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Clinical Investigation

Long-Term Health-Related Quality of Life in Kawasaki Disease–Related Coronary Artery Aneurysm: A Large Single-Center Assessment in Nanjing, China

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Abstract

Background: The impact of coronary artery aneurysms (CAAs) caused by Kawasaki disease (KD) on long-term health-related quality of life (HRQOL) in children has not been well documented.

Methods: This study investigated long-term HRQOL in a large sample of children diagnosed with KD-related CAAs. A case-control, retrospective study included 66 patients with KD-related CAAs. A total of 98 hospitalized patients were matched as controls based on age and sex: 49 patients were allocated to a group with pneumonia and 49 patients were allocated to a group with arterio-arterial fistula. Both child-reported and parent-proxy–reported Pediatric Quality of Life Inventory surveys were collected.

Results: The median (IQR) follow-up period was 5.64 (3.81-7.47) years (range, 1.03-10.67 years). The mean (SD) age at diagnosis was 3.73 (1.93) years. At baseline, children and parents as their proxies reported similar HRQOL scores for KD-related CAAs and arterio-arterial fistula that were considerably lower than for pneumonia, respectively. At long-term follow-up, children in the small and medium-sized aneurysms group reported a mean (SD) score of 81.61 (19.50), which was comparable to the arterio-arterial fistula group (83.32 [18.24]), 9.51 points lower than that of the pneumonia group (P = .014), and 9.70 points higher than that of the giant aneurysms group (P = .012). Parents also reported a comparable mean (SD) score of 81.03 (12.57) vs 83.30 (15.17) in the small and medium-sized aneurysms group and arterio-arterial fistula group, both of which had statistically significantly lower scores than the pneumonia group (P = .010) and higher scores than the giant aneurysms group (P = .009).

Conclusion: Despite improvement in HRQOL scores, children with documented KD-related CAAs without complete recovery often encountered issues that disrupted their well-being during long-term follow-up. Routine outpatient HRQOL screening could be instituted to help eliminate the risk of long-term disability following initial clinical improvement.

Keywords: Mucocutaneous lymph node syndrome; coronary aneurysms; arterio-arterial fistula; quality of life

Introduction

Kawasaki disease (KD) is an acute, self-limited form of vasculitis with an intense inflammatory process that accounts for the most common cause of acquired heart disease in children, especially in children younger than 5 years of age.[1] Epidemiological surveys from China have reported an increasing trend in the incidence of KD of approximately 46.3 to 55.1 per 100,000 population in patients younger than 5 years of age over the past few decades.[2] Diagnosing KD is challenging because of the variety of associated clinical symptoms, which creates difficulties and delays clinical treatment.[3] During the disease's acute phase, the patient is susceptible to cardiovascular

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complications, including valvulitis, myocarditis, pericarditis, and KD syndrome. Approximately 15% to 25% of patients will develop coronary artery aneurysms (CAAs) in the subacute to convalescent phase, leading to serious long-term consequences, including aneurysm, arterial thrombotic occlusion, or even sudden death if left untreated.[4,5] Rapid infusion of high-dose intravenous immunoglobulin within the first 10 days of illness, however, was reported to reduce the rate of aneurysm to 3% to 5%.[6] In addition to cardiac complications, extreme irritability, seizures, hemiplegia, facial palsy, and aseptic meningitis were reported during the disease's acute phase. Kawasaki disease can therefore substantially impair patients' function in a variety of aspects of life, from the first episode of disease onward. Although the majority of patients recover after the acute phase, some children who have poor coronary artery outcomes may have to face a long-term daily impairment in health-related quality of life (HRQOL) resulting from potentially serious cardiovascular sequelae. The limited existing literature, however, has not documented the impact of KD-related CAAs on the long-term HRQOL of surviving children well.

This study hypothesized that patients with KD-related CAAs exhibited poorer QOL because of the uncertain long-term prognosis of coronary artery lesions. This case-control retrospective study was designed to compare the long-term HRQOL reported by children and their parent proxies in a cohort of patients with KD-related CAAs with patients diagnosed with pneumonia or arterio-arterial fistula during contemporary hospitalization in the Nanjing region of China using a large sample.

Key Points

- Kawasaki disease is a life-threatening disorder in children for which the incidence in China has increased over the past decades.
- Children with KD experience a considerable burden of illness leading to functional impairment in various aspects of life following the acute disease episode.
- The limited existing literature has not documented the long-term impact on HRQOL in children with acute KD-related CAAs well.
- This case-control retrospective study estimated the long-term HRQOL using both child self-reported and parent-proxy–reported formats in a large sample of children diagnosed with CAAs during acute KD.
- Patients with a history of CAAs should be identified and closely monitored using routine outpatient HRQOL screening to reduce the risk of long-term disability.

Abbreviations

CAA, coronary artery aneurysm
HRQOL, health-related quality of life
KD, Kawasaki disease
PedsQL, Pediatric Quality of Life Inventory

Patients and Methods

Study Design and Participant Recruitment

The study's protocol was approved by the Ethics Examining Committee of Human Research of the Children's Hospital of Nanjing Medical University (institutional review board No. NJFCETH-20230616). Informed consent was obtained from each participant or their parent. In all, 66 patients with KD-related CAAs, 49 patients with pneumonia as a normal control group, and 49 patients with arterio-arterial fistula as another control group were enrolled from the Department of Cardiovascular Medicine and Respiratory Medicine in the Children's Hospital of Nanjing Medical University.

