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Original article

Giant aneurysms: A gender-specific complication of Kawasaki disease?

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ABSTRACT

Background: Kawasaki disease (KD) is a pediatric vasculitis of unknown origin. Its main complication is the development of coronary artery aneurysms (CAA) with giant CAA at the end of the spectrum.
Methods: In this cohort study, we evaluated the association between patient characteristics and the development of giant CAA based on *z*-scores. Multivariable, multinomial logistic regression analysis was used to identify variables associated with giant CAA.
Results: A total of 301 KD patients, comprising 216 patients without enlargement, 45 with small-sized, 19 with medium-sized, and 21 with giant CAA with all echocardiographies at our center were retrospectively included. Remarkably, 95% of patients with giant CAA were boys. In addition to 'no/late intravenous immunoglobulin (IVIG) treatment', 'male gender' (OR 16.23, 95% CI 1.88–140.13), 'age < 1 year' (OR 7.49, 95% CI 2.29–24.46), and 'IVIG re-treatment (9.79, 95% CI 2.79–34.37)' were significantly associated with an increased risk of giant CAA, with patients without enlargement as reference. Compared to patients with medium-sized CAA, 'IVIG re-treatment' was significantly associated with giant CAA. The majority of giant CAA continued to increase in size during the first 40 days.
Conclusions: We identified risk factors associated with an increased risk of giant CAA. The difference in variables between the giant CAA group and the other CAA subgroups suggests a separation between patients with the treatment-resistant giant CAA and the other IVIG-responsive patients, in which gender may be factored as a most relevant genetic trait. The increase in size during the first 2 months indicates the need for repeated echocardiography.

Introduction

Kawasaki disease (KD) is a pediatric vasculitis mainly occurring in children under the age of 5 years. Even though the disease was first described in 1967, its origin is still unknown. The main complication of KD is the development of coronary artery aneurysms (CAA). Treatment with intravenous immunoglobulins (IVIG) has been found to significantly reduce the risk of CAA formation [1].

At the extreme end of the spectrum of CAA are giant CAA, which severely affect the prognosis of the patient due to a higher risk of myocardial ischemia, infarction, and death [2]. (Giant) CAA can be defined by Japanese criteria, which are based on the absolute diameter of the coronary artery [3]. For example, following this criterion, giant CAA are defined as a lumen of ≥8 mm. In the past years it has become clear that *z*-scores, diameters adjusted for basal body-surface area (BSA), may be a better measure for abnormality [4,5]. By using these *z*-scores, small dilatations and/or giant CAA can be classified as such in young children without being above the absolute diameter threshold [3].

Multiple studies have looked at risk factors for the development of giant CAA, yet all of these studies are performed in a Japanese population with the use of Japanese criteria for CAA, thus possibly

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excluding small children with giant CAA according to *z*-scores from the giant CAA group [6,7]. Also, studies have shown that Japanese risk factor scores, often used to determine treatment, have a low sensitivity to predict IVIG resistance in American and Western Mediterranean populations and differed substantially between ethnicities [8–10]. As a consequence, these risk factor scores will not apply to children with a Western background [11].

The aim of this study is thus to evaluate possible risk factors for giant CAA based on *z*-scores in a Western population of KD children as well as the location and rate of development following the onset of fever.

Materials and methods

Study population and data collection

The Academic Medical Center in Amsterdam (The Netherlands) is a tertiary referral center for patients with KD, and patients visit our multidisciplinary outpatient clinic for cardiologic and/or for (immunologic) long-term follow-up. It is also the primary center for echocardiography during the acute phase for children being admitted to hospitals in the proximity of our center. These hospitals do not have pediatric cardiologists available, and therefore refer children to our center for cardiac evaluation.

Patients with KD who visited our (multidisciplinary) outpatient clinic between January 1999 and December 2015 were eligible. Patients were included if their echocardiography monitoring during the acute phase and follow-up had been performed at our center.

