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# Progression of Coronary Artery Abnormalities Following Timely Intravenous Immunoglobulin Administration in Children With Incomplete Kawasaki Disease: A Retrospective Cohort Study

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## Abstract

### Introduction

Incomplete Kawasaki disease (iKD) may be associated with coronary artery involvement despite treatment with intravenous immunoglobulin (IVIG). This study evaluated the occurrence and progression of coronary artery abnormalities following IVIG administration in children with iKD.

### Materials and methods

This retrospective cohort study included children aged <18 years with iKD who received an initial IVIG dose of 2 g/kg within 10 days of fever onset and underwent baseline and follow-up echocardiography. Demographic, clinical, laboratory, treatment, and echocardiographic variables were also evaluated. The coronary artery dimensions were assessed using body-surface-area-adjusted z-scores. Coronary artery abnormality was defined as a maximum coronary artery z-score ⩾2.5, and progression was defined as an increase of ⩾1.0 in the maximum coronary z-score between baseline and the highest follow-up assessment.

### Results

A total of 396 children were included, with a mean age of 24.1 ± 18.7 months; 228 (57.6%) were male. IVIG was administered within seven days of fever onset in 279 (70.5%) children and between days eight and 10 in 117 (29.5%). IVIG resistance was observed in 45 (11.4%) children. At baseline, 36 (9.1%) children had coronary artery abnormalities (maximum z-score ⩾2.5), while 72 (18.2%) had coronary artery dilation (maximum z-score 2.0-<2.5). The 36 children with baseline coronary artery abnormalities were excluded from the analysis of newly developed abnormalities, leaving 360 children without baseline coronary artery abnormalities. Among these 360 children, 24 (6.7%) developed new coronary artery abnormalities during follow-up. These children were younger, were more frequently aged <12 months, had longer fever duration, received IVIG later, had more frequent IVIG resistance, had higher C-reactive protein (CRP), leukocyte, and platelet counts, had lower albumin concentrations, and had higher baseline maximum coronary artery z-scores. Coronary progression occurred in 42 (10.6%) of the 396 children. The mean maximum coronary artery z-score increased from 1.09 ± 0.72 at baseline to 1.32 ± 0.96 at the highest follow-up assessment (mean difference, 0.23; 95% CI, 0.08-0.38; p = 0.003). The proportion of children with coronary artery abnormalities increased from 36 (9.1%) at baseline to 51 (12.9%) during follow-up (p = 0.015).

### Conclusion

Coronary artery abnormalities may develop or progress after IVIG treatment in children with iKD. Younger age, delayed IVIG administration, IVIG resistance, greater systemic inflammation, and higher baseline coronary z-scores are associated with adverse coronary outcomes. Therefore, serial echocardiographic surveillance may be important following IVIG treatment, particularly in children with these risk characteristics.

**Categories:** Pediatrics
**Keywords:** child, coronary artery aneurysm, echocardiography, immunoglobulins, intravenous, kawasaki disease

## Introduction

Kawasaki disease (KD) is an acute, self-limiting systemic vasculitis that predominantly affects young children and has important cardiovascular consequences, particularly coronary artery dilation and coronary artery aneurysm formation [1]. Despite advances in diagnosis and treatment, coronary artery involvement remains the principal clinically significant complication of KD [2]. In untreated children, coronary aneurysms may develop in approximately 25% of cases, and timely treatment with intravenous immunoglobulin (IVIG) substantially reduces this risk [3,4]. Because no single diagnostic laboratory test

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confirms KD, diagnosis relies on characteristic clinical features, supported by laboratory and echocardiographic findings [3,4]. This diagnostic challenge is particularly relevant in children with incomplete Kawasaki disease (iKD), who present with prolonged fever but fewer than four of the principal clinical manifestations and may therefore be more difficult to recognize promptly [5].

Incomplete presentation has important implications for coronary outcomes. Previous studies have demonstrated that children with iKD may have a greater burden of coronary artery abnormalities (CAAs) than those with complete clinical presentations, particularly when diagnosis and treatment are delayed [6,7]. IVIG administered within the first 10 days of illness is an established therapy for reducing coronary complications; however, CAAs may still develop or progress despite timely treatment [8]. Previous studies have also shown that some children who respond clinically to IVIG can subsequently develop or demonstrate progression of coronary aneurysms during follow-up, indicating that resolution of fever does not necessarily correspond to the complete resolution of coronary vascular inflammation [9]. Younger age, persistent inflammation, IVIG resistance, and abnormalities already present on initial echocardiography have been associated with an increased risk of adverse coronary outcomes [10].

