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ORIGINAL RESEARCH

Kawasaki Disease With Coronary Artery Lesions Detected at Initial Echocardiography

Ryusuke Ae, MD, PhD; Ryan A. Maddox, PhD; Joseph Y. Abrams, PhD; Lawrence B. Schonberger, MD; Yosikazu Nakamura, MD, MPH; Masanari Kuwabara, MD, PhD; Nobuko Makino, MD, PhD; Koki Kosami, MD; Yuri Matsubara, MD; Daisuke Matsubara, MD, PhD; Teppei Sasahara, MD, PhD; Ermias D. Belay, MD

BACKGROUND: Detection of coronary artery lesions (CALs) at initial echocardiography can aid in diagnosing Kawasaki disease (KD) and inform primary adjunctive treatments. We aimed to characterize patients with KD with CALs detected at initial echocardiography.

METHODS AND RESULTS: We analyzed data from the nationwide Japanese KD survey that contained information on 103 222 population-based patients diagnosed with KD across Japan during 2011 to 2018. Patients with CALs detected at initial echocardiography were assessed by age, day of illness, and number of principal KD signs (≥3). Multivariable logistic regression analysis was performed to evaluate factors independently associated with CAL detection. Overall, 3707 (3.6%) patients had CALs detected at initial echocardiography. Patients aged <12 and ≥60 months were associated with CAL detection (adjusted odds ratio [95% CI], 1.28 [1.18–1.39] and 1.32 [1.20–1.45], respectively; reference, 12–59 months). Patients with delayed hospital visits were increasingly at higher risk for CAL detection (days 7–8, 1.84 [1.63–2.08]; days 9–10, 4.30 [3.58–5.15]; and days ≥11, 9.12 [7.63–10.90]; reference, days 1–4). Patients with 3 or 4 principal KD signs were independently associated with CAL detection (1.75 [1.63–1.88]). These patients were significantly more likely to be aged <12 months but were not associated with delayed hospital visit. Younger patients visited at earlier days of illness.

CONCLUSIONS: Timely diagnosis could be beneficial for patients with KD. However, even when the hospital visit occurred early in the course of illness, patients with 3 or 4 principal KD signs, especially younger patients, were at higher risk of CAL detection at initial echocardiography.

Key Words: coronary artery abnormality ■ echocardiography ■ Kawasaki disease

Kawasaki disease (KD) is an acute febrile illness of childhood characterized by systemic vasculitis.[1,2] Coronary artery lesions (CALs), such as coronary artery aneurysms, are among the most serious cardiac complications of KD, which has been shown to be the most common cause of acquired heart disease among children in developed countries.[3–5] The incidence of KD, for which the cause remains unknown, continues to increase globally, especially in Japan.[6–12]

Echocardiography should be promptly performed when KD is first suspected. Detection of CALs can help distinguish KD from other febrile illnesses.[13–17] Patients with fewer clinical signs consistent with KD, especially those aged <12 months, pose challenges to KD diagnosis and have higher prevalence of CALs at initial echocardiography.[18–24] Additionally, patients with CALs at initial echocardiography have higher risk for initial intravenous immunoglobulin (IVIG) treatment failure or subsequent progression of CALs.[20,25–28] Therefore, CAL detection at initial coronary screening is important not only to aid KD diagnosis but also to inform primary adjunctive treatments.[29–35] However,

Correspondence to: Ryusuke Ae, MD, PhD, Division of High–Consequence Pathogens and Pathology, National Center for Emerging and Zoonotic Infectious Diseases, Centers for Disease Control and Prevention, 1600 Clifton Road, Atlanta, GA 30333. E-mail: shirouae@jichi.ac.jp

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CLINICAL PERSPECTIVE

What Is New?

