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MAJOR ARTICLE

Coronary Artery Outcomes in Kawasaki Disease by Treatment Day Within 10 Days of Fever Onset

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Background. Kawasaki disease (KD) is an acute febrile illness of childhood that can lead to coronary artery aneurysms (CAAs) and myocardial infarction. Intravenous immunoglobulin reduces the prevalence of CAA when given to patients with KD within 10 days of fever onset. Children with KD may undergo evaluation for other diagnoses before treatment, particularly those with incomplete KD criteria. If KD outcomes are improved with early treatment, a delay in treatment while evaluating for other causes might place these patients at risk.

Methods. We performed a retrospective cohort study of children treated for KD within the first 10 days of illness at our KD center from 2014 to 2021 to determine the prevalence of CAA by day of treatment.

Results. A total of 290 patients met the study criteria. No statistically significant difference was found in the odds of developing a maximum z score $\geq$2.5 for each day of delayed treatment within 10 days of fever onset (adjusted odds ratio, 0.87; 95% CI, .72–1.05; $P = .13$). Subgroup analyses by age, sex, and year of treatment did not reveal a significant association between treatment day and maximum z score $\geq$2.5, although the number of patients <6 months of age was small.

Conclusions. Our study supports current recommendations. We found similar odds of developing adverse coronary outcomes regardless of treatment day within 10 days from fever onset.

Keywords. coronary artery aneurysms; Kawasaki disease; treatment day; treatment outcomes; coronary artery Z-scores.

Kawasaki disease (KD) is an acute febrile illness of young children that can lead to coronary artery aneurysms (CAAs) with the potential for myocardial infarction, aneurysm rupture, and sudden death [1, 2]. Randomized controlled trials have shown that intravenous immunoglobulin (IVIG) treatment is effective in reducing the prevalence of CAAs when given to patients with KD by the 10th day after fever onset [2]. However, it is unclear whether treatment earlier than the 10th day improves outcomes. Some studies have suggested that later treatment within the 10-day window increases the risk of adverse coronary artery outcomes [3–5]. We performed this retrospective single-center study to determine whether CAA prevalence varied when treatment was administered during the first 10 days of illness.

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METHODS

Study Design and Location

This retrospective cohort study included patients diagnosed with KD at the Ann & Robert H. Lurie Children's Hospital of Chicago at 4 to 10 days after fever onset from 2014 to 2021. This study was approved by the Lurie Children's Institutional Review Board.

Data Collection

Patient data were extracted from electronic medical records, and information was collected that included date of birth, date of KD diagnosis, date of first IVIG treatment, number of IVIG treatments, date of fever onset, race/ethnicity, sex, clinical features, blood test values, and echocardiography results. Date of fever onset was obtained from patient history. Z scores were calculated by using the Boston model for the right coronary artery and left anterior descending coronary artery, via methods uniformly employed for echocardiography reading at Lurie Children's Hospital [6]. Maximum (max) z score for each patient was defined as the larger of the left anterior descending or right coronary artery z score documented within the first 2 months after fever onset. Per American Heart Association (AHA) recommendations, we did not include left main coronary artery measurements in this study [2]. The echocardiogram performed on the day of initial IVIG treatment was defined as the baseline echocardiogram. If a study was not

performed on the day of initial treatment, we considered studies done 1 to 2 days before or 1 to 3 days after treatment as baseline studies, similar to prior studies [7]. Baseline coronary artery diameter z score was defined as the initial z score for the artery that developed the max z score. Age group was categorized as <6 months, ≥6 months and <1 year, ≥1 and <8 years, and ≥8 years, in accordance with potential variation in risk of adverse coronary artery outcomes by age [2]. Race and ethnicity were described as White, Black, Asian, Hispanic, more than 1 race, or unknown. Patients were diagnosed with classic KD or incomplete KD per AHA criteria [2]. Final data extraction was on 14 October 2022.