Therefore, serial echocardiography remains central to the assessment of coronary involvement in children with KD [11]. Body-surface-area-adjusted coronary artery z-scores provide a standardized method for evaluating coronary dimensions and identifying clinically meaningful changes over time [12]. However, limited data are available regarding the evolution of CAAs, specifically among children with iKD who receive IVIG within the recommended therapeutic window. Characterizing the development of new CAAs and the progression of pre-existing involvement may help identify children who require particularly careful echocardiographic surveillance even after timely treatment.

This study aimed to evaluate the occurrence and progression of CAAs following timely intravenous immunoglobulin (IVIG) administration, defined as administration of an initial IVIG dose of 2 g/kg within 10 days of fever onset, in children with incomplete Kawasaki disease (iKD). The objectives were to determine the frequency of new coronary artery abnormalities during follow-up; assess the progression of pre-existing coronary artery abnormalities; evaluate longitudinal changes in maximum coronary artery z-scores; and examine demographic, clinical, laboratory, treatment-related, and baseline echocardiographic factors associated with these coronary outcomes in univariate analyses.

# Materials And Methods

## Study design and setting

This retrospective institutional cohort study was conducted using the electronic medical records between January 2018 and October 2022 at the Department of General Surgery, Kalpana Chawla Government Medical College, Karnal, India. The study protocol was reviewed and approved by the Institutional Ethics Committee of the college (KCGMC/IEC/2022/11/26, dated: 21-11-2022). As the study involved a retrospective review of existing medical records and did not involve direct patient intervention, the committee waived the requirement for individual informed consent. All extracted data were anonymized before the statistical analysis, and patient identifiers were not included in the analytical dataset.

## Study population and eligibility criteria

An institutional database was searched to identify children diagnosed with KD during the study period. Patient eligibility is summarized in Table *1*.

| Inclusion criteria | Exclusion criteria |
|---|---|
| Patients younger than 18 years of age. | Patients with complete KD. |
| Patients who fulfilled the diagnostic criteria for iKD. | Patients who received IVIG more than 10 days after fever onset. |
| Patients who received an initial IVIG dose of 2 g/kg within 10 days of fever onset. | Patients who had received previous IVIG during the same illness episode. |
| Patients with a baseline echocardiographic examination available. | Patients with pre-existing coronary artery disease or congenital coronary abnormality. |
| Patients with at least one follow-up echocardiographic examination after IVIG. | Patients with inadequate documentation of fever onset or IVIG administration and insufficient echocardiographic follow-up. |

**TABLE 1: Inclusion and exclusion criteria.**

KD: Kawasaki disease, iKD: incomplete Kawasaki disease, IVIG: intravenous immunoglobulin.

During the study period from March 2018 to March 2022, a total of 458 children diagnosed with KD were identified from the institutional clinical database and screened for eligibility. Of these, 62 children were excluded: 24 had complete KD, 10 received IVIG more than 10 days after fever onset, six had received IVIG previously during the same illness episode, five had pre-existing coronary artery disease or congenital coronary abnormalities, four had another systemic inflammatory or vasculitic disorder, seven had inadequate documentation of fever onset or IVIG administration, and six had insufficient echocardiographic follow-up. Following application of the predefined eligibility and exclusion criteria, 396 children with iKD who received an initial IVIG dose of 2 g/kg within 10 days of fever onset and had both baseline and follow-up echocardiographic examinations were included in the final cohort. iKD was defined as prolonged fever with fewer than four principal clinical features of KD, supported by appropriate laboratory and/or echocardiographic findings, and after exclusion of alternative diagnoses [3,4]. The five principal clinical features considered were bilateral non-exudative conjunctival injection, oral mucosal changes, polymorphous rash, peripheral extremity changes, and cervical lymphadenopathy.

## Clinical and laboratory data

The demographic variables included age at diagnosis, sex, and weight. Clinical variables included duration of fever before IVIG, number of principal clinical features of KD, and the presence of rash, conjunctival involvement, oral mucosal changes, extremity changes, and cervical lymphadenopathy. To reduce the number of variables in the analysis, the individual clinical manifestations were summarized according to the number of principal KD features present (two, three, or four). The day of IVIG administration was recorded and categorized as ⩽7 days or >7-10 days [4,13].