Between January 1, 2012, and December 31, 2022, patients diagnosed with KD based on the criteria proposed by the KD Research Committee[7] were eligible for study enrollment if they (1) were aged between birth and 18 years, (2) had the presence of CAAs confirmed by echocardiography, and (3) had complete medical data for their hospitalization during the acute phase of KD. Patients who had incomplete KD, severe chronic illness, immunologic dysfunction unrelated to KD, or a mental health disorder were excluded. Cardio Z software (UBQO Ltd) was employed to calculate the study's *z* scores, and CAAs were predefined as having a maximum *z* score of at least 2.5 for the proximal right coronary artery or the proximal left anterior descending coronary artery on echocardiography.[8,9] Patients were allocated to 1 of 2 groups based on the *z* score definition: The small or medium-sized aneurysms group comprised patients with a small-sized CAA and a *z* score of at least 2.5 but no greater than 5.0 or with a medium-sized CAA and a *z* score of at least 5.0 but no greater than 10.0; the giant aneurysms group comprised patients whose coronary artery dilation met a *z* score of 10.0 or more with or without ischemic symptoms.[10] In addition, 2 control groups with different characteristics were employed in the present study. The normal control group comprised children admitted to the study hospital

for the treatment of pneumonia to control for the effects of the hospital environment. The other control group with coronary artery lesions resulting from coronary artery fistulae was used to control for the effect of cardiac disease. Patients in this group were children hospitalized with arterio-arterial fistula undergoing transcatheter closure during the same period.

Outcomes Measurement and Data Collection

Demographics, clinical characteristic, and echocardiographic data were retrospectively retrieved from a review of the electronic health record system; information obtained included patient age, gender, date of KD onset, duration of hospital admission, interval from KD onset to the study index date, CAA outcome during the disease's acute phase, and persistent CAA associated with KD at long-term follow-up. Multidimensional HRQOL was assessed using the validated instrument of the Pediatric Quality of Life Inventory (PedsQL), which integrates generic core scales and disease-specific modules into 1 measurement system for children aged from birth to 18 years both in general health status or with acute and chronic health conditions.[11] The PedsQL 4.0 questionnaire consists of 23 items: (1) physical function (8 items), (2) emotional function (5 items), (3) social function (5 items), and (4) school-related function (5 items). Each answer is scored on a 5-point scale: 0 = never a problem, 1 = almost never a problem, 2 = sometimes a problem, 3 = often a problem, and 4 = almost always a problem.[11] The reverse scores are summarized, ranging from 0 to 100, with higher scores indicating higher HRQOL.[11] The 2 versions of the PedsQL scale included the self-reported format for children aged 5 to 18 years and the parent-proxy–reported format for children aged from birth to 4 years, both of which were used at baseline and at long-term follow-up in the present study.[11] According to routine protocol, the baseline PedsQL scores reflecting HRQOL within 1 month of disease onset were collected within 72 hours of hospital admission and documented as an attachment to the patient's electronic health record. Data were available after each cycle of hospitalization. To measure long-term HRQOL, 4 investigators blinded to patients with KD-related CAAs and control patients were available to help participants (aged 5-18 years) or their parents (participating children aged 2-5 years) complete the self-administered instruments of the PedsQL 4.0 questionnaires by telephone. A total of 3 attempts would be made to verify the long-term follow-up assessment for all enrolled patients. The resulting data were registered in the electronic research database.

Sample Size Calculation

Sample size was calculated using Power Analysis & Sample Size, version 16, software (NCSS, LLC). According to consensus after a series of expert discussions based on the study's clinical experience, a set of Tukey-Kramer pairwise multiple comparison tests were conducted to detect at least a 30-point decrease in mean scores in the giant aneurysms group compared with the normal control group and a decrease in the mean of 20 points or more in the other 2 groups as opposed to the normal control group, with the largest SD being 15. A sample size of 164 patients (17 patients in the giant aneurysms group and 49 patients in each of the other 3 groups) was calculated to provide a power of 90%, a family-wise error rate of 0.05, and a dropout rate of 20% using a simulation of 1,000 interactions.

Statistical Analysis

Statistics were performed with IBM SPSS Statistics, version 22.0, software (IBM Corp), and $P < .05$ was considered statistically significant. Nearest-neighbor 1:1.5 matching was performed using age and sex as covariates to calculate propensity scores, which were evaluated by hierarchically fitting the patient's sex and age to the logistic regression model after exact-matching for sex. The Kolmogorov-Smirnov *z* test was employed to check for normality. Categorical data and non-normally distributed data were expressed as frequencies and percentages, mean (SD), or median (IQR) and compared using the χ^2 test, Mann-Whitney *U* test, and analysis of covariance models; these comparisons were adjusted for baseline scores (categorical data) and matching variables (non-normally distributed data). Missing data were processed by multiple imputation using chained equations, and sensitivity analyses were performed to test robustness.

Results

Figure 1 illustrates the design of the retrospective trial. Of the 164 patients included in the study, 12 were lost to follow-up because of unavailable questionnaires, in-

cluding 6 patients in the pneumonia group, 2 patients in the small or medium-sized aneurysms group, and 4 patients in the arterio-arterial fistula group. Table I shows the participants' baseline characteristics. The mean (SD) age at the time of diagnosis was 3.73 (1.93) years (range, 2.12-12.19 years).

