Long-term Cardiovascular Outcomes in Survivors of Kawasaki Disease

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KEY WORDS
Kawasaki disease, coronary aneurysm, vasculitis, cardiovascular outcomes

ABBREVIATIONS
CI—confidence interval
HR—hazard ratio
IVIg—intravenous immunoglobulin
KD—Kawasaki disease
KPNC—Kaiser Permanente Northern California

Dr Holve participated in the study design, data acquisition, data analysis, and data interpretation and drafted the manuscript; Dr Patel contributed substantially (>50%) to data acquisition, helped with data interpretation, and revised the manuscript critically; Ms Chau contributed to the study design and data acquisition and revised the manuscript critically; Ms Marks contributed to the study design, acquired the data from database programming, assisted with the statistical design and analysis, and revised the manuscript critically; Dr Meadows contributed to the study conception and design and interpretation of data and revised the manuscript critically; Dr Zaroff was the primary contributor to the study design, assisted with data acquisition, performed the statistical analysis, helped with data interpretation, and revised the manuscript critically; and all authors approved the final manuscript as submitted.

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WHAT'S KNOWN ON THIS SUBJECT: Kawasaki disease (KD) results in coronary aneurysm formation and an increased risk of cardiovascular complications. Modern treatment of acute KD with intravenous immunoglobulin substantially reduces the rate of acute aneurysm formation.

WHAT THIS STUDY ADDS: This study reveals that long-term cardiovascular outcomes for KD patients in the current era are not significantly different than matched controls without KD. Late cardiovascular complications are almost exclusively seen in patients with persistent coronary aneurysms.

abstract

BACKGROUND AND OBJECTIVE: Kawasaki disease (KD) may result in coronary aneurysm formation, but there is incomplete knowledge regarding its long-term effects. Our objective was to quantify the longer-term rates of adverse cardiac events in a modern North American KD cohort.

METHODS: Using the Kaiser Permanente Northern California population, we performed a retrospective cohort study in patients with a history of KD versus matched patients without KD. Chart review was used to confirm the diagnosis of KD and all outcomes of interest, including acute coronary syndrome, coronary revascularization, heart failure, ventricular arrhythmia, valve disease, aortic aneurysm, and all-cause mortality. All outcomes occurring at age ≥15 years were included in the primary analysis. Outcome rates were compared between the 2 groups by using Cox proportional hazards analysis.

RESULTS: The study included 546 KD patients and 2218 matched patients without KD. Seventy-nine percent of the KD patients received intravenous immunoglobulin and 5% had persistent coronary aneurysm. The average follow-up time was 14.9 years. Only 2 KD patients experienced outcomes after age 15 (0.246 events per 1000 person-years) compared with 7 events in the non-KD group (0.217 events per 1000 person-years), a nonsignificant difference (hazard ratio: 0.81; 95% confidence interval: 0.16–4.0). Within the KD subgroup, persistent coronary aneurysm predicted the occurrence of adverse events (P = .007).

CONCLUSIONS: This is the largest US study of longer-term cardiac outcomes after KD and reveals a low rate of adverse cardiovascular events through age 21. Additional validation studies, including studies with longer-term follow-up, should be performed. *Pediatrics* 2014;133:e305–e311

Kawasaki disease (KD) is the leading cause of acquired pediatric heart disease in the developed world.[1,2] Coronary aneurysm formation is the most significant complication of KD and is associated with early morbidity and mortality.[3–5] In recent times, early recognition of KD and treatment with intravenous immunoglobulin (IVIg) and aspirin have decreased the incidence of coronary aneurysm formation to between 3% and 5%.[4,6,7] There are few data describing long-term outcomes after KD in the modern treatment era. The primary aim of this study was to quantify the long-term rates of adverse cardiovascular events in an adult North American population with a history of childhood KD. The secondary aim was to define subgroups at increased risk of cardiovascular events on the basis of acute KD treatment and aneurysm status.