Baseline laboratory variables included hemoglobin, total leukocyte count, platelet count, C-reactive protein (CRP), serum albumin, and serum sodium levels. Laboratory values obtained before IVIG administration and closest to treatment initiation were used for analysis. IVIG-related variables included the illness day at treatment, IVIG dose, persistent or recurrent fever following IVIG, and the requirement for additional IVIG or other immunomodulatory treatment. IVIG resistance was defined as persistent or recrudescent fever ⩾36 h after completion of the initial IVIG treatment [4].

## Echocardiographic assessment

The baseline and follow-up transthoracic echocardiographic examinations were reviewed. The left main coronary artery (LMCA), left anterior descending artery (LAD), and right coronary artery (RCA) diameters were measured using echocardiography, and the corresponding body-surface-area-adjusted coronary artery z-scores were obtained using the validated reference equations of Dallaire et al. [14]. The same z-score system was consistently applied to all baseline and follow-up echocardiographic examinations to ensure comparability across time points. For each examination, the z-scores of the LMCA, LAD, and RCA were recorded, and the highest value among the evaluated coronary arteries was designated as the maximum coronary artery z-score and used for principal analysis. Coronary artery dimensions were classified according to the maximum z-score as normal (<2.0), dilated (2.0-<2.5), small CAA (2.5-<5.0), medium CAA (5.0-<10.0), or large/giant CAA (⩾10.0). Coronary artery involvement was defined as a maximum coronary artery z-score ⩾2.5 [4].

The baseline echocardiogram was defined as the examination performed before or around the time of initial IVIG administration. The first available echocardiogram after IVIG was considered the initial follow-up examination, and subsequent examinations were reviewed when available. For each patient, the baseline

maximum coronary z-score, highest follow-up maximum coronary z-score, date of the first abnormal coronary finding, and the presence or absence of coronary progression were recorded (Figure *1*).

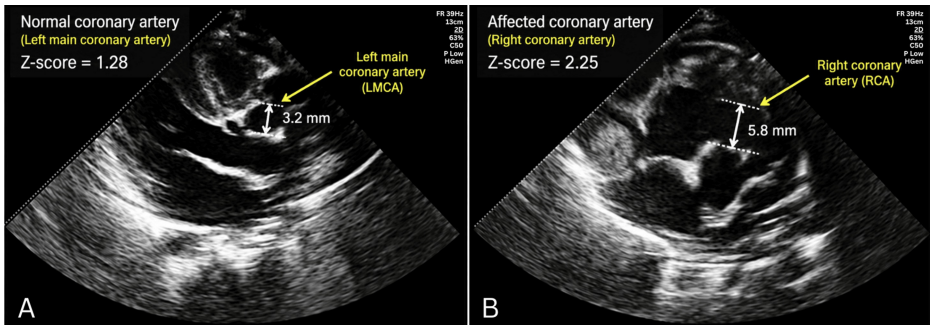



**FIGURE 1: Echocardiographic comparison of coronary artery dimensions.**

(A) Normal left main coronary artery (LMCA), demonstrating a measured diameter of 3.2 mm and a Z-score of 1.28. (B) right coronary artery (RCA) in the affected case, measuring 5.8 mm with a Z-score of 2.25.

### Study outcomes

Two primary coronary outcomes were assessed. The first was the development of a new coronary artery abnormality (CAA) during follow-up after IVIG. Coronary artery dimensions were classified according to the maximum coronary artery z-score, with a z-score of 2.0-<2.5 considered coronary artery dilation and a z-score ⩾2.5 considered a coronary artery abnormality. Patients who had no coronary artery abnormality at baseline but subsequently developed a maximum coronary artery z-score ⩾2.5 in any evaluated coronary artery during follow-up were classified as having a new coronary artery abnormality [4].

The second outcome was the progression of pre-existing CAA following IVIG therapy. Progression was defined as an increase of ⩾1.0 in the maximum coronary artery z-score between baseline and the highest follow-up examination [4]. Progression was also considered in relation to movement from a lower to higher coronary severity category. Children with coronary artery aneurysms already present at baseline were excluded from the analysis of new coronary abnormalities but were retained for the analysis of progression.

### Sample size estimation

The sample size was estimated a priori using G*Power software, version 3.1.9.7 (Heinrich Heine University Düsseldorf, Düsseldorf, Germany). Based on a previously published study reporting an expected prevalence of 50% for coronary artery abnormalities among children with iKD, a one-sample proportion approach was used, with a two-sided α error of 5%, 80% statistical power, and an absolute precision of 5% [15]. The calculated minimum sample size was 360. After allowing for approximately 10% of potentially incomplete or unavailable records, the estimated target sample size was 396 children.

