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Extracoronary echocardiographic findings as predictors of coronary artery lesions in the initial phase of Kawasaki disease

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ABSTRACT

Objective To describe the significance of pericardial effusion (PE), mitral regurgitation (MR) and impaired systolic function in predicting coronary artery lesions (CAL) at diagnosis and follow-up in Kawasaki disease (KD).

Design Echocardiographic records on admission, at 1–3 weeks of illness, and at 6–8 weeks of illness were retrospectively retrieved in children with acute KD treated by intravenous immunoglobulins.

Setting, patients The study included 194 consecutive children (113 male; median age 2.1 years) in a paediatric cardiology tertiary care centre, from 1988 to 2007.

Results Overall, children with CAL (64/194) were more likely to have PE (OR=3.00, CI 1.34 to 6.72) and MR (OR=2.51, CI 1.22 to 5.16) at diagnosis; PE was the sole echocardiographic abnormality associated with CAL in multivariable analysis. These abnormalities were predictive of the presence of CAL at the first echocardiography in the acute phase of the disease only. MR, systolic dysfunction and PE were not associated with persistence of CAL in the convalescent phase. Male gender, CAL size and resistance to immunoglobulin treatment were independent factors predictive of the persistence of CAL.

Conclusions Children with MR or PE should undergo careful assessment of coronary status at diagnosis. However, PE or MR at diagnosis is not predictive of persistent CAL at follow-up.

What is already known on this topic

- Echocardiography in Kawasaki disease may reveal coronary aneurysm, pericardial effusion (PE) and valvular dysfunction.
- High-dose intravenous immunoglobulin significantly reduces the risk of subsequent coronary artery aneurysm.
- Mitral regurgitation (MR) and PE are predictive markers of coronary artery lesions (CAL) at 1-month's follow-up in children not treated with intravenous immunoglobulins.

What this study adds

- Pericardial effusion and MR were associated with presence of CAL at diagnosis but not at follow-up.
- Consequently, the presence of such echocardiographic findings should lead to careful evaluation of coronary status.
- However, the presence of extracoronary abnormalities is not predictive of persistence or regression of CAL at follow-up.

INTRODUCTION

Kawasaki disease (KD) is an acute form of diffuse childhood vasculitis with a peculiar tropism for the heart, and is the leading cause of acquired coronary artery disease in children in the USA.[1] Diagnosis is based on the presence of fever plus at least four of five typical physical findings.[1] Echocardiography may reveal coronary abnormalities such as aneurysm, ectasia, brightness and irregularity, pericardial effusion (PE), mitral regurgitation (MR) and left ventricular (LV) dysfunction.[1] High-dose intravenous immunoglobulin (IVIg) significantly reduces the risk of subsequent coronary artery aneurysm.[2]

To our knowledge, KD and its cardiac manifestations in the light of the recent common utilisation of IVIg have been poorly described. The objectives of this study were (1) to describe a large-scale, long-term European experience with KD; (2) to determine the impact of the introduction of IVIg on cardiological involvement; and (3) to evaluate the relationship between signs of PE, LV failure, MR, on the one hand, and coronary arterial abnormality, on the other, at acute and late phases of incomplete and complete forms of KD.

PATIENTS AND METHODS

Patients

All echocardiographic records of patients referred with suspected KD were reviewed in the institution's paediatric cardiology database (FileMaker-Pro.4). All cases with confirmed diagnosis of complete or incomplete KD were included in the study. The cohort comprised 194 consecutive children diagnosed from January 1988 to June 2007, in the department of paediatric cardiology of the Lyon Claude Bernard University Medical Centre (France), which is a tertiary reference centre for paediatric and congenital heart disease for the southeast of France. The overall number of children (aged <18 years) in this area of France is about 1.5 million.

Clinical and echographic data were collected at diagnosis and during follow-up. Parameters included the usual demographic and clinical manifestations, such as standard American Heart

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Association clinical criteria, coronary artery lesions (CAL) status, LV dysfunction, mitral or aortic regurgitation, PE and outcome. Biological parameters—blood cell count, haemoglobin and C-reactive protein (CRP) level at diagnosis—were extracted retrospectively from medical charts (supplementary online Appendix 1). Patient data were compiled in a computerised database throughout follow-up (FileMaker-Pro.4).

