Corticosteroid Therapy Might be Associated with the Development of Coronary Aneurysm in Children with Kawasaki Disease

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Background: Coronary artery lesions (CALs) are known to be the main complication in children with Kawasaki disease (KD). Instead of intravenous immunoglobulin (IVIG), corticosteroid therapy has been accepted to be used for children with KD who are unresponsive to IVIG. This study aimed to evaluate risk factors for CALs in children with KD.

Methods: We retrospectively reviewed the clinical records of 2331 children with KD from January 2005 to December 2014. To identify the independent risk factors for CALs, multivariable logistic regression models were constructed using significant variables identified from univariate logistic regression analysis.

Results: The incidence of CALs was 36.0% (840 of 2331), including 625 (26.8%) coronary artery dilations and 215 (9.2%) coronary artery aneurysms (CAAs). Multivariable logistic regression analysis identified that male, incomplete KD, longer fever duration, and C-reactive protein (CRP) >100 mg/L were independent risk factors for coronary artery dilations. On the other hand, male, incomplete KD, longer fever duration, prolonged days of illness at the initial treatment, corticosteroid therapy, sodium ≤133 mmol/L, and albumin <35 g/L were the independent risk factors for CAAs. In addition, corticosteroid therapy, prolonged days of illness at the initial treatment, and albumin <35 g/L were the independent risk factors for giant CAAs.

Conclusions: CALs might be associated with male sex, incomplete KD, longer fever duration, prolonged days of illness at the initial treatment, albumin <35 g/L, sodium ≤133 mmol/L, CRP >100 mg/L, and corticosteroid therapy. Corticosteroid therapy was an independent risk factor for CAAs and giant CAAs. Thus, corticosteroids should be used with caution in the treatment of KD with the risk for CALs.

Key words: Coronary Artery Aneurysms; Coronary Artery Lesions; Corticosteroid Therapy; Kawasaki Disease; Risk Factors

INTRODUCTION

Kawasaki disease (KD), first described by Tomisaku Kawasaki in Japan in 1967, is an acute febrile vasculitis in childhood and is the leading cause of acquired pediatric heart disease in the developed world.[1,2] KD is characterized by prolonged fever, nonpurulent conjunctivitis, oral mucositis, cervical lymphadenopathy, induration and erythema of the extremities, and polymorphous skin rash.[3,4] There was a trend of increasing incidence of KD in Beijing, varying from 18 to 55/100,000 children <5 years of age from 1995 to 2004.[5] Although the inflammatory response is found in small and medium vessels of the body, the most common sites of inflammation and end-organ damage are the coronary arteries. Coronary artery lesions (CALs) develop in 15–25% of untreated children with KD.[6] Despite appropriate therapy with intravenous immunoglobulin (IVIG), CALs continue to develop in 5% of the affected children. Children who develop coronary artery aneurysms (CAAs), especially giant CAAs, have the risk of aneurysm thrombosis, coronary artery

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steno sis, myocardial infarction, or ischemic heart disease, and even sudden death, and require long-term follow-up and anticoagulant and antiplatelet therapy.[6–7] Prevention of CALs is, therefore, a priority.

Since 1995, we have organized a dataset of children with KD at our hospital, which is one of the largest tertiary children's medical centers in China. We noticed that the number of CAA cases gradually increased with the increase of KD cases, and many children with CAs who were referred to us had received corticosteroid therapy before the onset of the CAs. Therefore, we supposed that corticosteroid therapy might be associated with the increase in the number of children with CAs. Thus, we conducted this study to evaluate the relation between corticosteroid therapy and CAs.

Methods

In this retrospective study, we reviewed the medical records of all children with KD who had been admitted to our hospital from January 2005 to December 2014. The study was approved by the institutional ethics committee of our hospital. Information concerning the epidemiological characteristics, clinical manifestations, laboratory and echocardiographic findings, and treatment and outcome of each patient was obtained. The relation between the following factors and CALs was analyzed using univariate and multivariable logistic regression analyses: Age, sex, incomplete KD, total fever duration, days of illness at the time of echocardiography, and anticoagulant and antiplatelet therapy. The selection of the cutoffs of the variables was based on the more generally accepted cutoffs reported in the literature.