### Statistical analysis

Statistical analyses were performed using IBM SPSS Statistics version 25 (IBM Corp., Armonk, NY, USA). Continuous variables were assessed for normality using the Shapiro-Wilk test. Normally distributed variables are expressed as mean ± standard deviation (SD), whereas non-normally distributed variables are reported as median and interquartile range (IQR). Categorical variables are presented as frequencies and percentages.

For comparison according to the development of a new coronary artery abnormality or progression, the independent-samples t-test was used for normally distributed continuous variables and the Mann-Whitney U test for non-normally distributed variables. Categorical variables were compared using the chi-squared test or Fisher's exact test, as appropriate. The effect sizes were reported using Cohen's d for continuous variables and odds ratios (ORs) for categorical variables. The change in the maximum coronary artery z-score between baseline and the highest follow-up examination was assessed using a paired-samples t-test, while changes in paired categorical coronary status were evaluated using McNemar's test. A two-sided $p < 0.05$ was considered statistically significant.

## Results

In total, 396 children with iKD were included in this study. The mean age of the cohort was 24.1 ± 18.7 months, and 90 (22.7%) children were younger than 12 months. Males accounted for 228 (57.6%) children in the cohort. IVIG was administered within seven days of fever onset in 279 (70.5%) children and between 7 and 10 days in 117 (29.5%) children. IVIG resistance was observed in 45 (11.4%) children. The mean CRP

concentration was 10.6 ± 5.4 mg/dL, while the mean platelet count was 365 ± 120 × $10^9$/L. At the baseline echocardiographic assessment, 288 (72.7%) children had normal coronary arteries, 72 (18.2%) had coronary artery dilation, and 36 (9.1%) had CAAs. Normal left ventricular systolic function was observed in 378 children (95.5%) (Table 2).

| Variable | | Overall (n = 396) |
|---|---|---|
| Demographic | Age (months), mean ± SD | 24.1 ± 18.7 |
| | Age <12 months, n (%) | 90 (22.7) |
| | Male sex, n (%) | 228 (57.6) |
| | Weight, kg, mean ± SD | 10.8 ± 4.9 |
| Clinical | Fever duration before IVIG, days, mean ± SD | 6.9 ± 1.4 |
| | IVIG administered ≤7 days, n (%) | 279 (70.5) |
| | IVIG administered >7–10 days, n (%) | 117 (29.5) |
| | IVIG resistance, n (%) | 45 (11.4) |
| Laboratory | CRP, mg/dL, mean ± SD | 10.6 ± 5.4 |
| | Total leukocyte count, ×$10^9$/L, mean ± SD | 15.1 ± 5.2 |
| | Platelet count, ×$10^9$/L, mean ± SD | 365 ± 120 |
| | Hemoglobin, g/dL, mean ± SD | 10.9 ± 1.3 |
| | Serum albumin, g/dL, mean ± SD | 3.1 ± 0.5 |
| Echocardiography | Baseline maximum coronary z-score, mean ± SD | 1.09 ± 0.72 |
| | Normal coronary arteries (z <2.0), n (%) | 288 (72.7) |
| | Coronary dilation (z 2.0 – <2.5), n (%) | 72 (18.2) |
| | CAA (z ≥2.5), n (%) | 36 (9.1) |
| | Normal LV systolic function, n (%) | 378 (95.5) |

**TABLE 2: Baseline demographic, clinical, laboratory and echocardiographic characteristics of children with incomplete Kawasaki disease.**

Data are presented as mean ± standard deviation (SD) for normally distributed continuous variables, median (interquartile range) for non-normally distributed continuous variables, and number (percentage) for categorical variables, CAA: coronary artery abnormality, CRP: C-reactive protein, IVIG: intravenous immunoglobulin, LV: left ventricular, and z-score: coronary artery z-score.