Statistical Analysis

The independent variable for this study was days between fever onset and IVIG treatment. We used AHA criteria to define CAA as a coronary artery z score ≥2.5 [8]. Descriptive statistics were calculated for the independent and outcome variables. Because previous studies have shown baseline z scores to be predictive of development of CAA [7], we utilized descriptive statistics to compare baseline z score by day of IVIG treatment. Patient characteristics were compared between treatment days: sex, age group, race/ethnicity, clinical presentation (classic or incomplete), and initial laboratory tests (white blood cell count, C-reactive protein, and serum albumin). For this analysis, patient characteristics were summarized by mean and SD or number and percentage as appropriate. One-way analysis of variance tests were used to check for differences in the mean baseline z score and the mean max z score across treatment days within subgroups of age and sex.

A cumulative distribution function of day from fever onset to IVIG treatment was graphed. An analysis was conducted to evaluate max z score by day of treatment in patients with a max z score ≥2.5. Since a coronary artery z score ≥2.5 is a clinically relevant outcome, we utilized a dichotomized outcome variable for the development of CAA. Logistic regression analysis was used to evaluate the association between day of treatment and a max z score ≥2.5. In this analysis, we limited adjustment of confounders to well-studied variables, including age and sex [2, 9]. In our analyses, model 1 was crude; model 2 adjusted for age; model 3 adjusted for sex; and model 4 adjusted for age and sex. Interaction terms were added to model 4 to test for effect modification by age and sex in the association between day of treatment and a max z score ≥2.5. The analyses were repeated with a max z score ≥5.0 to include medium and large aneurysms by AHA criteria, which are associated with most adverse outcomes in KD. We also conducted similar logistic regression analyses stratifying by sex and age group, as defined previously. Finally, we conducted a similar analysis stratifying by treatment before or after 2017 to determine the effect of increased use of primary corticosteroid adjuvant therapy in high-risk KD treatment protocols. We conducted secondary analyses in patients who had a normal z score at baseline, received corticosteroids, and received more than 1 dose of IVIG.

RESULTS

Patient Demographic and Clinical Features

Of the initial 411 patients whose charts were examined, 121 (29.4%) were excluded. Exclusions were for those with an unclear final diagnosis (n = 3), KD diagnosis and treatment <4 days from fever onset (n = 4), unclear date of fever onset (n = 16), missing baseline or follow-up echocardiography information (n = 30), and KD diagnosis >10 days from fever onset (n = 68). Therefore, 290 patients were included in this study. Out of the total study population, 19 (6.6%) patients had a baseline echocardiography study 1 to 2 days before IVIG treatment, 200 (70.0%) had the baseline study on the day of IVIG treatment, 66 (22.8%) had a baseline study 1 to 2 days after IVIG treatment, and 5 (1.7%) had a baseline study 3 days after IVIG treatment.

Patient demographic and laboratory data are listed in Supplementary Table 1 and were similar to those reported in large KD studies [10, 11]. The mean number of days from fever onset to IVIG treatment was 6.7. Incomplete KD was common in this cohort (n = 162, 55.9%), similar to incomplete KD prevalence in reports from other large children's hospitals [11, 12]. To further ensure that our KD population was similar to others previously reported, we determined whether sex and age, 2 risk factors for the development of CAAs, were associated with this outcome in our population. In our study, a regression model not adjusting for treatment day showed that males had an odds ratio (OR) of 1.6 for a max z score ≥2.5 as compared with females, although this did not reach statistical significance (OR, 1.60; 95% CI, .90–2.85; $P = .11$). An unadjusted logistic regression revealed a significantly higher odds of developing a max z score of at least 2.5 among patients aged <6 months when compared with those ≥1 and <8 years old (OR, 4.76; 95% CI, 1.82–12.45; $P = .001$; Supplementary Table 2). These results showed that our KD population had features similar to those previously reported [2, 13–15].