A total of 152 PedsQL questionnaires were available, including 114 child self-reported questionnaires and 38 parent-proxy–reported questionnaires. The median (IQR) follow-up time was 5.64 (3.81-7.47) years (range, 1.03-10.67 years). At baseline, in the KD-related CAAs cohort, which included the small or medium-sized and

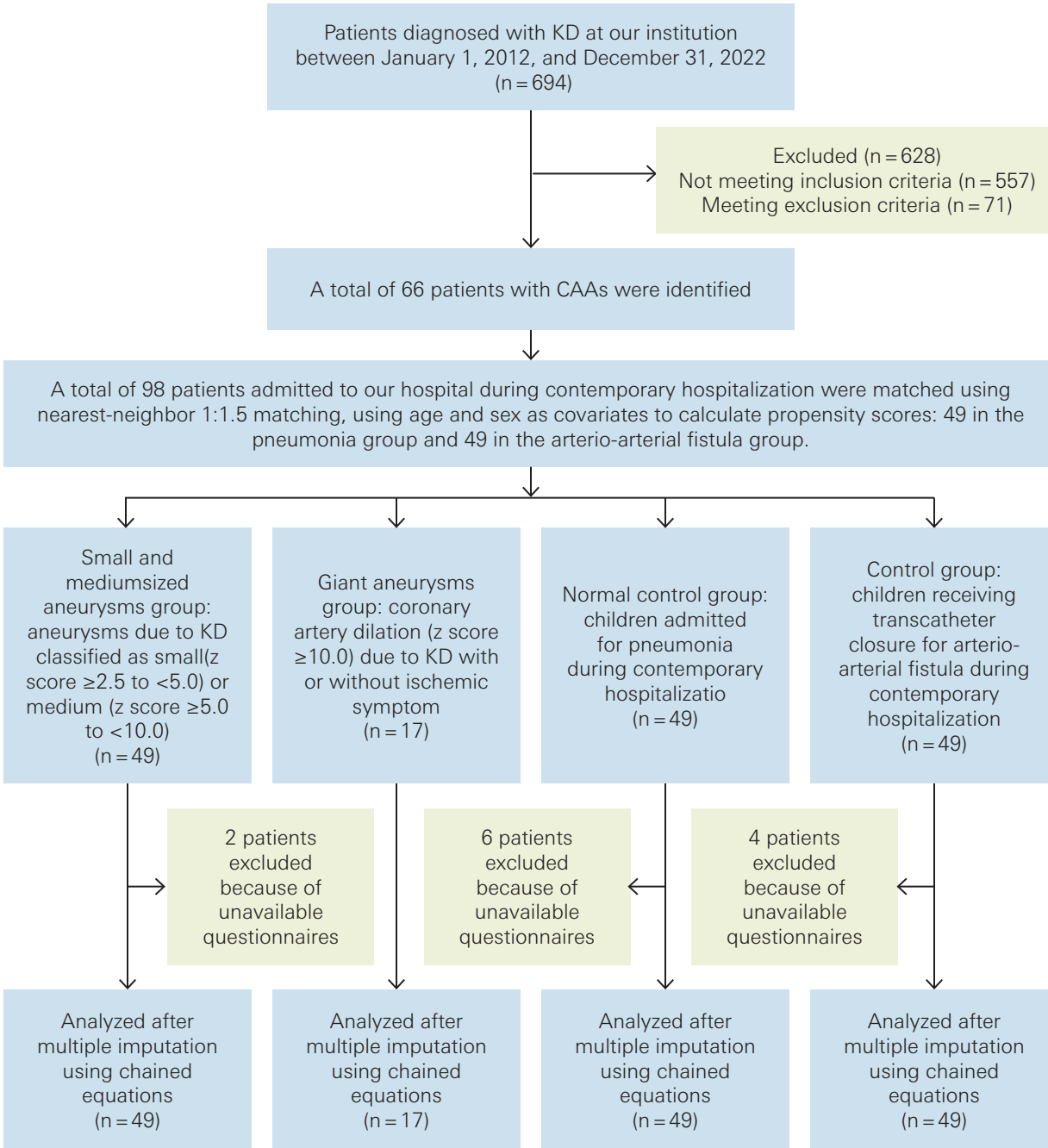

Fig. 1 Flowchart of the study.

CAA, coronary artery aneurysm; KD, Kawasaki disease.