Of the 396 children included in the overall cohort, 36 (9.0%) had CAAs at baseline and were excluded from the analysis of newly developed CAAs. The remaining 360 (91.0%) children were evaluated for the occurrence of new CAAs during follow-up. Among the 360 children without baseline CAAs, 24 (6.7%) developed a new CAA during follow-up, whereas 336 (93.3%) did not (Table 3). Children who developed new CAAs were younger than those who did not (13.2 ± 8.1 vs. 24.8 ± 19.3 months; $p < 0.001$), and children younger than 12 months were more frequently represented in the new abnormality group ($p < 0.001$). IVIG administration after seven days of illness was also more frequent among children who developed new CAAs ($p < 0.001$). IVIG resistance occurred in 9 (37.5%) children who developed new CAAs compared to 30 (8.9%) children without new CAAs ($p < 0.001$). The new-CAA group also demonstrated higher CRP concentrations (13.1 ± 4.7 vs. 10.4 ± 5.4 mg/dL; $p = 0.012$) and platelet counts (428 ± 106 vs. 361 ± 119 × $10^9$/L; $p = 0.006$). Importantly, the baseline maximum coronary artery z-score was substantially higher among children who subsequently developed new CAAs (1.72 ± 0.37 vs. 0.96 ± 0.51; $p < 0.001$; Cohen's $d = 1.51$) (Table 3).

| Variable | New-CAA group (n = 24) 6.7% | No new-CAA group (n = 336) 93.3% | Test value (df) | p-value | Effect size |
|---|---|---|---|---|---|
| Age (months), mean ± SD | 13.2 ± 8.1 | 24.8 ± 19.3 | t = −5.92 (358) | < 0.001* | Cohen's d = −0.62 |
| Age <12 months, n (%) | 15 (62.5) | 75 (22.3) | $\chi^2$ = 19.29 (1) | < 0.001* | OR = 5.78 |
| Male sex, n (%) | 18 (75.0) | 189 (56.3) | $\chi^2$ = 3.22 (1) | 0.088 | OR = 2.33 |
| Fever duration before IVIG, days | 7.4 ± 1.1 | 6.8 ± 1.4 | t = 2.53 (358) | 0.017* | Cohen's d = 0.43 |
| IVIG >7 days, n (%) | 15 (62.5) | 93 (27.7) | $\chi^2$ = 12.93 | < 0.001* | OR = 4.34 |
| IVIG resistance, n (%) | 9 (37.5) | 30 (8.9) | $\chi^2$ = 18.93 (1) | < 0.001* | OR = 6.13 |
| CRP, mg/dL | 13.1 ± 4.7 | 10.4 ± 5.4 | t = 2.69 (358) | 0.012* | Cohen's d = 0.50 |
| WBC, ×10⁹/L | 17.4 ± 5.1 | 14.9 ± 5.1 | t = 2.32 (358) | 0.028* | Cohen's d = 0.49 |
| Platelets, ×10⁹/L | 428 ± 106 | 361 ± 119 | t = 2.97 (358) | 0.006* | Cohen's d = 0.57 |
| Albumin, g/dL | 2.9 ± 0.4 | 3.1 ± 0.5 | t = −2.32 (358) | 0.028* | Cohen's d = −0.42 |
| Baseline maximum z-score | 1.72 ± 0.37 | 0.96 ± 0.51 | t = 9.44 (358) | < 0.001* | Cohen's d = 1.51 |

**TABLE 3: Comparison of demographic, clinical, laboratory and baseline echocardiographic characteristics according to development of new coronary artery abnormality after IVIG (n = 360).**

Data are presented as mean ± standard deviation (SD) for continuous variables and number (percentage) for categorical variables, this analysis was restricted to the 360 children without coronary artery abnormality (CAA) at baseline; the 36 children with CAA on the baseline echocardiogram were excluded because they were not eligible for assessment of newly developed coronary abnormalities, continuous variables were compared using the independent-samples t-test, and categorical variables were compared using Pearson's chi-square test, odds ratios (ORs) with 95% confidence intervals (CIs) were calculated for categorical variables, and Cohen's d was reported for continuous variables where applicable, all tests were two-sided, and *p < 0.05 was considered statistically significant, CRP: C-reactive protein, IVIG: intravenous immunoglobulin, z-score: coronary artery z-score, df: degree of freedom.