- Among patients with Kawasaki disease with ≥3 principal signs, approximately 4% had coronary artery lesions identified at initial echocardiography.
- Coronary artery lesions prevalence at initial echocardiography consistently increased after the fifth day of illness and was higher in patients with Kawasaki disease aged 0 to 5 months and ≥60 months compared with those at intermediate months of age, describing a U-shape trend.
- Patients with Kawasaki disease with 3 or 4 principal signs were independently associated with coronary artery lesions detection at initial echocardiography; these patients were significantly more likely to be aged <12 months but were not associated with delayed hospital visit.

What Are the Clinical Implications?

- While timely diagnosis and treatment could be beneficial for patients with Kawasaki disease with delayed hospital visit, patients with 3 or 4 principal signs, especially those <12 months of age, are at higher risk of having coronary artery lesions detected even when the hospital visit occurs early in the course of illness.

Nonstandard Abbreviations and Acronyms

CAL	coronary artery lesion
KD	Kawasaki disease

limited information is available on the prevalence among patients with KD of CALs detected at initial echocardiography and the risk factors that may be associated.

The nationwide Japanese KD survey has been conducted biennially since 1970 and contains substantial epidemiologic information.[9–12] Using the survey data of a large population of patients with KD, the study aimed to characterize patients with CALs detected at initial echocardiography and assess potential risk factors.

METHODS

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Study Setting and Participants

The study analyzed data derived from the nationwide KD surveys in Japan. The 22nd, 23rd, 24th, and 25th surveys were conducted in 2013, 2015, 2017, and 2019, respectively. Overviews of each survey have been previously documented.[9–12] These surveys obtained information for patients who were diagnosed with KD throughout Japan during an 8-year consecutive period (January 1, 2011 through December 31, 2018). The respondents represented 2 types of medical facilities throughout Japan: (1) hospitals specializing in pediatrics and (2) hospitals with ≥100 beds and a pediatric department. These facilities covered most hospitals across Japan where patients with KD are eventually hospitalized, diagnosed, and treated by pediatricians with KD expertise. The response rates were 72% to 77%.[9–12]

The 6 principal signs of KD are: (1) fever persisting ≥5 days (or until defervescence in response to treatment), (2) bilateral conjunctival injection, (3) oral mucosal changes, (4) polymorphous skin rash, (5) peripheral extremity changes, and (6) cervical lymphadenopathy. Complete KD was defined as the presence of 5 or 6 principal signs.

Outcome Measures and Exposures

Information for patients with the study outcome, CALs detected at initial echocardiography, was obtained from the survey data. The subtypes of CALs were based on the definition from the Japanese Ministry of Health.[36,37] Coronary artery dilatation was defined as a maximum absolute internal lumen diameter of ≥3 mm with any local dilatation finding in children aged <5 years or that of ≥4 mm in children aged ≥5 years. A coronary artery aneurysm was defined as a lumen size of 4 to 8 mm or ≥1.5 times greater than that of an adjacent segment. A giant coronary artery aneurysm was defined as a lumen size ≥8 mm. Larger CALs were noted if multiple CALs were detected in the same patient.

Patients with CALs detected at initial echocardiography were assessed by sex, age, day of illness at initial hospital visit, number of principal KD signs (≥3), sibling history of KD, and parental history of KD. The first day of illness onset was defined as the first day that the patient presented with signs related to KD. Age was categorized into 3 groups: <12, 12 to 59, and ≥60 months. Day of illness at initial hospital visit was categorized into 5 groups: 1 to 4, 5 to 6, 7 to 8, 9 to 10, and ≥11 days of illness. We also dichotomously classified initial hospital visit on 1 to 4 days and ≥7 days of illness, defining the former as “early hospital visit” and the latter as “delayed hospital visit.” The number of principal KD

signs were categorized into 2 groups: 3 or 4 signs and 5 or 6 signs.

Statistical Analysis

Patients were selected based on the criteria shown in Figure 1, excluding those without information on CALs at initial echocardiography, with a prior episode of KD (recurrent cases), with only 1 or 2 principal KD signs, aged ≥18 years, and with any missing value for any variable of the study. Patients with a prior episode of KD were excluded from the analysis because of the possibility that previous CALs could remain as coronary complications. Patients with 1 or 2 principal KD signs were also excluded because this group could include misdiagnosed patients with other febrile diseases.