The KD cardiac monitoring protocol included serial echocardiograms taken at least three times during the acute stage: on admission, at 1–3 weeks and at 6–8 weeks of illness, and then according to the cardiac findings. Complete KD was defined by fever (>120 h) and four or five of the five standard American Heart Association clinical criteria.[1] Incomplete KD was defined by prolonged fever, two or three of the five standard criteria, and either specific signs of coronary disease on echocardiography or particular laboratory criteria, based on Newburger's American Heart Association recommendations.[1] Rare cases (n=2: see 'Results') with only one major clinical criterion associated with fever but exhibiting specific CAL at diagnosis were included.

Disease onset was defined by onset of fever. The acute (or 'early') phase was defined by a continuing inflammatory process after the onset of fever and/or persistent fever and/or persistently abnormal biological inflammation markers (CRP). This period might differ from one case to another, with the acute phase thus spanning diagnosis up to 8 weeks of illness, in accordance with the recommendations of Newburger *et al*[1] for KD follow-up. The late (or 'at follow-up') phase was defined as the period beyond the acute phase thus defined.

Coronary artery lesions included either dilatation or aneurysm of one or more coronary arteries. Aneurysms were categorised, according to the 2004 American Heart Association statements, as small (<5 mm internal diameter), medium (5–8 mm) or giant (>8 mm).[1] Coronary artery brightness data were assessed but were not used in determining coronary artery abnormality, since no report has yet demonstrated the significance of isolated brightness of the coronary artery wall and because description is subjective and operator-dependent. Significant CAL were therefore defined by either dilatation or aneurysm.[3] Pericardial effusion was diagnosed by visualising the pericardial separation in both systole and diastole (figure 1). The percentage shortening fraction was calculated as the difference between end-diastole and end-systole length divided by end-diastole length, analysed from parasternal short-axis M-mode echocardiograms with the ultrasound beam at the tip of the mitral valve; abnormality was defined as ≤30% shortening. MR was detected by colour Doppler imaging on four-chamber and parasternal long-axis views of the left heart cavities (figure 2). All echocardiographic studies were performed by a paediatric cardiologist, using (successively over the study period) Aloka 2D-color, Toshiba and Philips HP 4500, HP 5500 and IE33 devices.

Shock was diagnosed in the sustained presence of any of the following conditions leading to initiation of volume expansion, infusion of vasoactive agents or transfer to an intensive care setting: systolic hypotension for age, a decrease in systolic blood pressure of >20% from baseline, or clinical signs of poor perfusion regardless of measured blood pressure.[4]

All children were treated with salicylates (30–100 mg/kg/day until regression of fever) associated with a complete course of IVIg (1.6–2 g/kg for 1–4 days).[1] IVIg resistance was defined as persistent or recrudescent fever (>38.0°C) ≥36 h after complete IVIg infusion (1.6–2 g/kg).[1] In children with multiple or severe CAL, dipyridamole (2–3 mg/kg/day) and warfarin (2–5 mg/kg/day) were added. The long-term coronary artery stenosis detection protocol is based on non-invasive tests, including exercise testing, thallium stress scintigraphy, dobutamine stress echocardiography and CT coronary artery scan, at 5–10 years' follow-up after KD or at any time when clinical symptoms are suggestive of myocardial ischaemia; invasive coronary artery angiography is performed if any abnormality is detected on non-invasive tests.

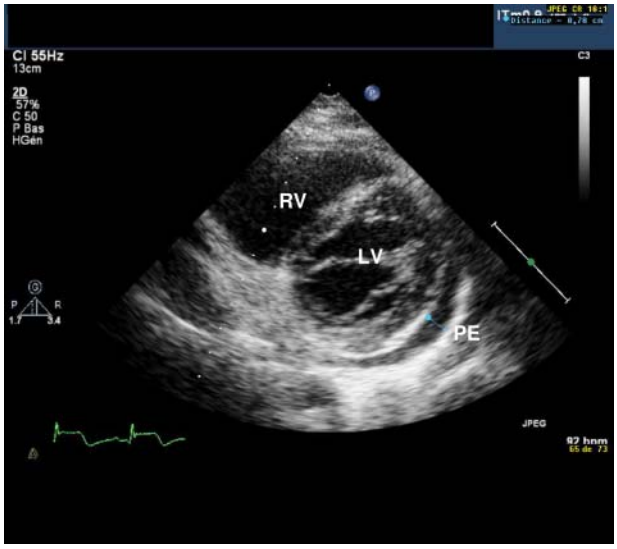

Figure 1 Pericardial effusion in the short-axis view of the left ventricle. LV, left ventricle; PE, pericardial effusion; RV, right ventricle.