KD and incomplete KD were diagnosed according to the criteria published by the American Heart Association in 2004.[6] Fever was defined as a body temperature of ≥38°C. Corticosteroid therapy was defined as intravenous methylprednisolone (2 mg·kg⁻¹·d⁻¹) or oral prednisone (2 mg·kg⁻¹·d⁻¹). IVIG treatment resistance was defined as a fever of ≥38.0°C at 36 h to 7 days after the completion of IVIG infusion without another likely source.[8] The Z-scores were calculated as the body surface area (BSA)-adjusted mean coronary internal diameters established by de Zorzi et al.[9] with the following equation: Z-score = (observed diameter – mean normal diameter)/(standard deviation of the normal diameter). The mean normal diameter and standard deviation of the left main coronary, left anterior descending, and right coronary arteries were 1.688 ± 0.995 BSA, 0.420; 1.186 ± 0.820 BSA, 0.356; and 1.503 ± 0.499 BSA, 0.398, respectively. CALs were defined as Z-scores of the left main coronary, left anterior descending, or right coronary arteries >2.5. Coronary artery dilations were defined as a Z-score >2.5 and a coronary internal diameter ≤4 mm; CAs were classified as small CAs (internal diameter >4 mm and <5 mm), medium CAs (5–8 mm internal diameter), or giant CAs (>8 mm internal diameter).[6] The time to evaluate CALs was 1 month after the KD onset. If an echocardiography was performed two or more times within 1 month, the maximum value of the coronary internal diameter was chosen for analysis.

Results

In total, 2467 children were enrolled in this study. One hundred thirty-six cases were excluded because of multiple admissions (not including relapse) or incomplete data of coronary internal diameters and 2331 cases were analyzed using SPSS. Of the 2331 cases, there were 1517 boys and 814 girls, with a male to female ratio of 1.86:1. The ages varied from 1 month to 17.6 years (median, 1.9 years). A total of 2294 (94.8%) children received IVIG treatment, 2180 (95.0%) received an IVIG dose of 2 g·kg⁻¹·d⁻¹ for 1 day, 99 (4.3%) received an IVIG dose of 1 g·kg⁻¹·d⁻¹ for 2 consecutive days, and 15 (0.7%) received an IVIG dose of 400–500 mg·kg⁻¹·d⁻¹ for 3–5 consecutive days.

The incidence of CALs within 1 month after KD was 36.0% (840 cases), including 625 (26.8%) coronary artery dilations and 215 (9.2%) CAs. Of the 215 children with CAs, 84 had small CAs, 103 had medium CAs, and 28 had giant CAs. There were 393 (16.9%) children with incomplete KD and 523 (22.4%) children with IVIG treatment resistance. Of the IVIG-resistant children, 506 (96.7%) were treated with additional IVIG therapy. In addition, 39 (7.5%) of the 523 IVIG-resistant children received corticosteroid therapy because of continuing fever. None of the children who responded to IVIG treatment received corticosteroid therapy. Of the 39 children, 36 received intravenous methylprednisolone (2 mg·kg⁻¹·d⁻¹) after one or more additional IVIG, 2 received intravenous methylprednisolone (2 mg·kg⁻¹·d⁻¹) after the initial IVIG, and 1 received oral prednisone (2 mg·kg⁻¹·d⁻¹) after one additional IVIG. CALs developed in 59.0% of the 39 children (23 of 39), including 13 coronary artery dilations, two small CAs, five medium CAs, and three giant CAs. Two children with small CAs, three with medium CAs, and two with giant CAs had coronary artery dilations before receiving corticosteroid therapy and developed CAs after receiving corticosteroid therapy. Among the 523 IVIG-resistant children, 484 did not receive corticosteroid therapy. The incidence of CALs in the noncorticosteroid-treated group was 40.7% (197 of 484), including 142 coronary artery dilations, 26 small CAs, 21 medium CAs, and 8 giant CAs. In the 523 IVIG-resistant children, the incidence of CALs and CAs...
in the corticosteroid group was significantly higher than that in the noncorticosteroid group (CALs; $\chi^2 = 4.944$, $P = 0.026$; CAAs; $\chi^2 = 5.512$, $P = 0.019$).