First, we determined the prevalence of CALs detected at initial echocardiography by age (every 6 months) and day of illness. We then compared the distributions of patient characteristics, stratified by age group and number of principal KD signs. Finally, we performed multivariable logistic regression analysis to compare patients with and without CALs at initial echocardiography, calculating adjusted odds ratios (ORs)

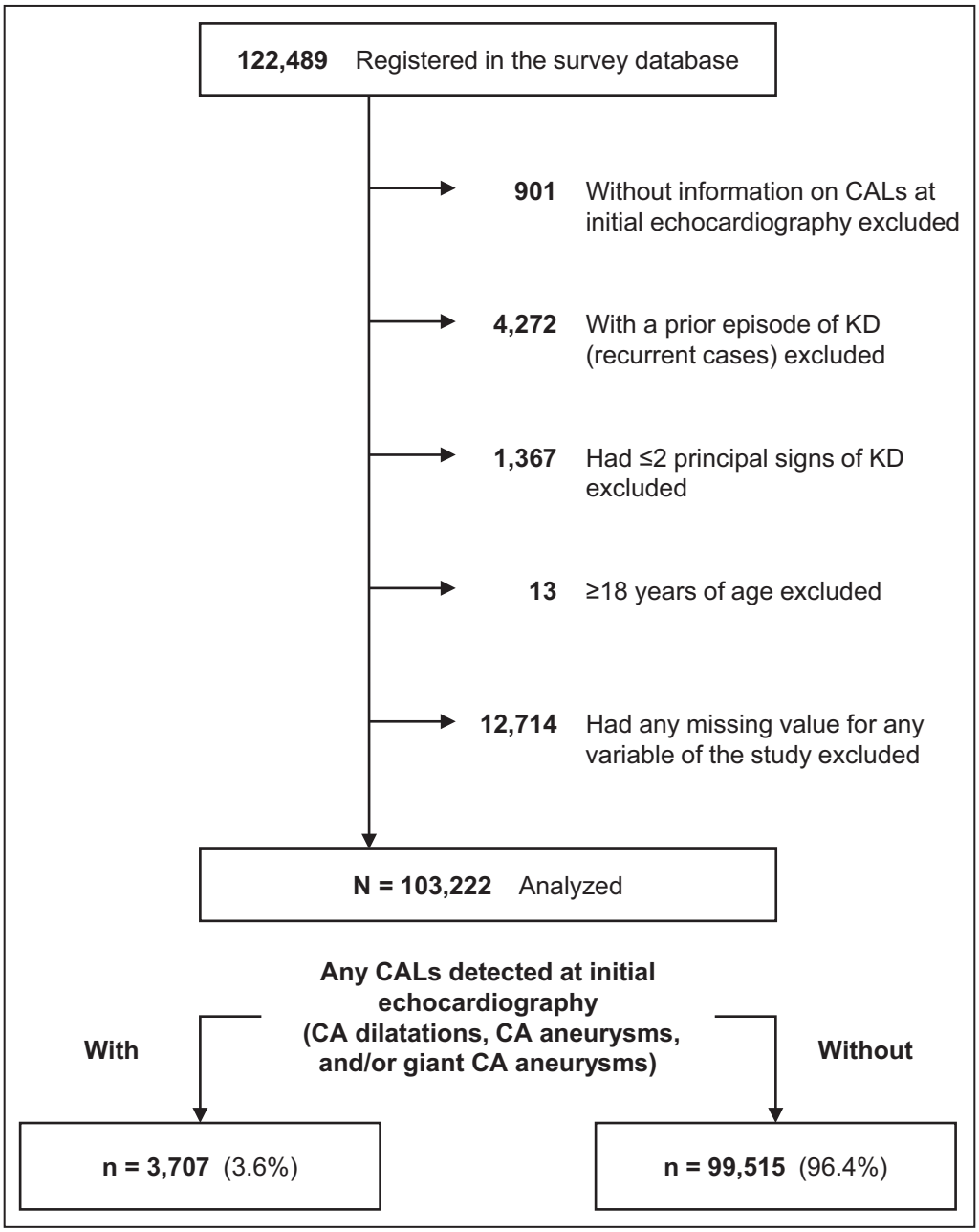

Figure 1. Patient selection (n=103 222).
CA indicates coronary artery; CAL, coronary artery lesion; and KD, Kawasaki disease.