Max Coronary Artery *Z* Score Was Not Associated With Treatment Day in the Study Population

All patients had at least 2 echocardiograms performed (baseline and 2–3 weeks after fever onset), and 275 (94.8%) had >3 echocardiograms performed. The mean baseline z score was 1.2. There were 6 patients with a baseline z score ≥5, indicating a medium- or large-sized aneurysm: 1 who presented on day 6, 2 on day 7, 2 on day 9, and 1 on day 10. The mean max z score among all patients in the study was 1.9. There were no statistically significant differences in mean max z score by day of treatment between 4 and 10 days after illness onset ($P = .29$) or

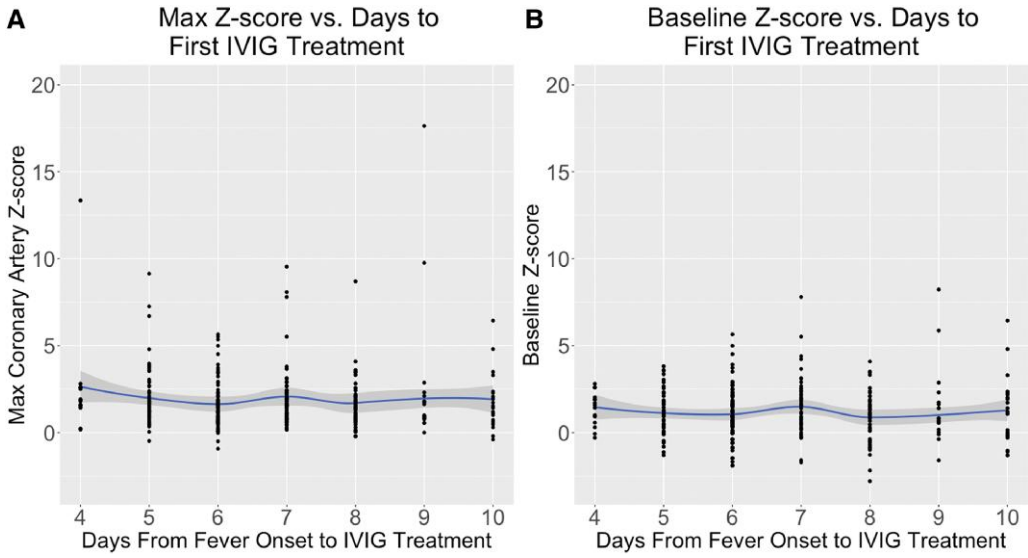

Figure 1. Maximum and baseline coronary artery *z* score by treatment day. No significant difference was found in either (*A*) the mean maximum *z* scores or (*B*) the mean baseline *z* scores by treatment day ($P = .29$ and $P = .49$, respectively). Gray shading, 95% CI. IVIG, intravenous gammaglobulin.

mean baseline *z* score among treatment days ($P = .49$; Figure 1*A* and 1*B*). Of the 245 patients with a normal baseline *z* score, 127 developed an increase in *z* score on subsequent echocardiogram, and 19 developed a max *z* score of at least 2.5 (7.8%). On sensitivity analysis, there was no association between day of treatment and development of CAA in those who had a normal baseline *z* score (Supplementary Table 3).

Subgroup Analyses by Sex, Age, or Classic/Incomplete Presentation Did Not Reveal Any Relationship Between Max Coronary Artery *Z* Score and Treatment Day