Statistical analysis

Distribution normality was assessed by the Kolmogorov–Smirnov test. Comparisons between groups used the Student t test for quantitative variables and the χ^2 test, or Fisher's exact test, as appropriate, for categorical variables. Multivariable analysis identified independent variables associated with CAL at diagnosis by stepwise elimination of variables with $p<0.1$ on univariate analysis. CAL regression was analysed by the Kaplan–Meier method: survival was calculated between CAL diagnosis and either regression on echocardiography, death or end of follow-up. To identify variables associated with CAL regression,

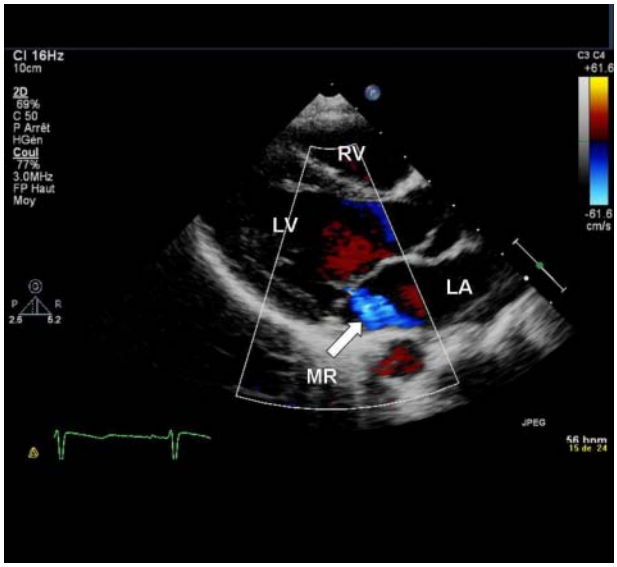

Figure 2 Mitral regurgitation by colour Doppler in the long-axis view of the left ventricle. LA, left atrium; LV, left ventricle; MR, mitral regurgitation; RV, right ventricle.

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a stepwise procedure selected variables for the final multivariable Cox proportional hazards model from variables with $p<0.1$ on univariate analysis. Significance was established at the $p<0.05$ level. Analyses were performed with SPSS V.17.0 (SPSS Inc, Chicago, Illinois, USA) for Windows.

RESULTS

Patient characteristics and cardiac findings

The demographic and clinical characteristics of the 194 children are summarised in table 1 according to the presence (64 patients, 33%) or absence of CAL (130 patients, 67%). Seventeen patients were seen in the 1980s, 70 in the 1990s and 107 from 2000 onward.

Sixty-four patients (33%) were diagnosed with CAL, detected in 47 children on the first and in 17 on the second echocardiogram. Coronary brightness without CAL was seen in 12/194 children (6.2%), two of whom developed CAL at the 11th and 22nd day of follow-up, respectively (non-significant). According to the American Heart Association classification, 51 had small, 12 medium and three giant aneurysms (respectively, 26.3%, 6.2% and 1.5%). Only one coronary artery was involved in 25 cases, two in 23 cases, three in nine cases and all four coronary arteries in two cases. The right coronary artery was the most frequently involved (38 cases), followed by the left main coronary (34 cases), the left anterior interventricular coronary (33 cases) and the circumflex artery (only eight cases).

MR (figure 2) was found in 19 patients (9.8%)—on the first echocardiogram in 16 patients and on the second in the other three cases. MR severity was estimated as mild in 15 cases, moderate in three and severe in one. All cases of MR except one regressed, at a median of 22 days (range 4–63).

Pericardial effusion (figure 1) was found in 29 patients (14.9%), all but four on the first echocardiogram. Size ranged from 1 mm to 8 mm (median 2 mm). No tamponade was seen. Effusion was circumferential in 10 patients. Pericardial abnormalities disappeared in all patients at a median of 9 days (range 4–151).

Comparisons showed that MR and PE were significantly intercorrelated (OR=5.33, CI 1.92 to 14.8; $p<0.001$), with no correlation between MR or PE and decreased LV shortening fraction.