TABLE I. Baseline Demographics and Clinical Characteristics

Variable	KD-related CAAs (n = 66)	Pneumonia (n = 49)	*P* value	Arterio-arterial fistula (n = 50)	*P* value
Age, mean (SD), y	3.06 (1.72)	3.10 (1.54)	.68	3.25 (1.49)	.24
Gender, No. (%)					
Female	19 (28.8)	14 (28.6)	.98	18 (36.7)	.42
Male	47 (71.2)	35 (71.4)		31 (63.3)	
Race, No. (%)			.93		.50
Han Chinese	53 (80.3)	39 (79.6)		36 (73.5)	
Minority[a]	13 (19.7)	10 (20.4)		13 (26.5)	
Residential address, No. (%)			.33		.92
Cities and towns	41 (62.1)	35 (71.4)		30 (61.2)	
Rural	25 (37.9)	14 (28.6)		19 (38.8)	
Centers for Disease Control and Prevention's child-teen body mass index, No. (%)					
Underweight (<5th percentile)	7 (10.6)	4 (8.2)	.23	7 (14.3)	.52
Healthy weight (≥5th percentile and <85th percentile)	46 (69.7)	35 (71.4)		32 (65.3)	
Overweight (≥85th percentile and <95th percentile)	8 (12.1)	2 (4.1)		5 (10.2)	
Obesity (≥95th percentile)	5 (7.6)	6 (12.2)		3 (6.1)	
Severe obesity (≥120% of the 95th percentile)	0 (0)	2 (4.1)		2 (4.1)	
Duration of fever,[b] median (IQR), d	10 (8-13)	5 (3-7)	<.001		
Resistant to intravenous immunoglobulin treatment, No. (%)					
No	52 (78.8)				
Yes	14 (21.2)				
Time to initial echocardiogram, median (IQR), d	6 (5-7)			1 (0-2)	<.001
Admission to the pediatric intensive care unit, No. (%)			.51		.58
No	59 (89.4)	46 (93.9)		43 (86.0)	
Yes	7 (10.6)	3 (6.1)		7 (14.0)	
Duration of hospital admission, mean (SD), d	16.43 (5.97)	7.01 (3.73)	<.001	8.91 (1.52)	<.001
Period of long-term follow-up, No. (%), y[c]			.92		.73
<5	21 (31.8)	14 (28.6)		15 (30.6)	
≥5 and ≤10	34 (51.5)	27 (55.1)		23 (46.9)	
>10	11 (16.7)	8 (16.3)		11 (22.4)	

CAA, coronary artery aneurysm; KD, Kawasaki disease.

[a] "Minority" was used as a binary comparison against people of Han Chinese race because not enough patients from each racial group were available for their own statistically significant comparison.

[b] No complications of bacterial endocarditis could lead to the clinical symptom of fever, observed in all patients with arterio-arterial fistula.

[c] Percentages for period of long-term follow-up in the cohort with arterio-arterial fistula do not total 100% because of rounding.

$P < .05$ was considered statistically significant.

the giant aneurysms groups, children reported a total mean (SD) score of 48.63 (16.60), while parents reported a mean (SD) score of 46.76 (14.77). In the pneumonia group, children reported a mean (SD) score of 63.60 (18.82), and parents reported a mean (SD) score of 62.71 (17.72), both of which were statistically significantly higher than those of the KD-related CAAs cohort (children, $P = .028$; parents, $P = .042$). Among children with arterio-arterial fistula before treatment, the mean (SD) total scores of both formats were comparable to those of the KD-related CAAs cohort (child self-report, 50.80 [13.16], $P = .97$; parent-proxy–reported, 52.73 [13.34], $P = .96$). No statistically significant difference for the matched arterio-arterial fistula groups was observed for either child or parent reports at baseline in the detailed scores from the PedsQL 4.0 functional assessment subscales. In contrast, statistically significant differences were observed between the matched pneumonia group in multiple specific domains of emotional, social, and school-related functioning by parent-proxy report or child self-report (as provided in Table II). Starting at baseline, the total HRQOL scores improved over time in the total sample. Within each subgroup, as well, scores improved statistically significantly over time. At the time of long-term follow-up, children in the small or medium-sized aneurysms group reported a mean (SD) total score of 81.61 (19.50), which was comparable with children in the arterio-arterial fistula group (83.32 [18.24]; $P = .54$), though it was 9.51 points lower (95% CI, 2.02-16.98) than the mean total score in the pneumonia group ($P = .014$) and 9.70 points higher (95% CI, 2.22-17.18) than the mean total score in the giant aneurysms group ($P = .012$). Parents in the small or medium-sized aneurysms group also reported a comparable mean (SD) score of 81.03 (12.57) vs 83.30 (15.17) in the arterio-arterial fistula group ($P = .53$), scores that were statistically significantly higher than those in the giant aneurysms group (65.93 [13.69]; $P = .009$). The score reported by parents in the small or medium-sized aneurysms group, however, was statistically significantly worse (–9.9 points [95% CI, –17.27 to –2.53]) than the mean total score reported by parents in the pneumonia group ($P = .010$). Analysis of the 4 functional PedsQL subscales revealed that patients in the giant aneurysms group reported the lowest scores for both the child self-reported and parent-proxy–reported formats, while the matched pneumonia control group showed the highest scores. Mean scores, however, did not differ in a statistically significant way between patients in the small or medium-sized aneurysms group and the matched arterio-arterial fistula control group. Sensitivity analysis yielded results that were consistent with the primary findings of the long-term HRQOL scores using multiple imputation data (Table II).

Discussion

Although the incidence of KD in the Nanjing region of China remains uncertain because of the lack of accurate population statistics and a centralized database, to the authors' knowledge, the study hospital is the largest referral center for the treatment of coronary artery sequelae of KD and has admitted the vast majority of patients in the Nanjing region over the past few decades. Studies investigating the long-term HRQOL consequences of cardiovascular sequelae of KD on children were nevertheless scarce. The study's results established comprehensive comparisons of long-term QOL between children with KD-related CAAs and 2 control patients during their contemporary hospitalization period. The study found that coronary artery sequelae indeed had a negative influence on a patient's life: The long-term HRQOL in children with a history of giant aneurysms during acute KD was substantially impaired.