We evaluated for differences in mean baseline *z* scores and mean max *z* scores by treatment day for male vs female patients (Figure 2*A* and 2*C*) and found no statistically significant differences. No significant differences were found in either the mean max *z* scores or the mean baseline *z* scores by treatment day for patients within age groups ≥6 months and <1 year, ≥1 year and <8 years, and ≥8 years (Figure 2*B* and 2*D*). There were too few patients in the <6-month age group to draw conclusions about risk of coronary artery abnormalities by treatment day (n = 1, day 4; n = 3, day 5; n = 7, day 6; n = 3, day 7; n = 3, day 8; n = 1, day 9; n = 1, day 10). Supplementary Table 1 and Figure 3*A* demonstrate that patients with a classic KD presentation were treated earlier in the illness than patients who presented with incomplete KD. This was likely because of the more rapid diagnosis of KD in patients with classic diagnostic criteria. Max *z* score by treatment day was similar for patients with classic and incomplete KD (Figure 3*B*). There was no association between race/ethnicity and treatment (data not shown). We also analyzed initial laboratory values for white blood cell count, C-reactive protein, and albumin and found no significant differences by treatment day even when adjusting for age (data not shown).

Subgroup Analyses of Children With CAAs of Varying Severity Do Not Reveal Any Association Between Max *Z* Score and Treatment Day

Supplementary Figure 1 demonstrates a lack of association between max *z* score and treatment day in the subset of the patient population (n = 64) who developed a max *z* score ≥2.5. Patients who had a max *z* score <2.5 and those with a max *z* score ≥2.5 showed a similar cumulative distribution of days from fever onset to treatment (Figure 4). Analyses by logistic regression revealed no statistically significant differences in the odds of developing a max *z* score ≥2.5 by each day of treatment within 10 days from fever onset (Table 1). These results persisted after adjusting for age and sex (Table 1, models 2–4). To determine whether patients were at increased risk for more severe CAAs (medium or large aneurysms), we also performed secondary analyses using a max *z* score of 5.0 and found no association with treatment day (within 10 days of fever onset), even after adjustment for covariates (Supplementary Table 4). Finally, when analyzing for increasing utilization of primary adjunctive corticosteroid therapy for high-risk KD treatment [2], we found no difference in the association of day of treatment with max *z* score ≥2.5 when comparing the years 2014–2017 vs 2018–2021 (Supplementary Table 5*A* and 5*B*). When doing a secondary analysis limited to children who received corticosteroids (n = 105), we similarly found no difference in max *z* score by day of IVIG treatment (Supplementary Table 6). A similar analysis was conducted for the 72 patients who received more than 1 dose of IVIG treatment, which yielded similar results (Supplementary Table 7).