We extracted retrospectively the clinical details from the medical records, i.e.: gender, age at disease onset, complete or incomplete disease presentation, treatment with IVIG including the day of first IVIG treatment, IVIG re-treatment, treatment with steroids, and presence of CAA. In our hospital, standard KD-therapy consists of a single IVIG dose of 2 g/kg, given over 8–12 h. The criteria for IVIG-retreatment are persisting or recurrent fever, 36–48 h after the original IVIG-treatment.

Coronary artery aneurysms

At our hospital, coronary arteries are routinely evaluated by two-dimensional echocardiography in the acute phase of KD, i.e. in the first week and second week. If no abnormalities were detected, another echocardiography is made in week 6, after 6–12 months, and every 3–5 years during follow-up. In case of an abnormality, echocardiography is repeated every 1 or 2 weeks, depending on the extent of the abnormality. All echocardiographies are performed by experienced pediatric cardiologists. From echocardiography reports, we registered information on CAA status. We specified CAA by the worst *z*-score within the first 6 weeks. BSA and *z*-scores were calculated according to the 'Boston method' [4,5]. The *z*-scores of the left main coronary artery (LMCA), right coronary artery (RCA), or left anterior descending artery (LAD) were calculated. *z*-Scores define small CAA as a *z*-score of 2.5–5, medium CAA as a *z*-score of 5–10, and giant CAA as a *z*-score of $\geq$10 or a diameter of $\geq$8 mm. If no exact diameters were available, we categorized these patients based on the description of the echocardiography report.

After the CAA status of all patients was established, we aimed to visualize the development of giant CAA, calculating the *z*-scores of the coronary arteries until the maximal *z*-score of the artery was reached during follow-up echocardiography during the (sub)acute stage of the disease. The *z*-scores were depicted against time, to evaluate how the size of the CAA evolved over time. Also, we aimed to determine on which day the CAA approximately crossed the line of a *z*-score of 10 and thus 'became giant'. Therefore, we assumed the *z*-score was zero before disease onset. By drawing a line from zero to the *z*-score at the first echocardiography and by connecting the *z*-scores from the different echocardiographies we estimated the days the CAA acquired the dimensions of a giant CAA (i.e. a *z*-score of $\geq$10).

Statistics

We compared demographic and clinical characteristics of patients with giant CAA with patients without enlargement, small CAA, or medium CAA by univariable multinomial logistic regression analyses. Variables included were complete or incomplete disease presentation, age, gender, IVIG re-treatment, and day of first IVIG treatment. IVIG treatment and timeliness of IVIG treatment were included because these variables are known to decrease the chances of developing CAA [1]. Other variables were chosen based on existing literature and clinical relevance [6,7].

Complete disease presentation was defined as the presence of 5 or more KD criteria. Age during day of onset was divided in 3 groups, i.e. $<$1 year, 1–5 years and $\geq$5 years. Day of first IVIG treatment was also subdivided in 4 categories; i.e. 1–5 days, 6–10 days, 11–15 days, and more than 15 days after disease onset or no IVIG treatment. Although it is possible that a late gift of IVIG will improve the course of already existing (giant) CAA, it is unlikely that it will prevent the development of such abnormalities all-together. Hence we believe that it will not influence the outcome of this study [12]. Therefore, we categorized all patients who received IVIG after day 15 in the same category as patients who did not receive IVIG at all.

Variables with a *p*-value of 0.2 or less from a univariable analysis were entered into a multivariable multinomial logistic regression model. Results are presented as odds ratios (OR) and their 95% confidence intervals (CI).

Statistical analyses were performed using SPSS version 22.0 software (SPSS Inc., Chicago, IL, USA).