Since it was first described in Japan in 1967 by Tomisaku Kawasaki,[12] KD has surpassed acute rheumatic fever as the leading cause of acquired heart disease among young children. The cause of KD remains poorly understood; it appears to be an interplay of genetic susceptibility and an infectious trigger followed by an abnormal immune response, mainly resulting in multisystemic vasculitis that shows a predilection for the coronary arteries.[13] Possible delays in diagnosis and treatment occur in many children because of the disease's lack of typical manifestations, which challenges young children and their parents with the physical and psychological consequences of having a serious disease of unknown etiology and future outcome.[3] Extreme irritability was described as a common symptom during the acute phase; children described an overwhelming range of emotions that had a heavy negative influence on their life.[14] Previous data compared caregivers' perceptions of their child with KD's health with the perceptions of caregivers of patients with other common childhood diseases and found that HRQOL plummeted after hospital admission as a result of the acute KD episode.[15] The current study's results illustrate that children with CAAs during acute KD showed deteriorating HRQOL compared with the matched cohort of patients with

TABLE II. Change in PedsQL Scores From Baseline to Follow-Up Among Patients With KD-Related CAAs vs Control Patients, Before and After Multiple Imputation

			Total score	Post hoc		Physical health	Post hoc	Emotional function	Post hoc	Social function	Post hoc	School-related function	Post hoc
Time	Reporting format	Group	Mean (SD)	Comparison	*P* value	Mean (SD)	*P* value	Mean (SD)	*P* value	Mean (SD)	*P* value	Mean (SD)	*P* value
Baseline (N = 164)	Child self-report (n = 55)[a]	KD-CAA[b] (n = 19)	48.63 (16.60)	KD vs arterio-arterial fistula	.97	48.23 (16.51)	.89	45.61 (14.32)	.73	42.6 (11.98)	.76	44.63 (13.37)	.78
		Arterio-arterial fistula (n = 21)	50.80 (13.16)	KD vs pneumonia	.028	53.75 (13.89)	.013	50.73 (12.14)	.011	50.75 (12.24)	.001	49.25 (10.43)	.014
		Pneumonia (n = 15)	63.60 (18.82)	Pneumonia vs arterio-arterial fistula	.031	47.19 (16.99)	.018	63.53 (13.89)	.024	64.37 (14.06)	.003	66.36 (16.82)	.027
	Parent-proxy report (n = 109)	KD-CAA[b] (n = 47)	46.76 (14.77)	KD vs arterio-arterial fistula	.96	45.32 (13.34)	.94	44.35 (12.18)	.76	41.23 (10.14)	.93	43.50 (11.59)	.94
		Arterio-arterial fistula (n = 28)	52.73 (13.34)	KD vs pneumonia	.042	52.25 (12.03)	.008	48.73 (9.63)	.008	42.85 (13.33)	.006	43.64 (13.84)	.006
		Pneumonia (n = 34)	62.71 (17.72)	Pneumonia vs arterio-arterial fistula	.046	45.81 (15.41)	.009	56.56 (12.63)	.030	68.16 (12.79)	.007	66.68 (19.66)	.007
Long-term follow-up with multiple imputation using chained equations (N = 164)	Child self-report (n = 121)[a]	Giant aneurysm[b] (n = 14)	71.36 (17.41)	Giant aneurysms vs small or medium-sized aneurysms	.012	68.31 (19.27)	.001	70.96 (19.02)	.022	77.57 (17.62)	.036	77.52 (17.60)	.004
		Small or medium-sized aneurysms[b] (n = 38)	81.61 (19.50)	Giant aneurysm vs arterio-arterial fistula	.002	83.64 (11.18)	<.001	80.52 (10.09)	.003	85.28 (10.64)	.026	85.31 (11.58)	.002
		Arterio-arterial fistula (n = 36)	83.32 (18.24)	Giant aneurysm vs pneumonia	<.001	85.27 (11.48)	<0.001	85.69 (11.70)	<.001	85.50 (17.47)	<.001	85.50 (17.47)	<.001
		Pneumonia (n = 33)	90.90 (17.14)	Small or medium-sized aneurysms vs arterio-arterial fistula	.54	92.75 (14.03)	.708	88.93 (16.19)	.213	92.43 (13.29)	.886	90.48 (12.17)	.759
				Small or medium-sized aneurysms vs pneumonia	.014		.039		.044		.039		.052
				Arterio-arterial fistula vs pneumonia	.059		.085		.417		.053		.098

Continued

TABLE II. Change in PedsQL Scores From Baseline to Follow-Up Among Patients With KD-Related CAAs vs Control Patients, Before and After Multiple Imputation, *Continued*