Overall, 42 (10.6%) children demonstrated CAA progression during the follow-up, whereas 354 (89.4%) showed no progression. Children with progression were younger than those without progression (11.8 ± 7.2 vs. 24.5 ± 18.5 months; p < 0.001), and the proportion aged younger than 12 months was higher among those with progression (p < 0.001). IVIG resistance was observed in 12 (28.6%) children with progression compared with 33 (9.3%) without progression (p < 0.001). Children with CAA progression had higher CRP concentrations (13.2 ± 4.6 vs. 10.4 ± 5.5 mg/dL; p < 0.001) and platelet counts (432 ± 115 vs. 356 ± 120 × $10^9$/L; p < 0.001), together with lower serum albumin concentrations (2.9 ± 0.4 vs. 3.1 ± 0.5 g/dL; p = 0.004). The baseline maximum coronary artery z-score was markedly higher in the progression group than in the non-progression group (2.18 ± 0.68 vs. 0.96 ± 0.55, p < 0.001; Cohen's d = 2.16). IVIG administration after seven days was observed in 18 (42.9%) children with progression and 99 (28.0%) without progression, although this difference was not statistically significant (p = 0.051) (Table *4*).

| Variable | Progression (n = 42) | No progression (n = 354) | Test value (df) | p-value | Effect size |
|---|---|---|---|---|---|
| Age, months | 11.8 ± 7.2 | 24.5 ± 18.5 | t = −8.56 (394) | < 0.001* | Cohen's d = −0.72 |
| Age <12 months, n (%) | 24 (57.1) | 66 (18.6) | $\chi^2$ = 31.69 (1) | < 0.001* | OR = 5.83 |
| Male sex, n (%) | 27 (64.3) | 201 (56.8) | $\chi^2$ = 0.87 (1) | 0.411 | OR = 1.37 |
| Fever duration before IVIG, days | 7.3 ± 1.2 | 6.8 ± 1.4 | t = 2.51 (394) | 0.015* | Cohen's d = 0.38 |
| IVIG >7 days, n (%) | 18 (42.9) | 99 (28.0) | $\chi^2$ = 4.00 (1) | 0.051 | OR = 1.93 |
| IVIG resistance, n (%) | 12 (28.6) | 33 (9.3) | $\chi^2$ = 3.81 (1) | < 0.001* | OR = 3.89 |
| CRP, mg/dL | 13.2 ± 4.6 | 10.4 ± 5.5 | t = 3.65 (394) | < 0.001* | Cohen's d = 0.52 |
| WBC, ×10⁹/L | 17.2 ± 5.3 | 14.8 ± 5.1 | t = 2.79 (394) | 0.008* | Cohen's d = 0.47 |
| Platelets, ×10⁹/L | 432 ± 115 | 356 ± 120 | t = 4.03 (394) | < 0.001* | Cohen's d = 0.64 |
| Albumin, g/dL | 2.9 ± 0.4 | 3.1 ± 0.5 | t = −2.98 (394) | 0.004* | Cohen's d = −0.41 |
| Baseline maximum z-score | 2.18 ± 0.68 | 0.96 ± 0.55 | t = 11.20 (394) | < 0.001* | Cohen's d = 2.16 |

**TABLE 4: Comparison of characteristics according to coronary artery abnormality progression.**

Data are presented as mean ± standard deviation for normally distributed continuous variables and number (percentage) for categorical variables, continuous variables were compared using the independent-samples t-test, and categorical variables were compared using Pearson's chi-square test, odds ratios (ORs) with corresponding 95% confidence intervals (CIs) were calculated for categorical variables, and Cohen's d was reported for continuous variables where applicable, all tests were two-sided, and *p < 0.05 was considered statistically significant, CRP: C-reactive protein, IVIG: intravenous immunoglobulin, z-score: coronary artery z-score, df: degree of freedom.

Serial echocardiographic assessment demonstrated a significant increase in the maximum coronary artery z-score from 1.09 ± 0.72 at baseline to 1.32 ± 0.96 at the highest follow-up examination. The mean within-patient increase was 0.23 (95% CI, 0.08-0.38; p = 0.003), corresponding to a small within-patient effect size (Cohen's dz = 0.26). The proportion of children with a coronary artery z-score ⩾2.5 increased from 36 (9.1%) at baseline to 51 (12.9%) at the highest follow-up assessment. McNemar's analysis demonstrated a significant change in the paired coronary status ($\chi^2$ = 5.94; p = 0.015). During follow-up, 24 children developed new CAAs, whereas nine children with previously documented CAA demonstrated resolution (Table *5*).

| Echocardiographic parameter | Baseline (n = 396) | Highest follow-up (n = 396) | Mean difference (95% CI) | Test value (df) | p-value | Effect size |
|---|---|---|---|---|---|---|
| Maximum coronary z-score, mean ± SD | 1.09 ± 0.72 | 1.32 ± 0.96 | 0.23 (0.08–0.38) | t = 3.02 (395) | 0.003* | Cohen's dz = 0.26 |
| Coronary z-score ≥2.5, n (%) | 36 (9.1) | 51 (12.9) | — | McNemar $\chi^2$ = 5.94 (1) | 0.015* | OR = 2.61 (95% CI 0.86–7.25) |