Table 1 shows the assignment of each observed indicator. The laboratory parameters of WBC, CRP, PLT, sodium, and albumin were obtained before IVIG. Table 2 shows the statistical results of the risk factors for coronary artery dilatations from univariate logistic regression analysis. The results indicated that male, age ≤1 year, incomplete KD, longer fever duration, prolonged days of illness at the initial treatment, and CRP >100 mg/L were associated with coronary artery dilatations. When these six factors were subjected to multivariable logistic regression analysis $[\text{Table 3}]$, we obtained the independent risk factors for coronary artery dilatations, as follows: Male (OR: 1.434, 95% CI: 1.171–1.755, $P < 0.001$), incomplete KD (OR: 2.008, 95% CI: 1.576–2.558, $P < 0.001$), longer fever duration (OR: 1.037, 95% CI: 1.004–1.072, $P = 0.029$), and CRP >100 mg/L (OR: 1.343, 95% CI: 1.120–1.611, $P = 0.001$). With the same statistical methods, we obtained the risk factors for CAAs and giant CAAs. On the basis of the univariate logistic regression analysis, male, incomplete KD, longer fever duration, prolonged days of illness at the initial treatment, corticosteroid therapy, IVIG treatment resistance, sodium ≤133 mmol/L, and albumin <35 g/L were associated with CAAs $[\text{Table 4}]$. In addition, male, incomplete KD, longer fever duration, prolonged days of illness at the initial treatment, corticosteroid therapy, and albumin <35 g/L were associated with giant CAAs $[\text{Table 5}]$. In multivariable logistic regression analysis, male (OR: 1.425, 95% CI: 1.014–2.003, $P = 0.042$), incomplete KD (OR: 2.001, 95% CI: 1.408–2.846, $P < 0.001$), corticosteroid therapy (OR: 2.864, 95% CI: 1.210–6.777, $P = 0.017$), prolonged days of illness at the initial treatment (OR: 1.091, 95% CI: 1.047–1.137, $P < 0.001$), longer fever duration (OR: 1.078, 95% CI: 1.032–1.126, $P = 0.001$), sodium ≤133 mmol/L (OR: 1.341, 95% CI: 1.050–1.714, $P = 0.019$), and albumin <35 g/L (OR: 2.101, 95% CI: 1.496–2.949, $P < 0.001$) were independent risk factors for CAAs $[\text{Table 6}]$. In addition, corticosteroid therapy (OR: 8.315, 95% CI: 2.024–34.158, $P = 0.003$), prolonged days of illness at the initial treatment (OR: 1.112, 95% CI: 1.046–1.181, $P = 0.001$), and albumin <35 g/L (OR: 2.379, 95% CI: 1.186–4.770, $P = 0.015$) were independent risk factors for giant CAAs $[\text{Table 7}]$.

**DISCUSSION**

CALs are the main complications in children with KD, and the prediction of CALs is, therefore, the focus of this research. Several prediction systems have been developed to identify children at risk for CALs. Harada$^{[10]}$ developed a risk score to determine the risk of CAAs in children with KD. The risk factors included WBC >12,000/mm$^3$, PLT <350,000/mm$^3$, CRP >3+, hematocrit <35%, albumin <35 g/L, age ≤12 months, and male. In 2006, Kobayashi et al.$^{[11]}$ constructed a predictive system for the development of CAAs. The risk factors for CAAs included age ≤12 months, neutrophil ≥80%, CRP >100 mg/L, PLT <300,000/mm$^3$ sodium ≤133 mmol/L, aspartate transaminase ≥100 IU/L, and days of illness at the initial treatment ≤4. Another study showed that incomplete KD, IVIG treatment resistance, and longer fever duration were associated with CALs.$^{[12]}$ In our study, CALs were found to have possible associations with male, incomplete KD, longer fever duration, prolonged days of illness at the initial treatment, albumin <35 g/L, sodium ≤133 mmol/L, CRP >100 mg/L, and corticosteroid therapy.