METHODS

Patient Selection

This was a retrospective cohort study using Kaiser Permanente Northern California (KPNC) databases followed by review of the medical records of identified patients. KPNC is an integrated group practice health care plan that is the largest and one of the oldest health maintenance organizations in the United States. KPNC provides comprehensive medical services through 16 hospitals and 23 outpatient clinics to >3.2 million members in a 14-county region of northern California, serving ~30% of the general population in this region. The sociodemographic characteristics of the members are generally representative of the underlying population, except with respect to income, where KPNC members somewhat underrepresent the very poor and the very wealthy.[8,9]

Members with a current age of ≥15 years and a diagnostic code indicating a history of KD (International Classification of Diseases, Ninth Revision, code 446.1) occurring at age ≤5 years were included in the cohort. A current age of ≥15 years was chosen because the KPNC research databases were established in the late 1990s and because the focus of this study was longer-term outcomes. KD diagnoses were confirmed through review of the entire KPNC electronic and paper medical record; any patient judged to have not had KD was excluded. Patients who did not receive care at a KPNC medical facility at least 1 year after the KD diagnosis were also excluded. A comparison group of KPNC members with no history of KD were matched to the members with KD in a 4:1 ratio by gender, age, cumulative membership duration, and medical service area. The study was approved by the KPNC Institutional Review Board.

Chart Review for Acute KD Illness Variables

All chart review was performed by 2 physicians who searched for data elements characterizing the acute KD illness for each patient. The therapies administered at the time of the acute KD illness were categorized as aspirin, IVIg, both aspirin and IVIg, other therapy (eg, antibiotics or steroids), or unknown. Long-term therapy was defined as treatment given >6 months after the acute KD illness and was categorized as aspirin, warfarin, warfarin plus aspirin, other, or unknown on the basis of the available data. In some instances, the KD diagnosis occurred before patients' enrollment in KPNC, and there was no available documentation describing acute treatment or, less often, long-term treatment.

Echocardiography data to identify coronary status after the acute KD illness were available in the majority of cases. On the basis of the echocardiography reports and the documentation of the treating physicians, each patient's coronary status was categorized as no coronary involvement, transient ectasia, persistent ectasia, transient aneurysm, persistent aneurysm (beyond the acute KD episode), or not available. Persistent versus transient status was determined on the basis of the last echocardiographic data available. Ectasia was defined as borderline but uniform enlargement of coronary segments. Aneurysm was defined as a coronary artery segment with a diameter >2 SDs above the mean proximal coronary diameter plus a nonuniform appearance.

Assessment of Adverse Clinical Outcomes

The adverse long-term outcomes of interest for this study were acute coronary syndrome, congestive heart failure, percutaneous coronary intervention, coronary artery bypass grafting, life-threatening ventricular arrhythmia (sudden cardiac death, sustained ventricular tachycardia, ventricular fibrillation), significant valvular dysfunction (at least moderate regurgitation or valve surgery), aortic aneurysm, and all-cause mortality. For the primary analysis, events were only included if they occurred at age ≥15 years, to focus on long-term outcomes. A secondary analysis was also performed, which included events occurring after the acute KD hospitalization but before age 15.

These outcomes were identified by using a 2-step process. First, electronic KPNC databases were queried by using International Classification of Diseases, Ninth Revision, codes specific for each adverse outcome, and all-cause mortality data were obtained from medical records, membership files, California death certificates, and Social Security Administration databases.[10] The second step consisted of physician chart review of all available paper and electronic medical records for patients identified as experiencing an adverse outcome by database programming. Adverse outcomes were only included in the analysis if verified by physician chart review.

Quality Assurance for Chart Review

To measure interobserver variability, the 2 reviewing physicians both reviewed 40 charts, including all 41 required fields. A total of 46 disagreements were recorded among the 1640 fields reviewed (2.8%); thus, the agreement rate was 97.2%.

Statistical Analysis

The demographic and clinical characteristics of the KD patients and the matched members without KD were compared by using *t* tests for continuous variables and either χ^2 or Fisher's exact tests for categorical variables, depending on sample sizes. In addition, the characteristics of the KD patients excluded for having <1 year of follow-up time after the acute KD illness were compared with the remaining KD cohort members.