**TABLE 5: Longitudinal change in maximum coronary artery z-score.**

Data are presented as mean ± standard deviation or number (percentage), as appropriate, baseline and follow-up maximum coronary artery z-scores were compared using the paired-samples t-test, the proportions of children with coronary artery abnormalities at baseline and follow-up were compared using McNemar's test, the mean difference with 95% confidence interval (CI), test statistic, p-value, and Cohen's dz are reported for the paired continuous comparison, and the odds ratio (OR) with 95% CI is reported for the paired categorical comparison, All tests were two-sided, and *p < 0.05 was considered statistically significant, z-score: coronary artery z-score, df: degree of freedom.

## Discussion

The present study demonstrated that coronary artery involvement in children with iKD may continue to develop or progress despite IVIG treatment within the accepted treatment window. This finding is clinically important because IVIG substantially reduces the risk of coronary complications; however, treatment does not eliminate the possibility of subsequent CAAs [8]. Incomplete presentation itself may contribute to diagnostic uncertainty and delayed recognition because fewer characteristic clinical manifestations are present [9]. Previous studies have similarly reported a greater risk of coronary complications among children

with incomplete disease, particularly when the clinical presentation is less typical [7,16]. Therefore, the present findings support the concept that iKD should be regarded as a clinically important coronary-risk phenotype rather than a less severe form of KD [7].

Younger age is consistently associated with the development of new CAAs and subsequent coronary progression. This observation is in agreement with previous literature identifying infancy as an important risk factor for coronary complications in KD [17,18]. Younger children may be particularly vulnerable because their coronary arteries are smaller, inflammatory vascular injury may have a greater relative effect on vessel dimensions, and the diagnosis of incomplete disease can be more difficult when clinical manifestations are subtle. Previous evidence has also suggested that the association between incomplete presentation and CAAs is particularly pronounced among children in the first year of life [18]. From a clinical perspective, an infant with suspected iKD should therefore receive careful diagnostic assessment and close echocardiographic surveillance, even when the initial coronary examination is reassuring.

The timing of treatment also appears to be relevant to coronary evolution. Children who developed new CAAs more frequently received IVIG later in the first ten days of illness. This finding is biologically plausible because coronary vascular inflammation may continue during the period preceding effective immunomodulation, allowing structural changes to develop before treatment. Previous observational studies have associated delayed IVIG treatment with an increased risk of coronary lesions, whereas studies specifically examining iKD have emphasized that incomplete clinical manifestations can contribute to delayed diagnosis and treatment [19,20]. However, the relationship between treatment timing and disease progression was less definitive in the present study. This distinction is important because it suggests that treatment within ten days should not be interpreted as complete protection against coronary progression. Early diagnosis and treatment remain important; however, subsequent monitoring is necessary.

IVIG resistance has been consistently associated with adverse coronary outcomes. Persistent or recrudescent fever following IVIG therapy may reflect continuing inflammatory activity despite initial treatment, providing a plausible explanation for the greater occurrence of CAAs among resistant patients. This observation is supported by a previous systematic review identifying IVIG resistance as an important risk factor for CAA development [7]. Similarly, large observational studies have demonstrated that patients who fail to respond adequately to initial treatment have an increased likelihood of subsequent coronary involvement [21]. Clinically, IVIG resistance should, therefore, be considered a marker requiring intensified clinical assessment and echocardiographic surveillance rather than merely an indicator of treatment failure.

Laboratory findings provide additional evidence for the association between inflammatory burden and coronary involvement. Greater CRP and leukocyte responses, higher platelet counts, and lower albumin concentrations have been observed in children with adverse coronary outcomes. These findings are consistent with those of previous studies in which increased inflammatory markers, thrombocytosis, and hypoalbuminemia have been associated with more severe KD and increased coronary risk [22]. Persistent systemic inflammation may contribute to endothelial activation, vascular permeability, and inflammatory injury to the coronary arterial wall. Importantly, these laboratory variables should not be individually interpreted as definitive predictors. Their greatest clinical value is likely to arise when they are considered together with age, treatment response, treatment timing, and echocardiographic findings [22,23].