Table 1 Demographic, clinical, biological and echocardiographic findings in the acute phase

Characteristics	Absence of CAL (N=130)	Presence of CAL (N=64)
Sex: male	70 (54)	43 (67)
Median age (years) (range)	2.1 (10 days–14.7 year)	1.7 (0.2–14.5 year)
Extreme age (<6 months or >5 years)	33 (25)	28 (44)
LV shortening fraction <30%	14 (11)	5 (8)
Pericardial effusion	13 (10)	16 (25)
Mitral regurgitation	9 (7)	10 (16)
CRP (mg/l), mean±SD*	182±125	138±90
Haemoglobin (g/dl), mean±SD*	10.6±1.1	9.3±1.6
WBC ($\times10^9$/l), mean±SD*	10.7±5.6	13±7.8
Thrombocytosis in late phase >450000/mm^3)*	66 (60)	53 (96)
>2-day course of IVIg†	15 (16)	17 (27)
Late diagnosis (>10 days)	15 (12)	20 (31)
IVIg resistance	3 (2)	10 (16)

Results are shown as number (%) unless stated otherwise.
*Data available in 165 patients; †data available in 157 patients.
CAL, coronary artery lesions; CRP, C-reactive protein; LV, left ventricular; IVIg, intravenous immunoglobulins; WBC, white blood cell count.

Nineteen patients (10%) showed decreased LV shortening fraction—on the first echocardiogram in 16 cases (84%). KD-related shock occurred in six children, four of whom received catecholamine for haemodynamic stabilisation. Children with shock more often had CAL (p=0.04), MR (p=0.007) and PE (p=0.03). LV shortening fraction returned to normal in all patients within 2 weeks' follow-up (median 7 days; range 3–14).

Incomplete forms of KD

Incomplete KD was diagnosed in 30 children, 21 of whom had CAL (70%). In addition to fever, two patients showed one clinical criterion, seven showed two criteria and 21 three criteria. Incomplete KD did not differ significantly from complete KD with CAL for PE frequency, LV shortening fraction impairment or MR.

Factors associated with CAL in the acute phase

Extreme age, PE, MR, CRP level, platelet count >450 000/mm^3 in the late phase, haemoglobin level, >2 day IVIg course, late diagnosis (>10 days) and IVIg resistance were significantly associated with increased frequency of CAL on univariate logistic regression (table 2). Multivariable logistic regression (on 151 patients) identified male gender, extreme age, PE, haemoglobin level and IVIg resistance as independent predictive factors for CAL (table 2). At diagnosis, MR (OR=2.18; CI 0.42 to 11.32), PE (OR=1.46; CI 0.29 to 7.62) and decreased LV shortening fraction (OR=0.60; CI 0.0 to 4.98) were not associated with new CAL at follow-up on second and third echocardiograms.

CAL regression at follow-up and outcome

The median follow-up of children with CAL was 2.5 years (range 1 month to 14 years). One patient died of cardiogenic shock owing to ruptured chordae tendineae. Inferior myocardial infarction, confirmed by electrocardiographic ischaemic alteration, occurred in one patient. Ten children with CAL (16%) were lost to follow-up by 2 years. Regression occurred during follow-up in 43 patients. The persistence rate was 42% at 1 year, 38% at 2 years and 23% at 5 years, on Kaplan–Meier survival curves (figure 3). No coronary stenosis was found except in the child with inferior myocardial infarction.

On univariate analysis by Cox regression (table 3), factors influencing resolution were IVIg resistance, CAL size and initial CRP level. On multivariable analysis in 55 patients, CAL persistence was significantly related to CAL size, male gender and IVIg resistance. On Cox regression, MR and PE at admission were not predictive of persistent CAL at follow-up, or of regression of CAL.

DISCUSSION

The most striking finding of this study was that PE and MR were associated with presence of CAL at the early (acute) phase of KD. The link was particularly strong for PE (included in the multivariable model). Male gender, extreme age, recurrent or prolonged disease, delayed treatment and markers of the inflammatory process, including haemoglobin level or higher platelet count, higher white blood cell count and higher CRP level, were previously reported as correlated with CAL at diagnosis, and our results are concordant with these findings. However, few studies previously examined the frequency and implication of subclinical findings such as PE and/or MR after use of IVIg.[1 4–6] In this series, extracoronary echocardiographic abnormalities were mostly confined to the early phase of the vasculitis. Pericardial effusion was found in 14% of children, while prevalence ranged from 1% to 21% in previous series.[7–12] Given the association between PE and coronary involvement, this wide variation may be due both to variations in CAL

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Table 2 Univariate and multivariable analysis of factors associated with coronary artery lesions (CAL) in the acute phase