Although corticosteroid therapy is the treatment of choice for other types of vasculitis, the use of corticosteroids is still controversial in children with KD. In 1979, Kato et al.$^{[13]}$ used prednisolone for the initial treatment of children with KD. One or 2 months later, coronary angiography demonstrated CAAs in 64.7% of children treated with prednisolone and

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**Table 1: Assignment of each observed indicator**

| Observed indicators                  | Assignment |
|--------------------------------------|------------|
| Sex                                  |            |
| Male                                 | 1          |
| Female                               | 0          |
| Age                                  |            |
| >1 years                             | 1          |
| ≤1 years                             | 0          |
| Incomplete KD                        |            |
| Yes                                  | 1          |
| No                                   | 0          |
| Corticosteroid therapy               |            |
| Yes                                  | 1          |
| No                                   | 0          |
| Days of illness at the initial treatment | Continuous |
| Albumin                              |            |
| <35 g/L                              | 1          |
| ≥35 g/L                              | 0          |
| Coronary artery lesions              |            |
| Yes                                  | 1          |
| No                                   | 0          |
| Sodium                               |            |
| ≤133 mmol/L                          | 1          |
| >133 mmol/L                          | 0          |
| WBC                                  |            |
| >12 × 10$^9$/L                        | 1          |
| ≤12 × 10$^9$/L                        | 0          |
| CRP                                  |            |
| >100 mg/L                            | 1          |
| ≤100 mg/L                            | 0          |
| PLT                                  |            |
| >300 × 10$^9$/L                       | 1          |
| ≤300 × 10$^9$/L                       | 0          |
| Total fever duration (days)          | Continuous |
| Yes                                  | 1          |
| No                                   | 0          |

KD: Kawasaki disease; WBC: White blood cell count; CRP: C-reactive protein; PLT: Platelet count; IVIG: Intravenous immunoglobulin.
11% of those treated with aspirin. The findings suggested that steroids might act adversely to cause a progression of CALs. In 2003, Sundel et al. reported a prospective study that showed children who received steroids (30 mg/kg intravenous methylprednisolone) in the initial treatment of KD had shorter fever duration and shorter hospital stay, as well as lower erythrocyte sedimentation rate and CRP level. No differences were recorded for the coronary outcomes between the treatment groups. In 2004, the American Heart Association criteria showed that studies of corticosteroids in the initial therapy for KD, as well as in the treatment for nonresponders after the initial IVIG, have shown that corticosteroids reduce fever. The effects of corticosteroids on CALs are still uncertain. In addition, they recommended

Table 2: Risk factors for coronary artery dilatations from univariate logistic regression analysis

| Independent variables                              | B    | SE   | Wald  | P     | OR   | 95% CI     |
|--------------------------------------------------|------|------|-------|-------|------|------------|
|                                                   |      |      |       |       |      |            |
| Sex                                              | 0.378| 0.101| 14.002| 0.000*| 1.459| 1.197 – 1.778|
| Age                                              | −0.213| 0.103| 4.290 | 0.038*| 0.808| 0.660 – 0.989|
| Incomplete KD                                     | 0.683| 0.116| 34.557| 0.000*| 1.980| 1.577 – 2.486|
| Corticosteroid therapy                            | 0.317| 0.343| 0.853 | 0.356 | 1.373| 0.701 – 2.688|
| Total fever duration                              | 0.032| 0.011| 7.796 | 0.005*| 1.032| 1.010 – 1.056|
| Days of illness at the initial treatment          | 0.023| 0.011| 4.394 | 0.036*| 1.023| 1.002 – 1.046|
| IVIG treatment resistance                        | 0.185| 0.110| 2.840 | 0.092 | 1.203| 0.970 – 1.492|
| Sodium                                           | 0.015| 0.070| 0.047 | 0.828 |      |            |
| WBC                                              | −0.034| 0.101| 0.115 | 0.735 | 0.966| 0.793 – 1.177|
| CRP                                              | 0.285| 0.091| 9.809 | 0.002*| 1.330| 1.113 – 1.589|
| PLT                                              | 0.059| 0.089| 0.049 | 0.812 | 1.040| 0.873 – 1.239|
| Albumin                                          | 0.135| 0.083| 2.623 | 0.105 | 1.144| 0.972 – 1.347|

*P<0.05 was considered statistically significant. KD: Kawasaki disease; IVIG: Intravenous immunoglobulin; WBC: White blood cell count; CRP: C-reactive protein; PLT: Platelet count; SE: Standard error; OR: Odds ratio; CI: Confidence interval.