Due to the low number of events among both groups, adverse outcomes were combined into a single composite indicator. The rates and 95% confidence intervals (CIs) based on the binomial distribution were calculated per 1000 person-years. Survival analyses were performed by using Cox proportional hazard models, and both crude and adjusted hazard ratios (HRs) and 95% CIs are presented. Patients were censored at the time of a composite outcome event or at the last date of KPNC follow-up medical care. Potential confounders considered include age, race/ethnicity, gender, and comorbid conditions occurring at age ≥15 years, including hypertension, diabetes mellitus, and hyperlipidemia. BMI was determined whenever possible by using a combination of database programming and chart review, accepting the most recent available result. Variables found to be associated with the outcome in univariate models were included in a multivariate Cox proportional hazards model. An additional model was created for the secondary analysis, which included events occurring after the acute KD hospitalization but before age 15.

Secondary analyses were performed that compared the rates of the composite end point according to acute KD treatment category as well as the coronary status category, and statistical significance was defined by using Fisher's exact tests due to small sample sizes.

All analyses were performed by using Stata software (version 11; StataCorp, College Station, TX). *P* values <.05 were considered significant.

RESULTS

There were a total of 671 KD patients identified who met our initial database programming inclusion criteria (Fig 1). After chart review, 66 patients were excluded because KD was judged not to be the most likely diagnosis. An additional 59 patients were excluded for not having at least 1 year of KPNC follow-up after the initial KD diagnosis. The final analysis cohort for long-term outcomes included 546 KD cases. The majority (interquartile range) of these patients were diagnosed with acute KD between 1990 and 1998. The last date of follow-up (last KPNC encounter) for the majority (interquartile range) of these patients ranged from 2007 to 2011.

The demographic and clinical characteristics of the members with KD and the comparison group are shown in Table 1. The mean age of KD cases at most recent contact was 21.3 years (range: 15–41 years). Because the comparison group was not matched to cases by race/ethnicity, a different racial composition was observed; specifically, KD patients were more likely than non-KD members to be Asian (19% vs 10%) or African American (13% vs 8%). Patients with a history of KD were also more likely to have a diagnosis of hypertension after the age of 15 (3% vs 1.7%; *P* = .03). BMI data are not universally available in KPNC research databases, and supplemental chart review was performed to decrease the amount of missing data. By these methods, BMI data were available in 79% of KD patients and 69% of the non-KD cohort. There was no significant difference in mean BMI according to KD status, and the proportion of patients with BMI >30 was similar in the 2 groups (17% in the KD group versus

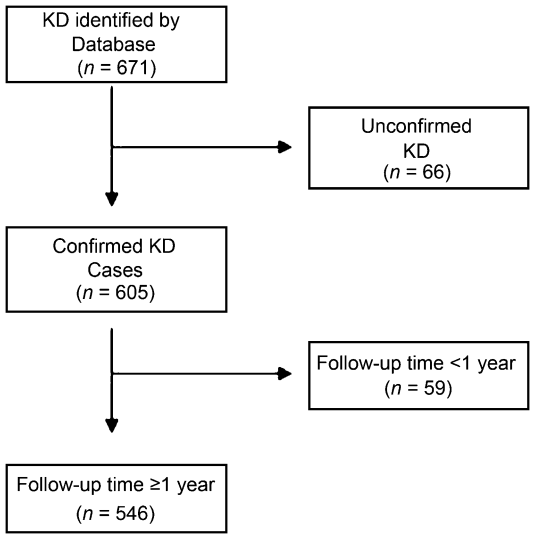

FIGURE 1
Flow diagram showing the effect of the chart review and exclusion criteria in producing the final analysis cohort of patients with KD.