Time	Reporting format	Group	Total score	Post hoc		Physical health	Post hoc	Emotional function	Post hoc	Social function	Post hoc	School-related function	Post hoc
			Mean (SD)	Comparison	*P* value	Mean (SD)	*P* value	Mean (SD)	*P* value	Mean (SD)	*P* value	Mean (SD)	*P* value
	Parent-proxy report (n = 43)	Giant aneurysm[b] (n = 3)	65.93 (13.69)	Giant aneurysms vs small or medium-sized aneurysms	.009	66.42 (19.63)	<.001	72.94 (16.97)	.026	75.73 (17.27)	.006	68.36 (10.82)	<.001
		Small or medium-sized aneurysms[b] (n = 11)	81.03 (12.57)	Giant aneurysm vs arterioarterial fistula	.002	84.57 (11.09)	<.001	85.69 (11.69)	.001	86.23 (11.65)	.004	84.13 (10.94)	<.001
		Arterio-arterial fistula (n = 13)	83.30 (15.17)	Giant aneurysm vs pneumonia	<.001	86.71 (18.43)	<.001	89.67 (19.48)	<.001	86.62 (17.15)	<.001	86.51 (14.49)	<.001
		Pneumonia (n = 16)	93.10 (11.29)	Small or medium-sized aneurysms vs arterio-arterial fistula	.56	93.95 (15.59)	.73	93.66 (16.87)	.18	94.78 (13.43)	.89	91.97 (15.55)	.51
				Small or medium-sized aneurysms vs pneumonia	.010		.04		.029		.033		.024
				Arterio-arterial fistula vs pneumonia	.04		.10		.41		.048		.11
Long-term follow-up without multiple imputation using chained equations (N = 152)	Child self-report (n = 114)[a]	Giant aneurysm[b] (n =14)	71.36 (17.41)	Giant aneurysms vs small or medium-sized aneurysms	.012	68.31 (19.27)	.001	70.96 (19.02)	.022	77.57 (17.62)	.036	77.52 (17.60)	.004
		Small or medium-sized aneurysms[b] (n = 37)	81.61 (21.84)	Giant aneurysm vs arterio-arterial fistula	.006	83.64 (13.65)	<.001	80.52 (12.61)	.008	85.28 (12.50)	.031	85.31 (12.73)	.007
		Arterio-arterial fistula (n = 34)	84.02 (19.62)	Giant aneurysm vs pneumonia	<.001	86.53 (12.48)	<.001	86.53 (12.82)	<.001	86.69 (18.30)	<.001	86.16 (18.99)	<.001
		Pneumonia (n = 29)	91.90 (18.22)	Small or medium-sized aneurysms vs arterio-arterial fistula	.49	93.66 (15.39)	.602	89.15 (17.56)	.202	93.42 (14.54)	.889	91.67 (13.327)	.586
				Small or medium-sized aneurysms vs pneumonia	.012		.041		.038		.017		.043
				Arterio-arterial fistula vs pneumonia	.061		.087		.596		.062		.096

Continued

TABLE II. Change in PedsQL Scores From Baseline to Follow-Up Among Patients With KD-Related CAAs vs Control Patients, Before and After Multiple Imputation, *Continued*

Time	Reporting format	Group	Total score	Post hoc		Physical health	Post hoc	Emotional function	Post hoc	Social function	Post hoc	School-related function	Post hoc
			Mean (SD)	Comparison	*P* value	Mean (SD)	*P* value	Mean (SD)	*P* value	Mean (SD)	*P* value	Mean (SD)	*P* value
	Parent-proxy-report (n = 38)	Giant aneurysm[b] (n = 3)	65.93 (13.69)	Giant aneurysms vs small or medium-sized aneurysms	.009	66.42 (19.63)	<.001	72.94 (16.97)	.026	75.73 (17.27)	.006	68.36 (10.82)	<.001
		Small or medium-sized aneurysms[b] (n = 10)	82.14 (13.12)	Giant aneurysm vs arterioarterial fistula	.010	85.42 (12.66)	<.001	8654 (12.91)	<.001	87.95 (12.43)	.002	85.24 (11.58)	<.001
		Arterio-arterial fistula (n = 11)	84.12 (16.10)	Giant aneurysm vs pneumonia	<.001	87.21 (19.14)	<.001	89.99 (20.16)	<.001	87.36 (18.09)	<.001	87.61 (15.27)	<.001
		Pneumonia (n = 14)	93.88 (11.86)	Small or medium-sized aneurysms vs arterio-arterial fistula	.64	93.12 (15.55)	0.76	93.06 (16.29)	0.23	94.116 (13.35)	0.89	91.36 (15.85)	.53
				Small or medium-sized aneurysms vs pneumonia	.09		<.001		.021		.045		.028
				Arterio-arterial fistula vs pneumonia	.07		0.15		0.39		.052		.13

CAA, coronary artery aneurysm; KD, Kawasaki disease; PedsQL, Pediatric Quality of Life Inventory.

[a] The number of children who self-reported their PedsQL scores increased from 55 patients at baseline to 121 patients with multiple imputation using chained equations and 114 patients without multiple imputation using chained equations at long-term follow-up because some children whose scores were reported by their parents at baseline were able to self-report at follow-up.

[b] The case group was referred to as "KD-CAA" at baseline but classified into small or medium-sized aneurysms and giant aneurysms at long-term follow-up because the z score of coronary artery diameter as a standard was not introduced until the American Heart Association's guidelines were announced in 2017. A few patients in the present study, however, were diagnosed between 2012 and 2016.

P < .05 was considered statistically significant.

similar serious cardiac problems, such as arterio-arterial fistula, while their PedsQL scores on admission were statistically significantly worse than those of the matched pneumonia cohort, findings that were consistent with those of 2 similar trials.[16,17] In turn, children with highly variable clinical presentations during the acute phase of KD experienced greater disability related to physical, social, emotional, and school-related functioning than children with acute pneumonia in the present study. Patients with KD-related CAAs experienced more substantial deterioration of HRQOL during the acute phase of KD than did patients with other common diseases, such as pneumonia, which potentially explains the profound decline of HRQOL at illness onset.