Table 3: Risk factors for coronary artery dilatations from multivariable logistic regression analysis

| Independent variables                              | B    | SE   | Wald  | P     | OR   | 95% CI     |
|--------------------------------------------------|------|------|-------|-------|------|------------|
|                                                   |      |      |       |       |      |            |
| Sex                                              | 0.360| 0.103| 12.183| 0.000*| 1.434| 1.171 – 1.755|
| Age                                              | −0.133| 0.107| 1.550 | 0.213 | 0.876| 0.711 – 1.079|
| Incomplete KD                                     | 0.697| 0.124| 31.836| 0.000*| 2.008| 1.576 – 2.558|
| Total fever duration                              | 0.037| 0.017| 4.794 | 0.029*| 1.037| 1.004 – 1.072|
| Days of illness at the initial treatment          | −0.013| 0.016| 0.681 | 0.490 | 0.987| 0.956 – 1.019|
| CRP                                              | 0.295| 0.093| 10.121| 0.001*| 1.343| 1.120 – 1.611|

*P<0.05 was considered statistically significant. KD: Kawasaki disease; CRP: C-reactive protein; SE: Standard error; OR: Odds ratio; CI: Confidence interval.

Table 4: Risk factors for CAAs from univariate logistic regression analysis

| Independent variables                              | B    | SE   | Wald  | P     | OR   | 95% CI     |
|--------------------------------------------------|------|------|-------|-------|------|------------|
|                                                   |      |      |       |       |      |            |
| Sex                                              | 0.447| 0.160| 7.794 | 0.005*| 1.564| 1.143 – 2.141|
| Age                                              | 0.015| 0.161| 0.008 | 0.927 | 1.015| 0.740 – 1.392|
| Incomplete KD                                     | 1.060| 0.156| 45.974| 0.000*| 2.885| 2.124 – 3.919|
| Corticosteroid therapy                            | 1.256| 0.374| 11.277| 0.001*| 3.511| 1.687 – 7.306|
| Total fever duration                              | 0.157| 0.014| 122.889| 0.000*| 1.170| 1.138 – 1.203|
| Days of illness at the initial treatment          | 0.134| 0.014| 92.430| 0.000*| 1.144| 1.113 – 1.175|
| IVIG treatment resistance                        | 0.428| 0.158| 7.321 | 0.007*| 1.534| 1.125 – 2.092|
| Sodium                                           | 0.668| 0.094| 50.318| 0.000*| 1.951| 1.622 – 2.346|
| WBC                                              | 0.211| 0.166| 1.630 | 0.202 | 1.235| 0.893 – 1.709|
| CRP                                              | 0.219| 0.143| 2.340 | 0.126 | 1.245| 0.940 – 1.649|
| PLT                                              | 0.169| 0.137| 1.536 | 0.215 | 1.184| 0.906 – 1.548|
| Albumin                                          | 1.027| 0.133| 59.409| 0.000*| 2.794| 2.151 – 3.628|

*P<0.05 was considered statistically significant. CAAs: Coronary artery aneurysms; KD: Kawasaki disease; IVIG: Intravenous immunoglobulin; WBC: White blood cell count; CRP: C-reactive protein; PLT: Platelet count; SE: Standard error; OR: Odds ratio; CI: Confidence interval.
that corticosteroid therapy is restricted to children in whom two or more infusions of IVIG have been ineffective in alleviating fever and acute inflammation. Newburger et al.\textsuperscript{[15]} reported a prospective study that showed that compared with children receiving placebo, children receiving intravenous methylprednisolone for the initial therapy had a shorter initial period of hospitalization, lower erythrocyte sedimentation rate, and lower CRP level but a similar incidence of CALs. Miura et al.\textsuperscript{[16,17]} revealed that intravenous methylprednisolone therapy for KD children who were unresponsive to the initial IVIG suppressed cytokine levels faster and suppressed the recurrence of fever. Ogata et al.\textsuperscript{[18]} reported that methylprednisolone therapy (30 mg·kg\textsuperscript{-1}·d\textsuperscript{-1} for 3 days) was useful in reducing the fever duration and medical costs for KD children who were unresponsive to the initial IVIG treatment. Methylprednisolone therapy and additional IVIG treatment were not significantly different in preventing the development of CAAs. In a retrospective study of 359 children with KD who were unresponsive to the initial IVIG, Kobayashi et al.\textsuperscript{[19]} noted that CALs up to 1 month after treatment were less common in the IVIG + prednisolone group than in the IVIG