	Univariate analysis			Multivariable analysis*		
	OR	CI	p Value	aOR	CI	p Value
Sex: male	1.76	0.94 to 3.28	0.08	2.99	1.12 to 7.97	0.03
Extreme age (<6 months or >5 years)	2.24	1.18 to 4.23	0.01	3.73	1.41 to 9.89	0.01
LV shortening fraction <30%	0.68	0.24 to 1.99	0.49	–	–	–
Pericardial effusion	3.00	1.34 to 6.72	0.01	5.26	1.53 to 18.03	0.01
Mitral regurgitation	2.51	1.22 to 5.16	0.01	–	–	–
CRP (10 mg/l increase)†	1.03	1.01 to 1.07	0.03	–	–	–
Haemoglobin (1 g/dl increase) †	0.50	0.38 to 0.67	<0.00001	0.59	0.42 to 0.83	0.003
WBC (1×10^9/l increase)†	1.05	1.00 to 1.11	0.06	–	–	–
Platelet count >450000/mm^3 in the late phase†	4.00	1.57 to 10.22	0.004	–	–	–
>2 Day-course of IVIg‡	2.60	1.18 to 5.61	0.02	–	–	–
Late diagnosis (>10 days)	3.81	1.76 to 8.24	0.001	–	–	–
IVIg resistance	7.82	2.07 to 29.58	0.002	23.58	2.45 to 226.58	0.006

*Regression performed with 151 patients; †data available in 165 patients; ‡data available in 157 patients.
CRP, C-reactive protein; IVIg, intravenous immunoglobulins; LV, left ventricular; WBC, white blood cell count.

frequency between series and to brief episodes of PE which might have escaped detection by echocardiography.

During the acute phase, MR may be secondary to endocarditis, papillary muscle dysfunction, myocardial ischaemia or active myocarditis, the first probably being the most common cause.[5 13 14] Earlier studies including children not treated by IVIg reported MR in 25–47% of children, compared with 7–20% in a recent series, including the present.[4–6 13]

A previous study reported MR and PE as predictive markers of CAL development at 1-month's follow-up (ie, acute or early phase as defined in this study) in 28 children not treated with IVIg.[5] The severity of the inflammatory process at disease onset and before IVIg administration might explain the relationship between PE and CAL during the acute phase. On the other hand, histological evidence of myocarditis appears to be universal in the acute phase.[15] Signs of myocarditis, consisting of abnormal uptake of Ga-67 on scintigraphy and decreased LV ejection fraction, were more prevalent in children with MR in the acute phase.[13 16 17] The significant associations between CAL, MR, myocardial function and PE support the assumption of an overt form of pancarditis in children with PE and/or MR.[5 13 18] When treated with IVIg within the first 10 days of illness, almost 5% of children without CAL at diagnosis developed at least transient coronary artery dilatation, compared with 15–20% in the placebo group.[2] IVIg treatment may have more influence on the prevention of late manifestations of pancarditis such as CAL than on early manifestations such as abnormal myocardial contractility, PE or MR.[16] This probably explains why this study failed to find an association between new CAL developing during follow-up and MR or PE, despite a larger sample size.

According to these results, PE and MR are significantly associated with CAL at the time of KD diagnosis. Consequently, the presence of such echocardiographic findings should lead to a careful evaluation of coronary status. These results show that PE (but not MR on multivariable analysis) can help to predict CAL in acute-phase KD, independently of other factors, and notably of IVIg administration. These results may alert the echocardiographer to a higher probability of CAL and recommendation for more frequent echocardiographic assessment and/or specific cardiac monitoring in a specialised centre (ie, paediatric cardiology department) in patients with PE, and possible changes in therapeutic management (eg, second dose of IVIg, steroid treatment, etc). The published scores[1] for early identification of patients at high risk of CAL implicate male gender, age at diagnosis, alanine aminotransferase level and haemoglobin level, and these results suggest that perhaps PE and/or MR should be added to these scoring criteria.[1]

Although the presence of PE and/or MR may be predictive of an increased risk of CAL in early KD, these results also show that (1) the absence of PE and/or MR does not exclude the risk of CAL; (2) the presence of PE and/or MR does not help to predict either regression or persistence of CAL in late follow-up and (3) as previously reported,[19–25] male gender and IVIg resistance are predictive factors for persistence of CAL.

Lastly, we specifically examined the group with incomplete KD and found a higher frequency of CAL in incomplete KD and no difference from cases of complete KD in the occurrence of slight echocardiographic extracoronary abnormalities. These findings bear out the current literature, suggesting that incomplete and complete KD probably involve a similar risk of CAL. This may be due to delay in diagnosis and IVIg administration in incomplete forms of KD, suggesting that particular attention should be paid to mild echocardiographic PE and/or MR.