TABLE 1 Demographic and Clinical Characteristics of Members With KD Versus the Matched Non-KD Members

Characteristic	KD Patients (n = 546)	Matched Non-KD Members (n = 2218)	P
Age at analysis[a], mean (SD), y	21.3 (5.1)	21.2 (5.1)	.74[b]
Male gender, n (%)	333 (61.0)	1362 (61.4)	.86[c]
Race/ethnicity, n (%)			<.001[c]
White	202 (37.0)	854 (38.5)	
Hispanic	98 (17.9)	379 (17.1)	
Asian/ Pacific Islander	101 (18.5)	224 (10.1)	
African American	71 (13.0)	182 (8.2)	
Multiracial/other	18 (3.3)	61 (2.8)	
Unknown	54 (9.9)	518 (23.4)	
Hypertension, n (%)	17 (3.1)	37 (1.7)	.029[c]
Hyperlipidemia, n (%)	12 (2.2)	32 (1.4)	.21[c]
Diabetes mellitus, n (%)	2 (0.4)	15 (0.7)	.55[d]
BMI, mean (SD)	25.3 (5.5)	25.6 (6.2)	.38[b]
Follow-up time, mean (SD), y	14.9 (6.3)	14.6 (6.2)	.26[b]

[a] Date of analysis: August 1, 2011.
[b] t test.
[c] χ^2 test.
[d] Fisher's exact test.

20% in the non-KD group). Patients who developed hypertension had a higher BMI than patients who did not develop hypertension (32.6 ± 7.6 vs 25.4 ± 5.9; t test, $P < .001$).

The degree of coronary involvement and the acute KD treatments received by the KD group are described in Table 2. A total of 12.8% of patients had some degree of coronary enlargement during the course of KD, but only 25 patients (5%) developed persistent coronary aneurysms that had not resolved as of the last echocardiogram discovered during the chart review process. Standard therapy with aspirin and IVIg was administered to 77% of patients during the acute illness, and 87% of the cohort received at least 1 of these medications. Additionally, 23% of patients received antibiotics, which reflects the significant clinical overlap of KD with many infectious processes. The remainder of the patients either did not receive these therapies due to presentation in the era before standardization of therapy or due to the KD diagnosis being made after the acute illness. Aspirin therapy continued in 52 cases (10%), and warfarin treatment was provided in 6 cases (1.4%) at ≥6 months after the acute KD diagnosis. For patients whose KD diagnosis occurred before enrolling in KPNC, information was unavailable regarding the acute KD therapy in 61 patients (11.2%) and the chronic KD therapy in 58 patients (10.6%). The KD patients excluded for having <1 year of follow-up time were compared with the remaining KD cohort members and showed similar documented rates of persistent aneurysm (3.4% vs 4.6% in the main KD cohort) and similar rates of acute treatment with aspirin and/or IVIg (73% vs 87%). No adverse events were noted among these 59 patients.

TABLE 2 Aneurysm and Treatment Status of Members With KD

Clinical Characteristic	n (%)
Aneurysm status	
None	436 (79.9)
Transient ectasia	19 (3.5)
Persistent ectasia	3 (0.5)
Transient aneurysm	23 (4.2)
Persistent aneurysm	25 (4.6)
Unknown	40 (7.3)
Acute KD treatment	
IVIg + aspirin	294 (53.8)
IVIg + aspirin + antibiotics	128 (23.4)
Aspirin	41 (7.5)
IVIg	9 (1.6)
Other	5 (0.9)
None	8 (1.5)
Unknown	61 (11.2)
Long-term KD treatment	
None	430 (78.8)
Aspirin	52 (9.5)
Aspirin + warfarin	4 (0.7)
Warfarin	2 (0.4)
Unknown	58 (10.6)

Table 3 describes the 5 adverse events observed in the entire cohort of confirmed KD patients. Of note, 3 of the 5 events occurred before age 15 and were thus not included in the survival analysis according to the a priori primary analysis plan, but these events were included in the secondary analysis.

Table 4 reports the incidence rates (per 1000 person-years) for each type of adverse event occurring at age ≥15 years, as well as the combined event rate. In unadjusted Cox models, there was no significant increase in the risk of adverse events in the KD group compared with the non-KD group (HR: 1.04; 95% CI: 0.22–5.02; P = .96) during an average follow-up period of 14.6 years (both groups). KD status, hypertension, age, and gender were associated with the combined outcome in univariate analyses and included in the final multivariate model. There was no significant association between KD status and the combined outcome (adjusted HR: 0.81; 95% CI: 0.16–4.03; P = .8). Only hypertension was significantly associated with the combined outcome (HR: 7.1; 95% CI: 1.6–31.8; P = .01). There was no significant association between gender and outcome (P = .9).