### Table 5: Risk factors for giant CAAs from univariate logistic regression analysis

| Independent variables          | B   | SE   | Wald | P      | OR       | 95% CI Lower | 95% CI Upper |
|-------------------------------|-----|------|------|--------|----------|--------------|--------------|
| Sex                           | 1.135 | 0.521 | 4.743 | 0.029* | 3.112    | 1.120        | 8.645        |
| Age                           | 0.118 | 0.439 | 0.072 | 0.789  | 1.125    | 0.476        | 2.659        |
| Incomplete KD                 | 1.024 | 0.398 | 6.611 | 0.010* | 2.785    | 1.276        | 6.080        |
| Corticosteroid therapy        | 2.022 | 0.634 | 10.186 | 0.001* | 7.557    | 2.182        | 26.165       |
| Total fever duration          | 0.161 | 0.024 | 46.391 | 0.000* | 1.142    | 1.096        | 1.191        |
| Days of illness at the initial treatment | 0.133 | 0.021 | 39.439 | 0.000* | 1.142    | 1.096        | 1.191        |
| IVIG treatment resistance     | 0.664 | 0.398 | 7.241 | 0.007* | 2.492    | 1.281        | 4.845        |
| Sodium                        | 0.392 | 0.253 | 2.397 | 0.122  | 1.480    | 0.901        | 2.430        |
| WBC                           | −0.247 | 0.424 | 0.338 | 0.561  | 0.782    | 0.340        | 1.794        |
| CRP                           | 0.546 | 0.393 | 1.931 | 0.165  | 1.727    | 0.799        | 3.733        |
| PLT                           | 0.289 | 0.363 | 6.35  | 0.246  | 1.336    | 0.655        | 2.723        |
| Albumin                       | 0.913 | 0.339 | 7.241 | 0.007* | 2.492    | 1.281        | 4.845        |

*P<0.05 was considered statistically significant. CAAs: Coronary artery aneurysms; KD: Kawasaki disease; IVIG: Intravenous immunoglobulin; SE: Standard error; OR: Odds ratio; CI: Confidence interval.

### Table 6: Risk factors for CAAs from multivariable logistic regression analysis

| Independent variables          | B   | SE   | Wald | P      | OR       | 95% CI Lower | 95% CI Upper |
|-------------------------------|-----|------|------|--------|----------|--------------|--------------|
| Sex                           | 0.354 | 0.174 | 4.151 | 0.042* | 1.425    | 1.014        | 2.003        |
| Incomplete KD                 | 0.694 | 0.180 | 14.928 | 0.000* | 2.001    | 1.408        | 2.846        |
| Corticosteroid therapy        | 1.052 | 0.439 | 5.734 | 0.017* | 2.864    | 1.210        | 6.777        |
| Days of illness at the initial treatment | 0.087 | 0.021 | 17.014 | 0.000* | 1.091    | 1.047        | 1.137        |
| Total fever duration          | 0.075 | 0.022 | 11.553 | 0.001* | 1.078    | 1.032        | 1.126        |
| IVIG treatment resistance     | 0.209 | 0.194 | 0.283 | 0.648  | 1.232    | 0.842        | 1.802        |
| Sodium                        | 0.294 | 0.125 | 5.509 | 0.019* | 1.341    | 1.050        | 1.714        |
| Albumin                       | 0.742 | 0.173 | 18.395 | 0.000* | 2.101    | 1.496        | 2.949        |

*P<0.05 was considered statistically significant. CAAs: Coronary artery aneurysms; KD: Kawasaki disease; IVIG: Intravenous immunoglobulin; SE: Standard error; OR: Odds ratio; CI: Confidence interval.