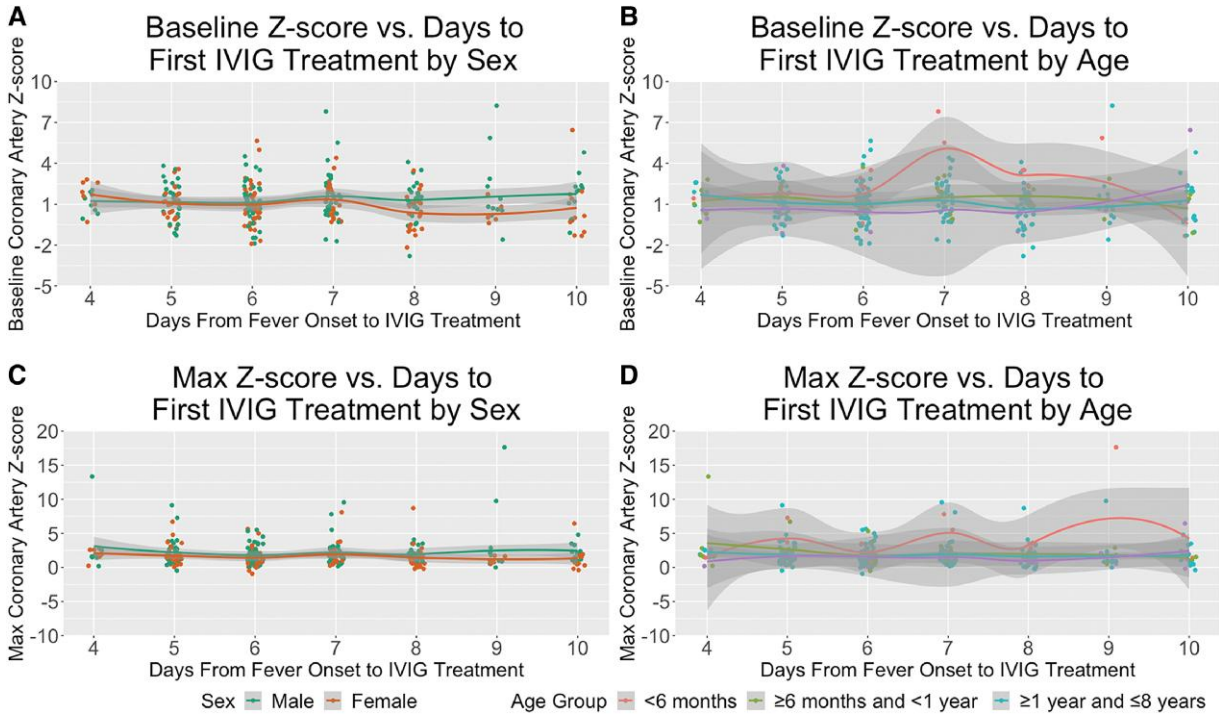

Figure 2. *Z* score vs days to first IVIG treatment by age and sex. No significant differences were found in either (*A*) the mean baseline *z* scores or (*C*) the mean maximum *z* scores by treatment day when grouped by sex. No differences were identified in either (*B*) the mean baseline *z* scores or (*D*) the mean maximum *z* scores by treatment day within 3 age groups: ≥6 months and <1 year, ≥1 and <8 years, and ≥8 years. No conclusions could be drawn for the <6-month age group due to the small number of patients. Gray shading, 95% CI. IVIG, intravenous gammaglobulin.

DISCUSSION

Diagnosing KD can sometimes be difficult, especially in patients with incomplete presentations, and evaluation for alternative diagnoses is routine in these cases. However, a study from China by Li et al reported a higher prevalence of CAA at 1 month in patients with KD treated on days 8 to 10 (6.4%) as compared with days 5 to 7 (1.7%), suggesting that therapy by day 7 might be optimal and that awaiting results of testing for other etiologies might put a child with KD at risk [4]. Two other studies suggested that earlier treatment leads to better outcomes, but these studies included patients treated after day 10 [3, 5]. In our study, the prevalence of max *z* score ≥2.5 was 22.3% (43/189) in patients treated on days 5 to 7 and 18.6% (16/86) in patients treated on days 8 to 10 (Supplementary Table 3), which does not support the concept that treatment by day 7 results in improved outcomes. This difference in the prevalence of CAA between our study and that of Li et al could reflect demographic differences, different methods to calculate *z* scores, or other unknown factors. Of the 64 patients in our study with CAA, 45 (70%) had abnormalities at diagnosis. This is similar to findings in previous studies showing that a majority of patients with KD who develop CAA have coronary artery dilation at diagnosis [10, 11], and these patients should be treated immediately.

Our study suggests that coronary artery inflammation in KD likely begins very early in the disease process, although the resulting dilation is most apparent by echocardiography at 2 to 3 weeks after fever onset. IVIG is effective in reducing further coronary artery dilation—and thus the overall prevalence of coronary artery dilation—but likely does not completely ameliorate the inflammatory process. Most of our patients already had coronary abnormalities at diagnosis, even prior to day 7, likely accounting for the lessened impact of treatment by day of illness in our cohort.