Results

Study population

In total, 676 KD patients were followed-up at our center. We included those patients who obtained their echocardiographies in the acute phase at our center and these 301 KD patients comprised our study population. The remaining 375 patients obtained echocardiographies at other centers during the acute phase. The median (interquartile range, IQR) age of disease onset was 2.1 years (0.9–4.0 years) and 184 (61.1%) of patients were boys. Seventy-four percent of patients were of Caucasian or of mixed Caucasian (with one parent of another ethnicity) descent. The remaining patients were of Mediterranean (Turkish or Moroccan), Surinamese (Indo-Surinamese or African-American), or Asian descent. Of all children, 282 (93.7%) were treated with IVIG and out of these 282, 82% were treated within 10 days after disease onset; 20% received a second IVIG treatment and 7% received additional steroid treatment. Almost all children were treated with aspirin.

We were able to calculate *z*-scores in 271 patients. Of the remaining 30 patients the exact diameters were not recorded, but 29 were described as being normal and only 1 had been described as having a small dilatation. When adding these patients to the 'no enlargement' and the 'small-sized CAA group', respectively, 216 (71.8%) patients had no enlargement, 45 (15.0%) had small CAA, 19 (6.3%) had medium CAA, and 21 (7.0%) had giant CAA. In Fig. 1, boxplots of the median worst *z*-score with IQR of the 4 CAA subgroups are shown. Demographic and clinical characteristics according to the different subgroups are shown in Table 1.

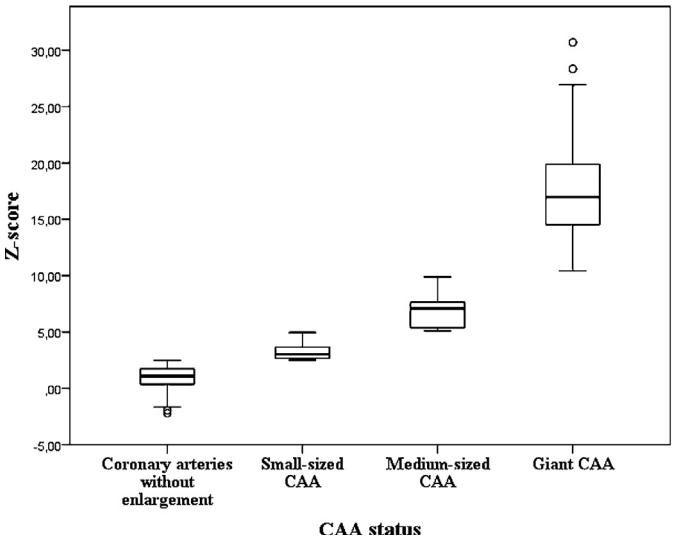

Fig. 1. Box plots of the *z*-max of all patients in the Kawasaki disease cohort. The box plots show the median and IQR, the *t*-bar represents the 5–95% interval, and the circles represent the outliers. CAA, coronary artery aneurysm; IQR, interquartile range.

Association between patient characteristics and giant CAA

We evaluated the association between patient characteristics and giant CAA. In Table 2, the ORs and their 95% CIs are shown for the different patient characteristics in patients with giant CAA compared with patients without enlargement, with small-sized CAA, and with medium-sized CAA. In multivariable analyses, 'male gender', 'young age (<1 year) during the acute disease', 'IVIG re-treatment', and 'IVIG treatment after day 10 (late treatment)' were significantly associated with an increased risk of developing a giant CAA, when compared to patients without enlargement. Compared with patients with small CAA, a young age, IVIG re-treatment, and treatment with IVIG after day 15 or no IVIG were significantly associated with an increased risk of developing giant CAA. Compared to patients with medium CAA, a second IVIG treatment was significantly associated with the development of giant CAA.