Table 1. Patient Characteristics (n=103 222)

Characteristics	Patients, n (%)		*P* Value*
	With CALs	Without CALs	
	n=3707	n=99 515	
Male sex	2518 (68)	56 659 (57)	<0.001
Age, median (interquartile interval), mo	27 (12–49)	26 (13–44)	0.064
<12	922 (25)	20 888 (21)	<0.001
12–59	2197 (59)	66 210 (67)	
≥60†	588 (16)	12 417 (13)	
Day of illness at initial hospital visit, median (interquartile interval), d	4 (3–6)	4 (3–5)	<0.001
1–4	2098 (57)	63 984 (64)	<0.001
5–6	952 (26)	28 604 (29)	
7–8	334 (9)	5407 (5)	
9–10	146 (4)	985 (1)	
≥11	177 (5)	535 (1)	
No. of principal signs of KD			<0.001
5 or 6 signs	2532 (68)	80 165 (81)	
3 or 4 signs	1175 (32)	19 350 (19)	
Sibling case of KD (+)	101 (3)	2476 (3)	0.365
Parental history of KD (+)	53 (1)	1174 (1)	0.168
Subtypes of CALs‡			
Coronary artery dilatations	3343 (90)	NA	NA
Coronary artery aneurysms	316 (9)	NA	NA
Giant coronary artery aneurysms	49 (1)	NA	NA

CAL indicates coronary artery lesion; KD, Kawasaki disease; and NA, not applicable.
*Mann–Whitney *U* tests for median age and median day of illness at initial hospital visit; Chi-square tests for other categorical variables.
†Excluding patients aged ≥18 years.
‡Larger coronary artery lesions were noted if multiple coronary artery lesions were detected in the same patient.

with 95% CIs for each factor. All analyses were performed using IBM SPSS Statistics for Windows, Version 25 (IBM Corporation, Armonk, NY, USA). Categorical variables are presented as percentage of patients. Numerical variables are presented as medians with interquartile interval (25th percentile, 75th percentile). For

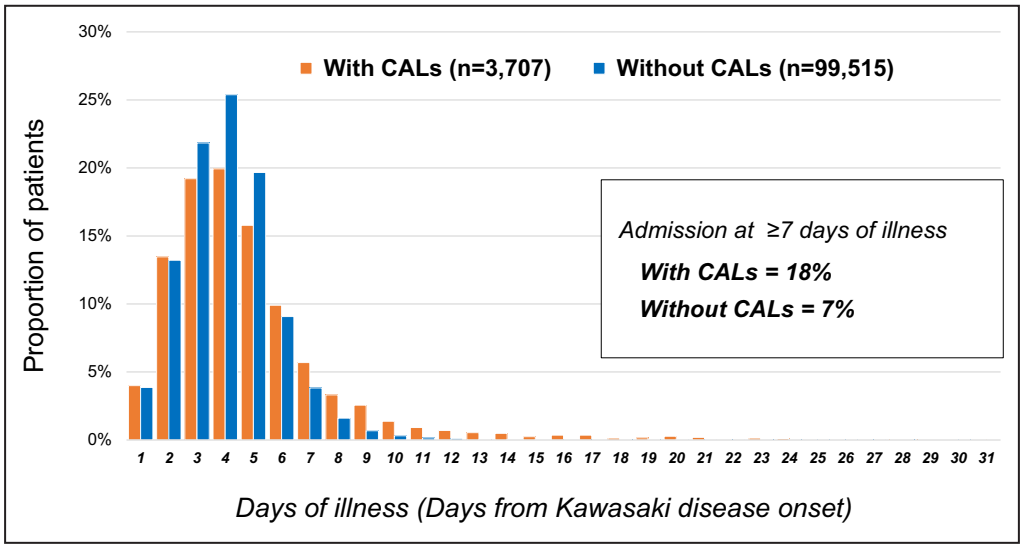

Figure 2. Days of illness at initial hospital visit by coronary artery lesion status (n=103 222).
CAL indicates coronary artery lesion.