### Table 7: Risk factors for giant CAAs from multivariable logistic regression analysis

| Independent variables          | B   | SE   | Wald | P      | OR       | 95% CI Lower | 95% CI Upper |
|-------------------------------|-----|------|------|--------|----------|--------------|--------------|
| Sex                           | 1.065 | 0.572 | 3.462 | 0.063  | 2.899    | 0.945        | 8.898        |
| Incomplete KD                 | 0.201 | 0.498 | 0.163 | 0.686  | 1.223    | 0.461        | 3.246        |
| Corticosteroid therapy        | 2.118 | 0.721 | 8.632 | 0.003* | 8.315    | 2.024        | 34.158       |
| Total fever duration          | 0.056 | 0.037 | 2.279 | 0.131  | 1.058    | 0.983        | 1.138        |
| Days of illness at the initial treatment | 0.106 | 0.031 | 11.660 | 0.001* | 1.112    | 1.046        | 1.181        |
| Albumin                       | 0.867 | 0.355 | 5.960 | 0.015* | 2.379    | 1.186        | 4.770        |

*P<0.05 was considered statistically significant. CAAs: Coronary artery aneurysms; KD: Kawasaki disease; SE: Standard error; OR: Odds ratio; CI: Confidence interval.
group \((P = 0.005)\) and the pravastatin group \((P = 0.01)\). IVIG + prednisolone may be superior to prednisolone or IVIG as a first-line rescue therapy for children with KD who were unresponsive to IVIG. Teraguchi et al.\(^2\) showed that the changes in WBC, CRP, and albumin were significantly greater in Group A (receiving methylprednisolone pulse therapy) than in Group B (receiving the second IVIG) for IVIG nonresponders. However, the prevalence of CALs did not differ between the groups \((36% \text{ in Group A and } 26\% \text{ in Group B, } P > 0.05)\). Methylprednisolone pulse therapy did not reduce the risk for the development of CALs and did not seem to be beneficial as a single-agent therapy for IVIG-resistant KD. Millat et al.\(^3\) reviewed the experience of 80 children with CAAs after KD, among whom 19 children received corticosteroids in the acute phase. The corticosteroid-treated group and noncorticosteroid-treated group had similar CAA Z-scores at baseline \((P > 0.05)\); however, 2–3 months and 1 year after the acute phase, the CAA Z-scores decreased in children not only treated with corticosteroids but also progressed for those treated with corticosteroids. Their study showed that use of corticosteroids for children with KD may aggravate CALs and cause impaired vascular remodeling.

At present, the relation between corticosteroid therapy and CALs in children with KD has not yet been clarified. Most studies showed that corticosteroid therapy cannot reduce the incidence of CALs. The present study was a retrospective study with a large sample. We found that corticosteroid therapy was an independent risk factor for the development of CAAs, especially giant CAAs, by analyzing 12 factors that might be associated with CALs in children with KD. The children who received corticosteroids were nonresponders to IVIG and had more severe disease, which increases their risk for CALs; thus, we put some potentially confounding variables that may reflect the group who received corticosteroids into the statistical model (such as total fever duration and IVIG treatment resistance). After adjusting for these confounding variables, corticosteroid therapy was still an independent risk factor for CAAs, especially giant CAAs. In the 523 IVIG-resistant children, the incidence of CALs and CAAs in the corticosteroid group was significantly higher than in the noncorticosteroid group \((P < 0.05)\).

Currently, the first dose of IVIG is well-established whereas corticosteroid or additional IVIG for IVIG-resistant children requires further investigation. The safety and efficacy of corticosteroid therapy in children with KD are still uncertain.\(^2\) Thus, larger, prospective, multicenter controlled trials are needed.

The incidence of CALs in our study was higher than that reported in the literature. This may be because many children with severe KD or those with unsuccessful treatment from other hospitals were referred to our hospital. In addition, the diagnosis standard of CALs established by the Japanese Ministry of Health was not based on the patients’ age or body size and also did not distinguish between different coronary artery branches, thus resulting in possible missed diagnoses of CALs.

This study had some limitations. First, bias may have occurred because of the retrospective design. Second, measurement of the coronary internal diameter by means of echocardiography was not done by the same ultrasound technologists, and this may have affected the accuracy of the results.

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**Conflicts of interest**

There are no conflicts of interest.

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