Since many patients did not receive IVIG within the recommended 10 days, we further explored the association between patient characteristics and giant CAA in patients who received IVIG treatment within 10 days. Since all of the remaining patients with giant CAA were boys, we performed this next analysis for males only. For this analysis, age was divided into a younger-than-1 and an older-than-1 group. Compared to patients without CAA, age < 1 year (OR 16.36, 95% CI 2.69–99.48, $p = 0.002$) and a second IVIG dose (OR 41.70, 95% CI 4.42–393.71, $p = 0.001$) were significantly associated with the development of giant CAA. This was similar when patients with giant CAA were compared to patients with small CAA (OR 9.36, 95% CI 1.41–62.37, $p = 0.021$ and OR 30.63, 95% CI 3.00–312.41, $p = 0.004$, respectively) and to patients with medium-sized CAA (OR 8.70, 95% CI 1.00–75.80, $p = 0.05$ and OR 19.30, 95% CI 1.52–244.77, $p = 0.02$).

Giant CAA: location and evolvement over time

We also studied the major braches of the coronary arteries separately in the patients with giant CAA to evaluate which of the coronary arteries were most often and most severely affected. The coronary arteries affected by giant CAA, their diameters, and corresponding *z*-scores are summarized in Table 3. The median diameter of all giant CAA was <8 mm, which indicates that part of these CAA would not have qualified as a giant CAA based on the criteria of the Japanese Ministry of Health [3]. The RCA was most often affected by a giant CAA, in 81% of all patients with giant CAA. The LAD was affected in 67%, and the LMCA in 43% of all patients with giant CAA. Seven patients also had dilatations of the left circumflex artery (LCX), although *z*-scores are not available for this artery. Nine patients also had small- or medium-sized CAA of the RCA or LMCA next to their giant CAA.

In Supplemental Table 1, the location of CAA and the presence of other, smaller CAA of the patients with giant CAA are shown. In Fig. 2 we plotted the *z*-scores separately against days since disease onset for the coronary arteries (A–C), the days from the onset of disease until these CAA had become giant (D) by extrapolating the available echocardiographic data as well as the distribution of coronary arteries affected by giant CAA (E). As can be observed in panels A-C, the majority of giant CAA continued to increase in size during the first 20–40 days and many CAA were not defined as giant at their first echocardiography. As can be observed in panel D, the median time of the LMCA to become giant (35 days, IQR 18–43 days) was longer than the median time of the RCA (17 days, IQR 11–22 days) and the LAD (14 days, IQR 10–17 days), although these numbers represent the maximum number of days of becoming giant. Especially for CAA that were already giant at the first echocardiography, it is not possible to know when the CAA developed; for the remaining CAA, the interval between 2 echocardiographies was often a whole week.

Discussion

We found that 'male gender', 'IVIG re-treatment', 'age < 1 year' in addition to 'late or no IVIG treatment' were significantly

Table 1
Demographic and clinical characteristics of the KD patients per CAA-group based on *z*-scores.

	No enlargement (*z*-score < 2.5) *n* = 216	Small CAA (*z*-score 2.5–5) *n* = 45	Medium CAA (*z*-score 5–10) *n* = 19	Giant CAA (*z*-score ≥10) *n* = 21
Male gender, no (%)	120 (55.6)	31 (69)	13 (68)	20 (95)
Age (years)[a]	2.4 (1.1–4.0)	1.9 (0.6–3.9)	1.6 (0.4–4.6)	0.8 (0.3–1.6)
Complete KD, no (%)	177 (81.9)	32 (73)	13 (68)	14 (67)
IVIG treatment, no (% treated)	199 (92)	42 (93)	19 (100)	21 (100)
Day of IVIG treatment[a,b]	7 (6–9)	6 (6–10)	8 (5–13)	11 (6–18)
IVIG re-treatment, no (%)	34 (15.7)	9 (22)	5 (26)	11 (52)
Steroid treatment, no (%)	5 (2.3)	5 (11)	3 (16)	8 (38)
Maximal *z*-score	1.1 (0.4–1.8)	3.0 (2.7–3.7)	7.0 (5.3–7.7)	17.0 (14.3–21.4)
Maximal diameter	2.4 (2.0–2.7)	3.3 (2.7–3.5)	4.0 (3.6–5.4)	6.5 (5.7–7.5)

[a] Median (interquartile range).
[b] Counted from the first day of fever.
CAA, coronary artery aneurysm; IVIG, intravenous immunoglobulin; KD, Kawasaki disease.