The strongest association observed in the present study was for the baseline maximum coronary z-score. Children who subsequently developed new CAAs or progression had relatively greater coronary dimensions at the initial examination, even when these findings did not necessarily meet the threshold for established CAAs. This observation has important clinical implications because coronary enlargement may represent an early manifestation of ongoing vascular inflammation, rather than a static finding. Previous prospective evidence has similarly demonstrated that a higher baseline maximum z-score is associated with the subsequent development of CAAs [24,25]. Thus, clinicians should not rely solely on whether the initial examination result crosses the conventional abnormality threshold. A relatively elevated baseline z-score, particularly in children with persistent inflammatory features or other risk characteristics, may justify careful follow-up.

Serial echocardiographic assessments further demonstrated that the coronary dimensions were dynamic after treatment. Some children developed new CAAs during the follow-up, whereas others showed subsequent resolution. This pattern is consistent with the known temporal evolution of Kawasaki vasculitis, in which coronary inflammation and vascular remodeling can continue after acute clinical manifestations have improved [26]. Previous studies have documented that coronary lesions may appear after the initial echocardiographic assessment, reinforcing the importance of repeated imaging rather than relying on a single baseline examination [26,27]. The observed dynamic nature of coronary status also emphasizes the value of the longitudinal interpretation of echocardiographic findings, particularly in children with incomplete disease.

## Clinical implications and limitations

These findings have practical implications in clinical management. Children with iKD should undergo structured coronary assessments and continued echocardiographic surveillance after the initial IVIG

treatment. Particular vigilance may be warranted in younger children, those with delayed treatment within the first ten days, persistent or recurrent fever following IVIG therapy, greater inflammatory activity, or relatively increased baseline coronary z-scores. Importantly, these characteristics should be viewed as indicators of increased clinical attention, rather than as independent determinants of coronary outcomes.

This study has several limitations. Its retrospective, single-center design limits causal inference and may restrict generalizability to other populations. Dependence on existing medical records may have resulted in incomplete or missing documentation of clinical and laboratory variables, and the retrospective design did not allow standardized prospective handling of missing data. The timing and frequency of follow-up echocardiography varied between children because examinations were performed as part of routine clinical care, which may have influenced the detection and timing of coronary changes. Differences in post-IVIG management and additional treatment may also have been influenced by disease severity, introducing potential confounding by indication.

The absence of comprehensive adjusted multivariable analysis limits determination of whether the observed associations remain independent after accounting for correlated risk factors; therefore, the reported associations should not be interpreted as independent predictors. The predefined progression criterion, based on an increase of ⩾1.0 in the maximum coronary artery z-score, was useful for assessing longitudinal change but may not fully capture changes in individual coronary arteries or reflect long-term cardiovascular outcomes. In addition, formal interobserver or intraobserver reliability assessment of echocardiographic measurements was not available because this was a retrospective review of existing clinical records. Prospective multicenter studies with standardized echocardiographic schedules, predefined missing-data procedures, reproducible imaging assessment, and multivariable risk analysis are warranted to validate and extend these findings.

## Conclusions

Coronary artery abnormalities may develop or progress after timely IVIG treatment in children with incomplete Kawasaki disease, highlighting the potential importance of continued echocardiographic surveillance beyond initial therapy. Younger age, IVIG resistance, greater inflammatory activity, delayed IVIG administration, and higher baseline coronary artery z-scores were associated with adverse coronary outcomes in this cohort; however, these associations should be interpreted cautiously because multivariable analysis was not performed and independent effects could not be established. Serial echocardiography demonstrated changes in coronary status during follow-up, including the development and subsequent resolution of coronary artery abnormalities. These findings support continued risk-informed echocardiographic monitoring, particularly in children with features associated with adverse coronary evolution.

## Additional Information

### Author Contributions

All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work.

**Acquisition, analysis, or interpretation of data:** Humairah Tabassum, Rubeena Hameed, Jasmine Kalsi

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### Disclosures

**Human subjects:** Informed consent for treatment and open access publication was obtained or waived by all participants in this study. Institutional Ethical Committee of Kalpana Chawla Government Medical College issued approval KCGMC/IEC/2022/11/26. The study protocol was reviewed and approved by the Institutional Ethics Committee of the college (KCGMC/IEC/2022/11/26, dated 21-11-2022). . **Animal subjects:** All authors have confirmed that this study did not involve animal subjects or tissue. **Conflicts of interest:** In compliance with the ICMJE uniform disclosure form, all authors declare the following: **Payment/services info:** All authors have declared that no financial support was received from any organization for the submitted work. **Financial relationships:** All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work. **Other relationships:** All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

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