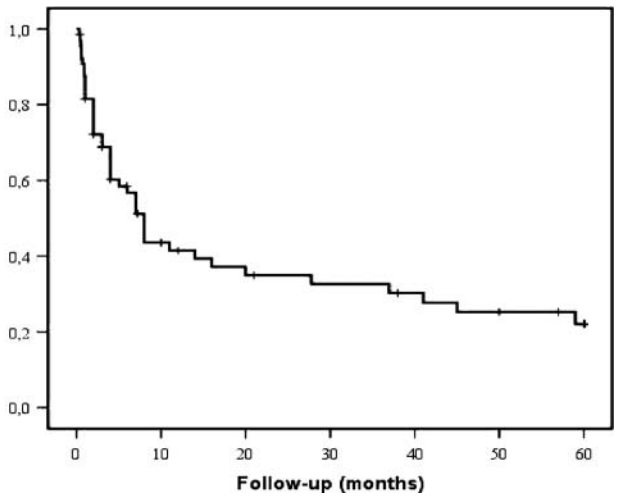

Figure 3 Persistence of coronary artery lesions. Kaplan–Meier curves of the 64 patients with coronary artery lesions at 5 years' follow-up. (+) indicates censored patients.

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Table 3 Univariate and multivariable analysis of predictive factors for coronary artery lesion regression

	Univariate analysis			Multivariable analysis*		
	HR	CI	p Value	aHR	CI	p Value
Male gender	0.16	0.34 to 1.20	0.18	0.52	0.27 to 0.99	0.05
Age >1 year	1.15	0.62 to 2.11	0.65	–	–	–
Pericardial effusion	0.85	0.42 to 1.74	0.66	–	–	–
Mitral regurgitation	1.43	0.60 to 3.42	0.42	–	–	–
LV shortening fraction <30%	0.80	0.28 to 2.32	0.69	–	–	–
CRP level (10 mg/l increase)†	0.96	0.93 to 0.99	0.04	–	–	–
Haemoglobin level (1 g/dl increase)†	1.17	0.96 to 1.42	0.11	–	–	–
WBC (1×10^9 increase)†	1.00	0.99 to 1.00	0.60	–	–	–
Platelet count >450000/mm^3 in the late phase†	0.94	0.33 to 2.67	0.91	–	–	–
Late diagnosis (>10 days)	0.83	0.42 to 1.68	0.62	–	–	–
>2 Day-course of IVIg	0.93	0.46 to 1.92	0.86	–	–	–
IVIg resistance	0.24	0.07 to 0.78	0.02	0.27	0.09 to 0.94	0.04
Incomplete form of KD	1.24	0.67 to 2.31	0.50	–	–	–
Number of involved coronaries	0.69	0.44 to 1.08	0.10	–	–	–
Proximal coronary involvement	0.70	0.21 to 2.72	0.55	–	–	–
Maximum size of CAL (1 mm increase)	0.59	0.43 to 0.79	<0.0001	0.52	0.43–0.81	0.001

aHR, adjusted HR; CAL, coronary artery lesions; CRP, C-reactive protein; IVIg, intravenous immunoglobulins; KD, Kawasaki disease; WBC, white blood cell count.
*Regression performed with 55 patients; †data available in 55 patients.

Study limitations

Despite these significant new findings, this study had several limitations. First, albumin was reported by many studies as an important predictive factor for coronary abnormality in the acute phase; the albumin level, however, is not routinely assessed at admission in our institution and this factor could not be included in the regression model. Second, two-dimensional echocardiography was employed to detect coronary artery abnormality during the acute phase, while its sensitivity in the detection of distal or stenotic lesions has not always been satisfactory. Third, the echocardiographers were not blinded, and the presence of CAL might have influenced their search for minimal echocardiographic abnormalities. Fourth, 10 children with coronary lesions were lost during the 2-year follow-up period, which might have led to information bias. Fifth, dedicated testing to exclude coronary stenosis during follow-up was not possible in 30 children. Lastly, the quality of echocardiograph imaging has changed over time, and this might have affected the sensitivity of echocardiographic diagnosis.

CONCLUSION

Children with MR or PE in the early phase of KD should undergo careful assessment of coronary status at diagnosis. However, these early extracoronary cardiac findings at diagnosis are not predictive of CAL at late follow-up.

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Contributors I certify that all listed authors have contributed to the submitted manuscript, by writing (JCL, SDF), reviewing (AB, RC), planning or collecting data (DF, MV, CD, PR). Responsible person for the overall content as a guarantor: SDF

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