Table 2
Relationship between risk factors and the formation of giant CAA, compared to other CAA-groups.

	Univariate						Multivariate					
	No enlargement		Small CAA		Medium CAA		No enlargement		Small CAA		Medium CAA	
	OR (95%CI)	*p*-Value	OR (95% CI)	*p*-Value	OR (95% CI)	*p*-Value	OR (95%CI)	*p*-Value	OR (95% CI)	*p*-Value	OR (95% CI)	*p*-Value
Type of KD (reference: complete)												
In-complete	2.60 (0.98–6.93)	0.06	1.33 (0.43–4.10)	0.62	1.08 (0.29–4.08)	0.91	1.47 (0.41–5.32)	0.56				
Gender (reference: female)												
Male	16.00 (2.11–121.37)	0.007	9.03 (1.10–74.14)	0.04	9.23 (0.99–85.78)	0.05	16.23 (1.88–140.13)	0.01	7.80 (0.87–69.79)	0.07	7.06 (0.74–67.13)	0.09
IVIG re-treatment (reference: no re-treatment)												
Yes	5.86 (2.30–14.86)	<0.001	4.28 (1.39–13.20)	0.01	3.10 (0.81–11.68)	0.10	9.79 (2.79–34.37)	<0.001	8.26 (2.08–32.84)	0.003	4.93 (1.08–22.47)	0.04
Age (reference: age 1–5 years)												
Age <1 year	5.69 (2.14–15.13)	<0.001	2.67 (0.87–8.17)	0.09	1.86 (0.49–7.12)	0.37	7.49 (2.29–24.46)	0.001	3.91 (1.12–13.69)	0.03		
Age >5 years	0.70 (0.08–5.86)	0.74	0.55 (0.06–5.35)	0.61	0.38 (0.03–4.55)	0.45	0.43 (0.04–4.60)	0.48	0.34 (0.03–4.09)	0.40		
Day of IVIG (reference: Days 6–10)												
Days 3–5	2.24 (0.60–8.34)	0.23	1.67 (0.39–7.19)	0.49	1.07 (0.20–5.77)	0.94	1.65 (0.37–7.49)	0.51	1.21 (0.24–6.07)	0.82	0.85 (0.15–4.87)	0.86
Days 11–15	4.60 (1.19–17.79)	0.03	3.33 (0.68–16.32)	0.14	1.78 (0.28–11.12)	0.54	5.48 (1.08–27.95)	0.04	3.89 (0.66–22.85)	0.13	1.96 (0.29–13.21)	0.49
Day >15 or no IVIG	6.37 (1.97–20.60)	0.002	5.83 (1.36–24.94)	0.02	3.11 (0.56–17.33)	0.20	17.02 (3.40–85.08)	0.001	16.05 (2.82–91.20)	0.002	4.89 (0.75–31.82)	0.10

CAA, coronary artery aneurysm; CI, confidence interval; IVIG, intravenous immunoglobulins; KD, Kawasaki disease; OR, odds ratio.

associated with an increased risk of developing giant CAA when compared to patients without enlargement. Furthermore, we demonstrated that that giant CAA most frequently affect the RCA and that the majority of giant lesions continued to increase in the first 20–40 days after disease onset.

Multiple studies in Japan have studied risk factors for giant CAA. Nakamura et al. and Sudo et al. published 3 studies examining data from the 15th (1997–1998) plus 16th (1999–2000) and the 19th (2005–2006) nationwide surveys in Japan including children treated with IVIG within 10 days; and giant CAA were defined as having a diameter of ≥8 mm [6,7,13]. Although the data on gender remained inconclusive, these studies found 'young age' (i.e. <1 year) and a 'second IVIG dose' to be significantly associated with an increased risk of developing giant CAA.