comparison of different groups, Chi-square tests were used for categorical variables, and Mann–Whitney *U* tests and Kruskal–Wallis tests were used for continuous variables. The significance threshold was set at $P<0.05$. The Jichi Medical University Clinical Research Ethics Committee approved the study and waived the requirement for informed consent (Approval ID: 18–070).

RESULTS

Among 122 489 patients with KD identified from 2011 to 2018, 103 222 (84.3%) were eligible for analysis (Figure 1). Overall, 3707 (3.6%) patients had CALs detected at initial echocardiography; 3343 (90%) had coronary artery dilatations, 316 (9%) had coronary artery aneurysms, and 49 (1%) had giant coronary artery aneurysms. Compared with patients without CALs detected at initial echocardiography (Table 1), those with CALs were more likely to be male (68% versus 57%, $P<0.001$). More than half of patients with CALs at initial echocardiography visited a hospital at 1 to 4 days from disease onset (n=2098, 57%). However, 657 (18%) of 3707 patients with CALs visited at ≥7 days from onset, compared with 6927 (7%) of 99 515 patients without CALs at initial echocardiography (Figure 2). Patients

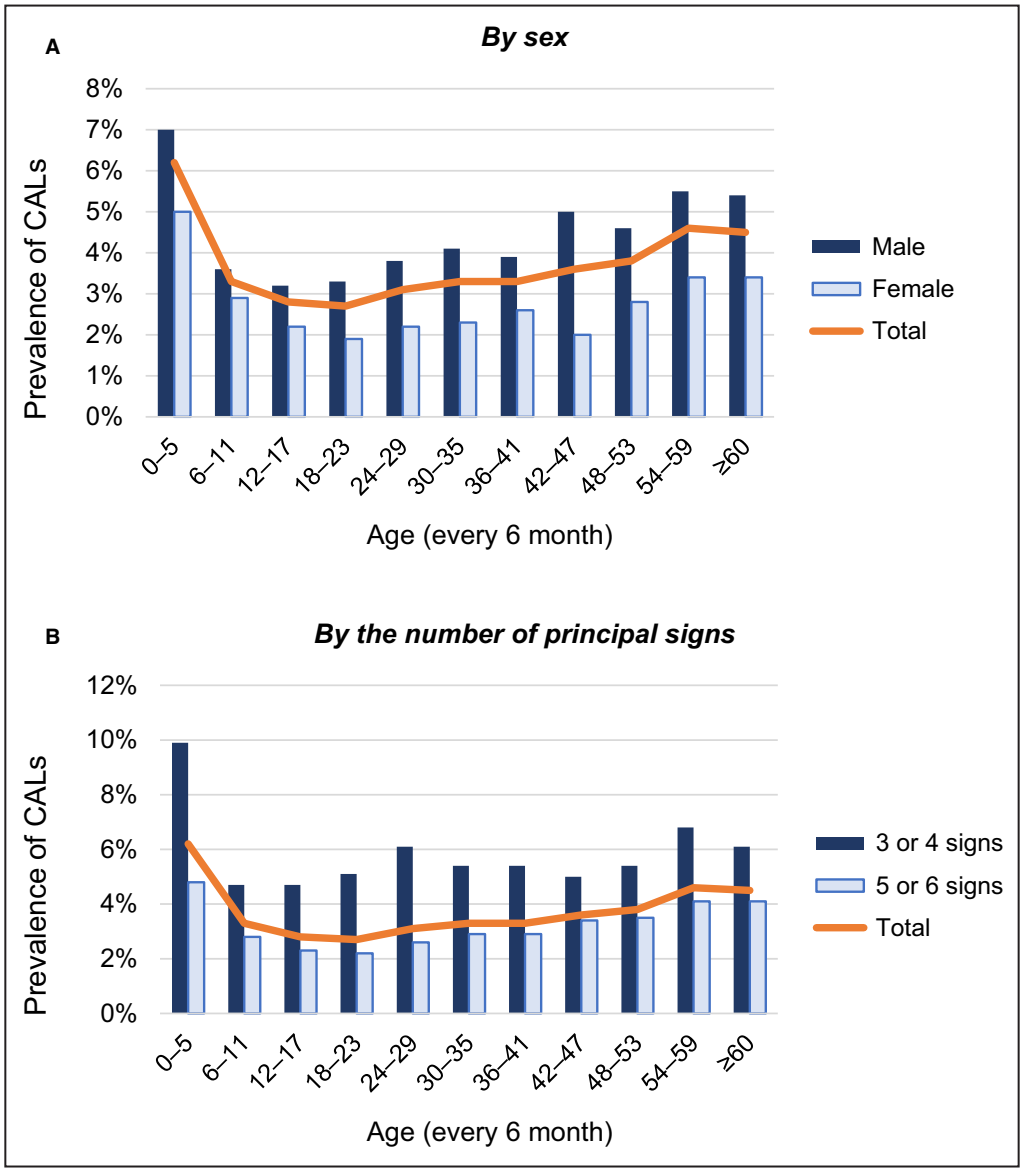

Figure 3. Prevalence of coronary artery lesions detected at initial echocardiography by 6-month age group (n=3707).
A, Stratified by sex; (**B**) Stratified by the number of principal signs. Percentage of the total prevalence (line in orange color) is common in both subfigures although the scale of the vertical axes may differ. CAL indicates coronary artery lesion.

with CALs detected at initial echocardiography were more likely to have 3 or 4 principal KD signs compared with patients without CALs (32% versus 19%, *P*<0.001, Table 1). Days of illness at the time of initial hospital visit ranged from 1 to 31 and 1 to 30 days among those with and without CALs at initial echocardiography, respectively.