Our study has several limitations. These include those inherent to a retrospective study design. Additionally, we had fewer patients treated on days 9 to 10 than on day 8 or earlier, but the outcome measure of max *z* score ≥2.5 was similar in patients treated on days 9 to 10 (18%) as compared with the total group (22%). Because KD is a clinical diagnosis and shares features with many other infectious and inflammatory illnesses of childhood, some patients may have been misdiagnosed, but we utilized robust inclusion and exclusion criteria to reduce this possibility. Stringent clinical decision making was utilized to distinguish children with KD from those with multisystem inflammatory syndrome in children (MIS-C) due to SARS-CoV-2. Children were diagnosed with MIS-C if they had typical features of this entity that are rare in KD,

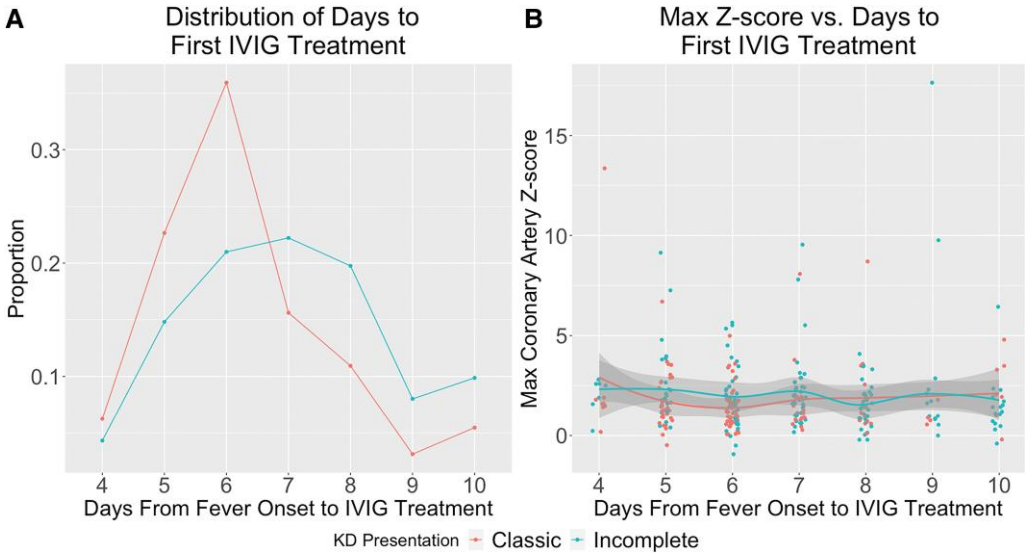

Figure 3. Treatment day and maximum *z* score in classic and incomplete KD. *A*, Patients with classic KD were treated at a mean of day 7, while those with incomplete KD were treated at a mean of day 8. *B*, Patients with classic and incomplete KD presentations had similar maximum *z* scores by treatment day. Gray shading, 95% CI. IVIG, intravenous gammaglobulin; KD, Kawasaki disease.