We should notice that direct comparison of these Japanese studies with Western studies is difficult because of the possible differences in clinical practice and data analysis. The current treatment regimen for KD in Japan consists of a single, high dose infusion of IVIG [3,14]. Conversely, in the era of the before mentioned studies, not all children received IVIG or used the same IVIG dosing regimen due to the medical insurance system in Japan [6]. This is in part caused by the use of scoring systems for IVIG resistance, which are not applicable to patients with a Western background [6,11]. Finally, these studies defined giant CAA as an artery diameter of ≥8 mm. We used *z*-scores adjusted for BSA instead, which may be a better indicator of abnormality [4,5]. Also, in previous studies patients with giant CAA were compared with all other KD patients irrespective of their coronary status, whereas we compared patients with giant CAA separately to patient groups based on CAA-status to also explore differences between the CAA-groups. To our knowledge, this is the first study searching for risk factors for the development of giant CAA based on *z*-scores in a Western population.

Our data suggest that there is a dichotomy between patients with giant CAA versus the other patients with CAA. First of all, practically all patients with giant CAA were male, at an age that hormones cannot yet explain any of the differences among these subgroups with or without large CAA. Although other studies have also found a male predominance in patients with giant CAA (Supplemental Table 2), this was never as outspoken. The surprising finding that CD40 has been repeatedly indicated as a potential genetic risk allele in KD [15], may suggest that its ligand on T cells (i.e. CD40L) plays a role, being an X-linked gene and hence affecting the male disease condition more dominantly than

Table 3
Diameters and *z*-scores of giant CAA per coronary artery.

	Diameters (mm) of giant CAA[a]	*z*-Scores of giant CAA[a]	No. of patients with giant CAA[b]	No. of patients with medium CAA[b]	No. of patients with small CAA[a]
RCA	6.7 (5.5–8.0)	16.2 (13.2–18.3)	17		1
LMCA	6.5 (5.8–7.5)	12.5 (10.5–15.0)	9	6	3
LAD	5.7 (4.7–7.2)	16.6 (14.3–23.7)	14		
RCA/LMCA/LAD			6		
RCA/LAD			5		1
RCA/LMCA			2		

CAA, coronary artery aneurysm; LAD, left anterior descending artery; LMCA, left main coronary artery; RCA, right coronary artery.
Diameters and *z*-scores are shown as median (interquartile range).
[a] Maximal or worst-ever *z*-score.
[b] Four patients had a single giant CAA of the RCA, three of the LAD and one of the LMCA; six patients had a single medium CAA of the LMCA and two patients had a single small CAA of the LMCA