A U-shape trend was found in the prevalence of CALs detected at initial echocardiography according to 6-month age groups, ranging from the highest at 0 to 5 months of age (6.2% in total) to the lowest at 18 to 23 months (2.7%) (Figure 3). Stratified by number of principal KD signs, the prevalence in patients with 3 or 4 signs was consistently higher than complete patients with KD regardless of the 6-month age group (Figure 3B). Analysis of patient characteristics by 3 age groups (Table 2) found that patients aged <12 months initially visited a hospital significantly earlier than older patients (visit at 1–4 days of illness: <12 months of age=68%, 12–59 months=54%, and ≥60 months=50%; *P*<0.001), while older patients were associated with delayed hospital visit (≥7 days of illness: 15%, 18%, and 21%, respectively; *P*<0.001). Additionally, younger patients were more likely to have 3 or 4 principal KD signs (<12 months of age=41%, 12–59 months=28%, and ≥60 months=30%; *P*<0.001).

The prevalence of CALs detected at initial echocardiography was almost unchanged within 5 days from KD onset but consistently increased with days from the sixth day of illness and exceeded 10% from the ninth day (prevalence in total: day 1=3.7%, day 4=2.8% [at minimum], day 5=2.9%, day 7=5.3%, day 10=14.1%, and days ≥11=24.9%) (Figure 4). This indicated that delayed hospital visit, specifically ≥5 days from disease onset, was strongly associated with CAL detection at initial echocardiography. Stratified by age group, the prevalence in patients aged <1 year drastically increased after 8 days from disease onset, resulting in >40% at ≥11 days (Figure 4B). Furthermore, stratified by the number of principal KD signs, the prevalence in patients with 3 or 4 signs was consistently higher than those with 5 or 6 signs regardless of days at initial hospital visit (Figure 4C). Patients with 3 or 4 principal KD signs were significantly younger than those with 5 or 6 signs (proportion of patients aged <1 year: 32% versus 22%; *P*<0.001, Table 3).