In the secondary analysis of adverse events occurring at any time after the hospitalization, the incidence rate of the combined outcome was higher in the KD group (0.615 per 1000 person-years) because 3 additional events were included. No additional events occurred in the non-KD group, such that the incidence rate was unchanged (0.217 per 1000 person-years). The Cox models showed larger, but nonsignificant, associations between KD status and the outcome (univariate HR: 2.67; 95% CI: 0.84–8.41; P = .09; multivariate HR: 2.29;

TABLE 3 Description of Short- and Long-term Outcomes in the KD Population

Patient	KD Diagnosis	Outcome
5-year-old boy	Age 2 years; treated with aspirin and IVIg with no resultant aneurysms identified.	Age 5 years; mortality from coronary artery disease (further details unavailable from state registry)
11-year-old boy	Age 5 years; treated with aspirin + IVIg + persantine. Developed persistent aneurysms managed with aspirin + warfarin + persantine.	Age 11 years; SCD with no evidence of thrombosis or infarct on autopsy
26-year-old man	Age 13 years; treated with steroids and antibiotics. Developed persistent aneurysms managed with aspirin and warfarin.	ACS due to aneurysm thrombosis requiring CABG at age 14 years
38-year-old man	Age 4 years; with development of persistent aneurysms.	Age 32 years; developed ACS
40-year-old man	Diagnosed as a child; uncertain age in another health system.	Age 19 years; ACS

ACS, acute coronary syndrome; CABG, coronary artery bypass graft; SCD, Sudden Cardiac Death; IVIg, Intravenous Immunoglobulin.

95% CI: 0.71–7.30; $P = .17$), although power was limited by small sample sizes.

Twenty-five (5%) of the KD patients had persistent coronary aneurysms; of these 25, 2 (8%) experienced a long-term complication, compared with no long-term complications in the KD patients without persistent aneurysm (Fisher's exact test, $P = .007$). In the secondary analysis including events occurring any time after the acute KD hospitalization, a similar result was observed; 4 (15%) of the 26 KD patients with persistent aneurysms experienced events compared with 1 event (0.2%) in the group without persistent aneurysm (Fisher's exact test, $P < .001$).

Acute KD treatment strategies were not significantly associated with short- or long-term complication rates, although the large majority of patients received IVIg. However, 2 adverse events occurred among the 61 (11% of total) KD patients for whom treatment data were missing, and thus a true association between acute KD treatment and cardiovascular outcomes cannot be excluded by the current study.

DISCUSSION

In this large North American cohort study in survivors of childhood KD, we found low rates of long-term cardiovascular complications over an average follow-up period of ~15 years after the KD illness. This cohort was managed in the era of IVIg and aspirin treatment. The rate of adverse events was similar to that experienced by a matched population without a previous history of KD. Only a minority (5%) of patients developed persistent coronary aneurysm after the acute KD illness, and long-term complications were restricted to this subgroup.

The secondary analysis, which included adverse events occurring any time after the KD hospitalization, revealed a larger association between KD status and the combined outcome because 3 additional events were included in the analysis and there were no events in the control population before the age of 15. The observed HRs were not statistically significant because the sample size was limited, but they suggest that a history of KD exposes patients to a small increase in cardiovascular risk before age 15.