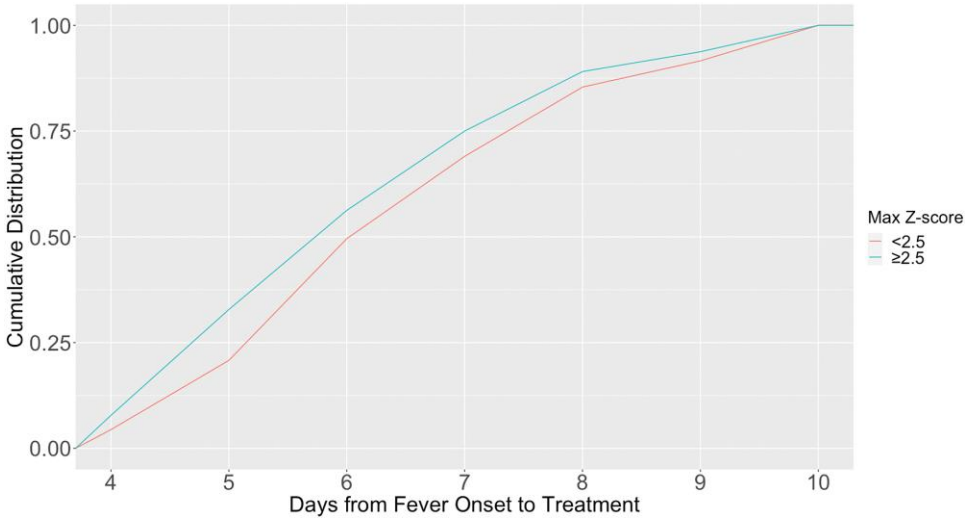

Figure 4. Cumulative distribution of day from fever onset to intravenous gammaglobulin treatment. Similar cumulative distributions of days from fever onset to treatment were seen between patients who had a maximum *z* score <2.5 and those with a maximum *z* score ≥2.5.

such as hypotension, myocardial dysfunction, prominent gastrointestinal symptoms, age >5 years, and lymphopenia. However, it is possible that an occasional patient with a milder form of MIS-C was misdiagnosed with KD. Our center is highly experienced in diagnosing and treating KD, and patients may have been treated earlier in their disease course than they might have at other centers. We had a relatively small sample size of patients with large/giant aneurysms and relatively few patients <6 months of age. Beginning in 2017, our center has treated children whom we deem to be at high risk for adverse outcomes of KD with adjunctive primary therapy comprising IVIG and corticosteroid [16], potentially affecting their max *z* scores. Yet, one study did not reveal a reduction in max coronary artery *z* scores with adjunctive corticosteroid therapy for high-risk patients in the United States, instead showing benefit in CAA regression once formed [17]. Similarly, multiple analyses in our study showed no difference in association of day of treatment with max *z* score in patients

Table 1. Odds Ratios of Maximum *Z* Score ≥2.5 by Days From Fever Onset to Intravenous Gammaglobulin Treatment

		Odds Ratio (95% CI)			
No. of Patients	No. of Outcomes[a]	Model 1	Model 2	Model 3	Model 4
290	64	0.87 (.72–1.04)	0.87 (.73–1.05)	0.87 (.72–1.04)	0.87 (.72–1.05)

Model 1: crude. Model 2: adjusted for age. Model 3: adjusted for sex. Model 4: adjusted for age and sex.

[a]Maximum *z* score ≥2.5.

who received adjunctive corticosteroid treatment as compared with those who did not. Although our center began administering low-dose aspirin rather than high-dose aspirin to all patients with KD at diagnosis beginning in 2017, multiple studies indicate no effect of aspirin dose on coronary artery outcomes in KD [18–22]. Data on use of infliximab were not collected at the time of study analysis. At our center, though, infliximab is rarely used in patients with KD and only as a rescue treatment in patients who do not respond to IVIG and corticosteroid therapies. Parental recall of onset of fever could have been incorrect in some cases. Finally, this is a single-center study, and larger multi-institutional studies are needed to confirm our findings.

In conclusion, our study supports current recommendations by the AHA that children with KD should receive treatment within 10 days of fever onset. We did not identify increased risk of coronary artery abnormalities by day of treatment within that time frame in our study. Our study suggests that evaluating children with possible incomplete KD for other etiologies does not pose undue risk if treatment is administered within 10 days of fever onset for those without a clear alternative diagnosis. This excludes the rare patient with possible KD who presents in shock and patients with a coronary artery *z* score ≥2.5 at presentation, who should be treated immediately. Given the increased risk of adverse coronary artery outcomes for infants <6 months of age and the small sample size of this group in our study, it may be prudent to administer the earliest possible treatment in these patients.

Supplementary Data

Supplementary materials are available at the *Journal of The Pediatric Infectious Diseases Society* online (http://jpids.oxfordjournals.org). Supplementary materials consist of data provided by the author that are published to benefit the reader. The posted materials are not copyedited. The contents of all supplementary data are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the author.

Notes

Patient consent statement. Our study was deemed exempt by the institutional review board, not requiring patient consent.

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Potential conflicts of interest. All authors: No reported conflicts.

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