Factors independently associated with patients with CALs detected at initial echocardiography compared with those without were assessed by multivariable logistic regression (Table 4). Male patients were more likely to have CALs detected at initial echocardiography (adjusted OR [95% CI], 1.59 [1.48–1.70]). Patients aged <12 and ≥60 months were more likely to have CALs detected at initial echocardiography compared with those aged 12 to 59 months (<12 months: 1.28 [1.18–1.39] and ≥60 months, 1.32 [1.20–1.45], respectively). Compared with patients who initially visited a hospital on days 1 to 4 of illness, odds of CAL detection at initial echocardiography significantly increased after days 7 to 8 (days 7–8, 1.84 [1.63–2.08]; and days ≥11, 9.12 [7.63–10.90]). Having 3 or 4 KD signs was also an independent factor associated with CAL detection at initial echocardiography (1.75 [1.63–1.88]). No significant association with CAL detection at initial echocardiography was found among patients with a sibling or parental history of KD.

DISCUSSION

The present study includes 4 key findings. First, among patients with KD with at least 3 principal signs of the disease, 3.6% had CALs detected at initial echocardiography. Second, prevalence of CALs detected at initial echocardiography consistently increased after the fifth day of illness and was beyond 10% after the ninth day; the prevalence sharply increased among patients aged <12 months. Third, the prevalence was higher in patients aged 0 to 5 months as well as ≥60 months compared with those at intermediate months of age,

Table 2. Patients With Coronary Artery Lesions Initially Detected at Initial Echocardiography by Age Group (n=3707)

Characteristics	Patients, n (%)			*P* Value*
	Age Groups, mo			
	<12 (n=922)	12–59 (n=2197)	≥60 (n=588)	
Male sex	613 (66)	1511 (69)	394 (67)	0.400
Day of illness at initial hospital visit, median (interquartile interval), d	3 (2–5)	4 (3–6)	4 (3–6)	<0.001
Initial hospital visit on 1–4 d of illness (early hospital visit)	626 (68)	1177 (54)	295 (50)	<0.001
Initial hospital visit on ≥7 d of illness (delayed hospital visit)	134 (15)	402 (18)	121 (21)	0.006
3 or 4 principal signs of KD	375 (41)	623 (28)	177 (30)	<0.001
Sibling case of KD (+)	12 (1)	72 (3)	17 (3)	0.008
Parental history of KD (+)	17 (2)	33 (2)	3 (1)	0.094

KD indicates Kawasaki disease.
*Kruskal–Wallis tests for median day of illness at initial hospital visit; Chi-square tests for other categorical variables.

