	P = 0.014	1.05 ± 0.46	0.71 ± 0.37
HDL-C, mmol/l	0.66 ± 0.31	0.48 ± 0.27	P = 0.046	0.84 ± 0.34	0.74 ± 0.22	NS	1.04 ± 0.38	1.14 ± 0.39
LDL-C, mmol/l	2.01 ± 0.80	2.04 ± 0.76	NS	2.91 ± 0.78	2.59 ± 0.77	NS	2.45 ± 0.63	2.33 ± 0.77
Apo A, g/l	0.85 ± 0.47	0.81 ± 0.42	NS	1.23 ± 0.48	1.21 ± 0.47	NS	1.35 ± 0.47	1.50 ± 0.44
Apo B, g/l	0.83 ± 0.31	0.86 ± 0.31	NS	0.97 ± 0.29	0.92 ± 0.24	NS	0.80 ± 0.33	0.80 ± 0.28
LPA, mg/dl	18.73 ± 4.82	17.66 ± 7.42	NS	14.77 ± 5.71	12.07 ± 5.77	NS	14.02 ± 4.20	11.10 ± 4.43

Data presented as mean ± SD.

<sup>a</sup>Differences in continuous data among the two groups at each phase of the disease were assessed using repeated measures analysis of variance.

NCAL, no coronary artery lesions; CAL, coronary artery lesions; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; Apo, apolipoprotein; LPA, lipoprotein A; NS, no significant between-group difference ( $P \geq 0.05$ ).





**Figure 4.** A receiver operating characteristic (ROC) curve analysis of the prognostic value of peroxisome proliferator-activated receptor gamma mRNA levels in patients with Kawasaki disease stratified according to the phase of the disease. Acute phase cut-off value of 1.8; subacute phase cut-off value of 1.6; convalescent phase cut-off value of 2.2. AUC, area under the curve.

**Table 4.** Pearson's correlation analysis of the potential association between the levels of peroxisome proliferator-activated receptor gamma (PPAR $\gamma$ ) mRNA and serum lipid and adiponectin (ADP) levels of patients with Kawasaki disease with coronary artery lesions.

Biochemical parameter	PPAR $\gamma$ mRNA level		
	Phase of Kawasaki disease		
	Acute	Subacute	Convalescent
ADP, $\mu\text{g/ml}$	0.174 ( $P = 0.489$ )	0.286 ( $P = 0.250$ )	-0.149 ( $P = 0.555$ )
Total cholesterol, mmol/l	-0.319 ( $P = 0.197$ )	0.156 ( $P = 0.535$ )	0.274 ( $P = 0.272$ )
Triglycerides, mmol/l	0.387 ( $P = 0.113$ )	-0.006 ( $P = 0.981$ )	0.248 ( $P = 0.321$ )
HDL-C, mmol/l	0.132 ( $P = 0.601$ )	-0.053 ( $P = 0.835$ )	0.073 ( $P = 0.772$ )
LDL-C, mmol/l	0.219 ( $P = 0.382$ )	0.186 ( $P = 0.460$ )	0.437 ( $P = 0.07$ )
Apo A, g/l	-0.293 ( $P = 0.239$ )	-0.323 ( $P = 0.191$ )	0.356 ( $P = 0.148$ )
Apo B, g/l	-0.07 ( $P = 0.782$ )	0.147 ( $P = 0.561$ )	0.473 ( $P = 0.047$ )
LPA, mg/dl	0.138 ( $P = 0.585$ )	-0.157 ( $P = 0.533$ )	0.144 ( $P = 0.567$ )

Data presented as correlation coefficient ( $P$ -value).

HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; Apo, apolipoprotein; LPA, lipoprotein A.

of which have been shown to be closely related to PPAR $\gamma$ .<sup>29</sup> Patients with KD may have lower HDL-C, higher TG and/or higher LDL-C.<sup>10,28,30–32</sup> Although the current study showed that children with KD had dyslipidaemia, it did not find a relationship between the elevated PPAR $\gamma$  and lipids. An anti-inflammatory effect might be the main role of PPAR $\gamma$  in the progression of KD.

In this current study, the serum ADP levels of patients with KD in the acute, subacute and convalescent phases were significantly lower than that of the healthy control group. During the acute period, the ADP level in the CAL group was significantly higher than that of the NCAL group. Previous research has reported that ADP exists in aortic endothelium and may play a protective role in the development of

atherosclerosis.<sup>33</sup> Increased ADP levels are significantly associated with increased coronary heart disease, cardiovascular disease and overall mortality,<sup>34</sup> so ADP may have a negative effect on KD. However, ADP is considered to be a multifaceted biomarker that has anti-inflammatory effects,<sup>35</sup> so it may be beneficial in KD. In our opinion, ADP might have multiple roles in the pathological processes involved in KD, including both positive and negative effects. Both ADP and PPAR $\gamma$  disorders are associated with metabolic disorders,<sup>24</sup> although this current study did not find a relationship between ADP, PPAR $\gamma$  and the lipids that were recorded.

This current study had several limitations. Firstly, the study concentrated on the influences of each adipokine on KD without further investigate of the mechanisms involved. Secondly, the data were confined to a limited number of samples and the study participants were from a very small local geographical region.

In conclusion, the current preliminary data suggest that PPAR $\gamma$  may be a predictor of CAL in patients with KD with good predictive accuracy, but further research with a larger sample size from multiple centres will be needed to confirm these findings.

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### Declaration of conflicting interest

The authors declare that there are no conflicts of interest.

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### Authors' contributions

J.Z. conceptualized and designed the study, designed data collection instruments, carried out data collection and initial analyses, and drafted the initial manuscript, and approved the final manuscript as submitted. M.H. carried out data collection, reviewed and revised the manuscript and approved the final manuscript as submitted. Y.Z. and H.P. designed data collection instruments, carried out the initial analysis, reviewed and revised the manuscript and approved the final manuscript as submitted. P. L. and L.W. designed data collection instruments, reviewed and revised the manuscript and approved the final manuscript as submitted. S.G. and G.D. helped interpret data, critically reviewed and revised the manuscript and approved the final manuscript as submitted.

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