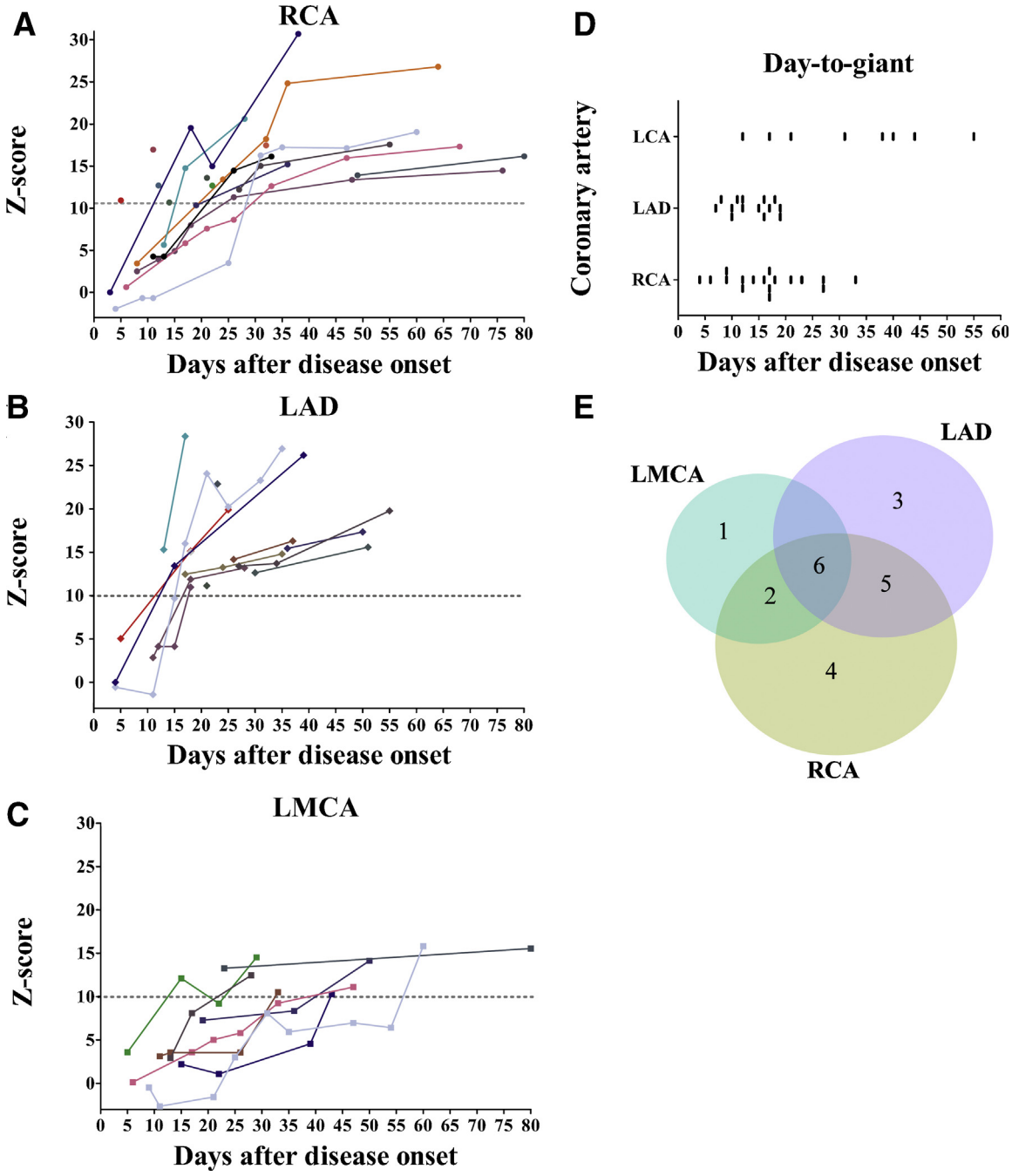

Fig. 2. *z*-Scores of the giant CAA until maximal *z*-score, day-to-giant and division of affected coronary arteries. (A–C) *z*-Scores of the giant CAA of the RCA, LAD, and LMCA, respectively, until the maximal *z*-score, against days since disease onset. Each color corresponds to one patient. (D) Approximate day of 'becoming giant' per coronary artery. (E) Venn-diagram of the distribution of the giant CAA of the 21 patients. The number corresponds to the number of patients with a giant CAA in that coronary artery. CAA, coronary artery aneurysm; LAD, left anterior descending artery; LMCA, left main coronary artery; RCA, right coronary artery.

in female patients. Secondly, patients with giant CAA received a second IVIG treatment far more often than all other CAA-positive patients, even when compared to patients with the larger medium-sized CAA. This implies that patients with giant CAA have a longer duration of fever, because a second IVIG-dose will be given for continued or recurrent fever, i.e. treatment-resistance. In 38% of all patients with giant CAA, patients received steroids after IVIG treatment, indicating that in a considerable proportion of children the duration of fever was truly extended. Whether this possible dichotomy – recognizing patients with giant CAA as a distinct subgroup – has a genetic base for the worst disease course in KD is unknown. Interestingly, our recent analysis of carotid intima-media thickness measurements performed in a large KD cohort also indicated that patients with giant CAA could be separated from the remainder of KD patients by their different behavior in progression in vascular wall changes over time [16].