The patients with KD were slightly more likely to develop hypertension during the follow-up period, a finding of uncertain significance that was not explained by a higher BMI in the KD group. We could find no previous studies in the medical literature associating KD with future clinical hypertension, although previous studies suggest that KD survivors have increased arterial stiffness.[11,12] The association between KD and future hypertension observed in the current study should be considered a hypothesis-generating finding. Longer-term follow-up data for KD disease have been published principally in Japan. The longest-term comprehensive cohort

TABLE 4 Long-term Rates of Adverse Outcomes in KD Versus Matched Non-KD Members

Outcome	KD Group			Non-KD Group		
	No. of Events	Person-Time, y	Incidence Rate[a] (95% CI)	No. of Events	Person-Time, y	Incidence Rate[a] (95% CI)
Acute coronary syndrome	2	8117	0.246 (0.062–0.985)	0	32 318	0 (—)
Coronary revascularization	1	8129	0.123 (0.017–0.873)	0	32 318	0 (—)
Heart failure	0	8135	0 (—)	1	32 318	0.031 (0.004–0.220)
SCD/ventricular arrhythmia	0	8135	0 (—)	1	32 318	0.031 (0.004–0.220)
Valvular disease or surgery	0	8135	0 (—)	0	32 318	0 (—)
Aortic aneurysm	0	8135	0 (—)	0	32 318	0 (—)
All-cause mortality	0	8135	0 (—)	6	32 322	0.186 (0.083–0.413)
Any adverse outcome	2	8129	0.246 (0.062–0.984)	7	32 322	0.217 (0.103–0.454)

SCD, Sudden Cardiac Death.

[a] Per 1000 patient-years.

study was published by Kato et al[13] and included KD cases treated during the pre-IVIg treatment era with follow-up periods of 10 to 21 years. Additionally, a Japanese registry study showed that for KD patients, mortality after the acute phase of the disease is increased only in the group of males with early cardiac lesions such as aneurysms. This group had a standardized mortality ratio of 2.6, with the majority of deaths from noncardiac causes.[14,15]

Similarly, the current study found that the adverse events occurred in male patients, but the gender effect was not statistically significant, and the overall rate of acute and longer-term adverse events in the cohort was smaller than that observed in the Japanese studies.[13–15] The observed reduction in adverse events is likely explained, at least partially if not primarily, by IVIg therapy during the era of the current study. Although a reduction in long-term events has been predicted in the IVIg era (because of a lower rate of persistent aneurysms),[4] no previous study has quantified the event rates in a large cohort.

Previous studies have described the pathophysiological mechanisms of KD's effects on coronary arteries.[4,13,15–17] It is believed that in the acute phase of the disease, there is coronary artery remodeling, disruption of the internal elastic lamina, and medial smooth muscle cell reconstruction with replacement by fibrosis and calcification. The underlying trigger is thought to be an inflammatory reaction, although it remains unclear what leads some KD patients to develop coronary aneurysms whereas others do not. During the acute phase, aneurysm formation is associated with a risk of coronary thrombosis and stenosis due to abnormal flow in these dysfunctional coronary arteries. In the long-term, it is believed that the changes in the architecture of the coronary artery walls result in endothelial cell dysfunction and, potentially, to increased rates of fatal and nonfatal cardiovascular events. There is evidence that endothelial function remains abnormal despite resolution of aneurysms in KD patients with aneurysm formation.[17]

The current study has several limitations. Because of the retrospective cohort design, potential outcomes could have been missed that were not documented in the available medical records or within the review parameters. For example, some of the patients changed insurance companies over time and thus their ongoing health history was not part of the KPNC medical record, although this was also true for the non-KD cohort members. For these reasons, the true rate of adverse cardiovascular events in the KPNC KD population may be higher than what was observed in the current study. In addition, the acute KD treatment data were missing in 11% of the cohort and a true association between treatment and outcome thus cannot be excluded by the current study. The study provided a mean follow-up period of 15 years, such that the average age of the KD cohort at the time of analysis was 21 years. It remains unknown whether these cohort members will have an increased risk of cardiovascular events as they age, especially as the incidence of coronary artery disease and coronary risk factors increases. We plan to follow this cohort approximately every 10 years.

Despite these limitations, this uniquely large North American KD cohort study provides novel and useful information relevant to the care of people who had KD in early childhood treated with IVIg and/or aspirin. These individuals appear to be at very low risk of adverse cardiovascular events through at least their early 20s. Additional validation studies are required as well as studies with longer-term follow-up.

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