The prevalence of CAAs, especially giant CAAs, exposes patients to the risk of coronary arterial stenosis, obstruction, and thrombosis, which could lead to consequent angina pectoris or even myocardial infarction and sudden death.[18] Although most patients have not been followed long enough to evaluate the long-term natural course of CAAs after the acute phase of KD, many CAAs were reported to regress to a normal diameter. The likelihood of regression seems to be highly dependent on the original size of the CAA.[19] A large Japanese study showed that 55% to 60% of patients experienced regression of CAAs, typically within 1 to 2 years after the acute phase, by analyzing serial angiograms in those patients. None of the patients with giant aneurysms in their study showed regression.[20] A 2-center retrospective study with a large sample similarly found that CAA size at diagnosis was strongly associated with the prediction of CAA regression, with a low regression rate of 16% in patients with large or giant CAAs and a high regression rate of 85% in patients with small or medium-sized CAAs.[21] Previous studies nevertheless emphasized that the long-term consequences of these changes were still largely unknown because even though many patients with KD-related CAAs regressed from aneurysmal dilatation, the coronary arteries remained abnormally thickened, and vessel-wall calcification was often detected.[22] Chahal et al[23] reviewed the caregivers of children with KD-related CAAs and found that the principal reason for their persistent anxiety was the uncertainty of prognosis, which was implied by the degree of coronary artery lesions. Research on long-term HRQOL has accordingly demonstrated discrepant results between patients with only a remote history of KD and patients with KD-related CAAs.[16] According to Iman Naimi's research,[17] which first investigated the long-term impact of KD on HRQOL, children with KD experienced an acute impairment in HRQOL exceeding that of children with newly diagnosed pneumonia, but the scores returned to baseline at long-term follow-up. In that study, only 7 of 61 patients had persistent coronary aneurysms at 6-week follow-up.[17] In contrast, the current study's results showed a statistically significant improvement in HRQOL over time in all cohorts, whereas a statistically significant difference in all domains of the PedsQL score was observed between the giant aneurysm group (17 patients) and the 2 matched pneumonia and arterio-arterial fistula groups at long-term follow-up. Long-term HRQOL scores between patients with small or medium-sized coronary aneurysms (47 patients) and control patients with arterio-arterial fistula undergoing transcatheter closure were comparable but were statistically significantly higher than the scores of patients diagnosed with pneumonia at contemporary hospitalization. All the previously mentioned results support the perspective that the majority of patients would recover fully and did not face long-term cardiac consequences after the acute phase, though 31% of patients struggled to meet their premorbid levels of age-appropriate function for weeks after presumed recovery. The presence of CAAs caused by KD, however, could add potentially serious cardiovascular sequelae, with a vague long-term prognosis. According to the current study's results, a long-term burden of CAAs after acute KD emerged if KD remained misdiagnosed or untreated or if optimal acute management was delayed. In addition, the presence of KD-related CAAs became a statistically significant contributory factor to possible long-term disabilities. It subsequently prolonged uncertainty as well as physical and psychological distress in relation to patients' long-term HRQOL. These findings were consistent with the above-mentioned research that aimed to identify statistically significant changes in physical and psychological health, as perceived by the caregivers of children with chronic illness. Their results demonstrated a similar trend in which patients and their caregivers experienced considerable anxiety during the long-term follow-up period, despite having a mostly favorable prognosis. The current study's data therefore support its principal hypothesis because the long-term HRQOL findings indicated that a proportion of children with KD-related CAAs without complete recovery often encountered issues that disrupted their well-being during long-term follow-up. Considering these outcomes, a routine HRQOL screening in

addition to monitoring for acquired heart disease could help reduce the risk of long-term disability in patients with KD-related CAAs following initial clinical improvement.

Limitations

There were some limitations to this study. First, the nature of retrospective analysis may have created undetected confounders and probable bias. Second, the study was conducted within a single center; therefore, the results may not be generally applicable. Third, only total PedsQL scores were reported as an outcome measure instead of individual subscales for physical, psychosocial, emotional, social, and school-related function. Fourth, although median long-term follow-up time was reported, the exact follow-up time point varied by individual, which could affect interpretation of the test results. Finally, there was a difference in reporting formats between baseline and follow-up for some participants because some children whose scores were reported by their parents at baseline were old enough to answer the inventory themselves during follow-up, which could lead to biased conclusions when comparing baseline scores with follow-up scores. Future large-scale, long-term randomized studies are therefore needed to validate this study's findings.

Conclusion

The results of the long-term HRQOL questionnaire in a cohort of children diagnosed with KD demonstrated that a proportion of these patients who had CAAs without complete recovery often encountered issues that disrupted their well-being during long-term follow-up, despite their HRQOL scores improving over time. Routine outpatient HRQOL screening may therefore be an appropriate support service to help identify patients with a history of KD-related CAAs during the disease's acute phase to eliminate the risk of long-term disability following initial clinical improvement.