The high percentage of unresponsiveness to IVIG in the giant CAA group asks for an improvement in primary therapy for severe KD cases. A recent meta-analysis showed that corticosteroids added to the initial gift of IVIG may have a beneficial effect [17]. However, the favorable outcome was only found in Japanese studies included in the review and was not found in two studies conducted in the USA. Thus, more research is needed to search for better and/or new primary treatment possibilities.

Most of the morbidity and mortality caused by KD are linked to giant CAA [2,18]. Results of a recent study showed that none of the giant CAA of ≥8 mm in their cohort regressed and ischemia event-free survival rates were 0.63 and 0.36 at 10 and 20 years, which was not altered by the implementation of IVIG therapy as standard care [19]. These studies indicate the impact and severity, but also show that a group of children may develop giant CAA irrespective of IVIG administration. Moreover, in our study, the progressive nature in size of many of the giant CAA lesions over time was remarkable, which is in line with a recent study reporting on coronary artery change beyond 1 month after disease onset [20]. This again reinforces that repeated echocardiography is necessary, also if CAA are not marked as 'giant' during the first echocardiography, and especially if fever did not resolve by IVIG (treatment refractoriness).

In our study >80% of our giant CAA group had giant CAA of the RCA, which seems in line with the results of a study from 1994 [21]. Findings of this study, mostly from the pre-IVIG era, showed that in 170 KD patients who had undergone myocardial revascularization, 70% had giant lesions in the RCA, 53% in the LAD, and 45% in the LMCA [21]. An explanation for the predilection for the larger lesions in the RCA is unclear to date. For instance, both sides of the coronary tree are considered to be of the same origin, making a predilection for 1 side unlikely [22]. Whether increased vulnerability of the RCA may relate to differences in the systolic pressure waves through the coronary vasculature, or the movement of the right ventricle causing more traction on the RCA compared to the LMCA and LAD contribute, is unclear.

Limitations

We should acknowledge that patients were included if they visited our multidisciplinary outpatient clinic from January 1999, as long as they had all acute echocardiographies performed at our center. Because children with coronary abnormalities are more likely to have further follow-up, this explains the relatively high proportion of patients with giant CAA in our study cohort. Second, this was a retrospective study using clinical care data rather than using a fixed research protocol, thus some deviations from standard protocol occurred.

The number of patients with giant CAA in our single-center cohort was limited, resulting in odds ratios with relatively large confidence intervals. We chose to categorize patients, who never received IVIG, in the 'no IVIG re-treatment' group to compare a 'second IVIG-treatment' to all other categories. This may have overestimated the significance of a 'second IVIG-treatment'.

We used the 'Boston *z*-scores' while multiple formulas are available. A recent study showed that although coronary artery measurements have high inter- and intra-rater agreement, these *z*-scores formulas differ at larger CAA dimensions, meaning some patients may have fallen into different categories for other formulas [23].

Conclusion

This study evaluating risk factors for the development of giant CAA showed that 'male gender', 'no or late IVIG treatment', 'IVIG re-treatment', as well as 'age < 1 year' were significantly associated with giant CAA when compared to patients without enlargement. When comparing patients with giant CAA to patients with medium-sized CAA, 'IVIG re-treatment' was still significantly different between the groups, suggesting a dichotomy between patients with giant, treatment-resistant CAA and responsive other patients in which male gender may be factored in as a relevant genetic trait. Of the coronary arteries, the RCA was most often affected by a giant CAA. Most giant CAA continued to increase in size during the first 20–40 days after disease onset, indicating the need for repeated echocardiographies, especially if fever is not resolved.

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Conflict of interest

The authors declare that there is no conflict of interest.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.jjcc.2016.12.014.

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