Article Information

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References

1. Wood LE, Tulloh RMR. Kawasaki disease in children. *Heart*. 2009;95(10):787-792. doi:10.1136/hrt.2008.143669
2. Jiao F, Jindal AK, Pandiarajan V, et al. The emergence of Kawasaki disease in India and China. *Glob Cardiol Sci Pract*. 2017;2017(3):e201721. doi:10.21542/gcsp.2017.21
3. Zhu F, Ang JY. 2021 update on the clinical management and diagnosis of Kawasaki disease. *Curr Infect Dis Rep*. 2021;23(3):3. doi:10.1007/s11908-021-00746-1
4. Barut K, Sahin S, Kasapcopur O. Pediatric vasculitis. *Curr Opin Rheumatol*. 2016;28(1):29-38. doi:10.1097/BOR.0000000000000236
5. Lee JJY, Lin E, Widdifield J, et al. The long-term cardiac and noncardiac prognosis of Kawasaki disease: a systematic review. *Pediatrics*. 2022;149(3):e2021052567. doi:10.1542/peds.2021-052567
6. Newburger JW, Takahashi M, Burns JC, et al. The treatment of Kawasaki syndrome with intravenous gamma globulin. *New Engl J Med*. 1986;315(6):341-347. doi:10.1056/NEJM198608073150601
7. Ayusawa M, Sonobe T, Uemura S, et al. Revision of diagnostic guidelines for Kawasaki disease (the 5th revised edition). *Pediatr Int*. 2005;47(2):232-234. doi:10.1111/j.1442-200x.2005.02033.x
8. Dallaire F, Dahdah N. New equations and a critical appraisal of coronary artery *Z* scores in healthy children. *J Am Soc Echocardiogr*. 2011;24(1):60-74. doi:10.1016/j.echo.2010.10.004
9. McCrindle BW, Li JS, Minich LL, et al; Pediatric Heart Network Investigators. Coronary artery involvement in children with Kawasaki disease: risk factors from analysis of serial normalized measurements. *Circulation*. 2007;116(2):174-179. doi:10.1161/CIRCULATIONAHA.107.690875
10. Manlhiot C, Millar K, Golding F, McCrindle BW. Improved classification of coronary artery abnormalities based only on coronary artery z-scores after Kawasaki disease. *Pediatr Cardiol*. 2010;31(2):242-249. doi:10.1007/s00246-009-9599-7
11. Gheissari A, Farajzadegan Z, Heidary M, et al. Validation of Persian version of PedsQL™ 4.0™ Generic Core Scales in toddlers and children. *Int J Prev Med*. 2012;3(5):341-350.

12. Kawasaki T. Acute febrile mucocutaneous syndrome with lymphoid involvement with specific desquamation of the fingers and toes in children. Article in Japanese. *Jpn J Allergy*. 1967;16(3):178-222.
13. Agarwal S, Agrawal DK. Kawasaki disease: etiopathogenesis and novel treatment strategies. *Expert Rev Clin Immunol*. 2017;13(3):247-258. doi:10.1080/1744666X.2017.1232165
14. Liu X, Zhou K, Hua Y, et al. Neurological involvement in Kawasaki disease: a retrospective study. *Pediatr Rheumatol Online J*. 2020;18(1):61. doi:10.1186/s12969-020-00452-7
15. van Oers HA, Tacke CE, Haverman L, et al. Health related quality of life and perceptions of child vulnerability among parents of children with a history of Kawasaki disease. *Acta Paediatr*. 2014;103(6):671-677. doi:10.1111/apa.12619
16. Kourtidou S, Slee AE, Bruce ME, Wren H, Mangione-Smith RM, Portman MA. Kawasaki disease substantially impacts health-related quality of life. *J Pediatr*. 2018;193:155-163.e5. doi:10.1016/j.jpeds.2017.09.070
17. Naimi I, Slee AE, Kourtidou S, Mangione-Smith RM, Portman MA. Long-term impact of hospitalization for Kawasaki disease on health-related quality of life. *Hosp Pediatr*. 2022;12(3):248-257. doi:10.1542/hpeds.2021-006308
18. Newburger JW, Takahashi M, Gerber MA, et al; Committee on Rheumatic Fever, Endocarditis and Kawasaki Disease; Council on Cardiovascular Disease in the Young; American Heart Association; American Academy of Pediatrics. Diagnosis, treatment, and long-term management of Kawasaki disease: a statement for health professionals from the Committee on Rheumatic Fever, Endocarditis and Kawasaki Disease, Council on Cardiovascular Disease in the Young, American Heart Association. *Circulation*. 2004;110(17):2747-2771. doi:10.1161/01.CIR.0000145143.19711.78
19. Tsuda E, Hashimoto S. Time course of coronary artery aneurysms in Kawasaki disease. *J Pediatr*. 2021;230:133-139.e2. doi:10.1016/j.jpeds.2020.12.004
20. Kato H, Sugimura T, Akagi T, et al. Long-term consequences of Kawasaki disease. A 10- to 21-year follow-up study of 594 patients. *Circulation*. 1996;94(6):1379-1385. doi:10.1161/01.cir.94.6.1379
21. Friedman KG, Gauvreau K, Hamaoka-Okamoto A, et al. Coronary artery aneurysms in Kawasaki disease: risk factors for progressive disease and adverse cardiac events in the US population. *J Am Heart Assoc*. 2016;5(9):e003289. doi:10.1161/JAHA.116.003289
22. Daniels LB, Gordon JB, Burns JC. Kawasaki disease: late cardiovascular sequelae. *Curr Opin Cardiol*. 2012;27(6):572-577. doi:10.1097/HCO.0b013e3283588f06
23. Chahal N, Jelen A, Rush J, et al. Kawasaki disease with coronary artery aneurysms: psychosocial impact on parents and children. *J Pediatr Health Care*. 2017;31(4):459-469. doi:10.1016/j.pedhc.2016.11.007