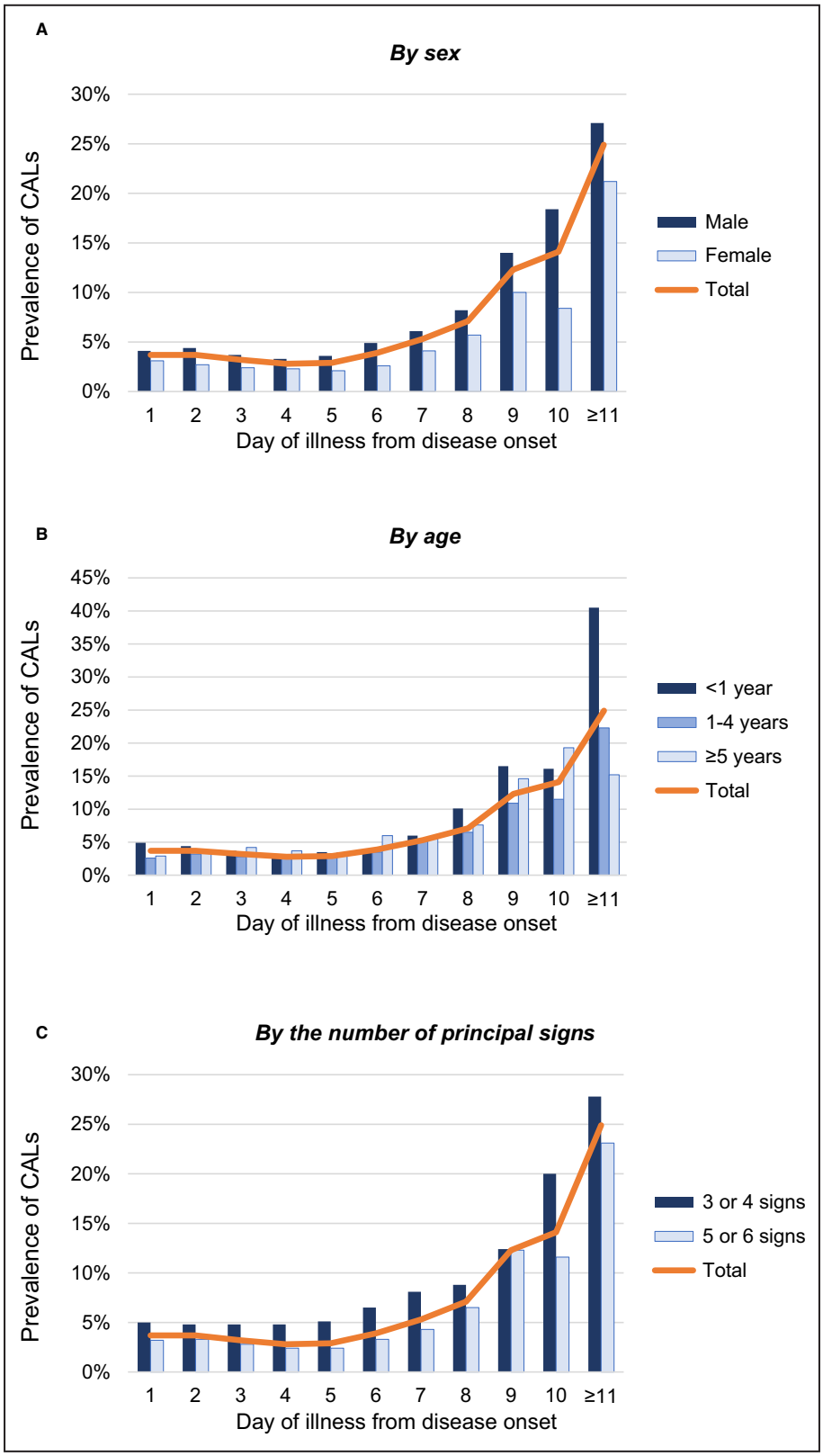

Figure 4. Prevalence of coronary artery lesions detected at initial echocardiography by day of illness (n=3707).
A, Stratified by sex; (**B**) Stratified by age groups; (**C**) Stratified by the number of principal signs. Percentage of the total prevalence (line in orange color) is common in all 3 subfigures although the scale of vertical axes may differ. CAL indicates coronary artery lesion.

Table 3. Patients With Coronary Artery Lesions Detected at Initial Echocardiography by Number of Principal Signs (n=3707)

Characteristics	Patients, n (%)		*P* Value*
	No. of Principal Signs of KD		
	3 or 4 Signs (n=1175)	5 or 6 Signs (n=2532)	
Male sex	779 (66)	1739 (69)	0.148
Age, median (interquartile interval), mo	21 (9–45)	30 (14–50)	<0.001
Age <12 mo	375 (32)	547 (22)	<0.001
Day of illness at initial hospital visit, median (interquartile interval), d	4 (3–6)	4 (3–6)	0.012
Initial hospital visit on 1–4 d of illness (early hospital visit)	629 (54)	1469 (58)	0.010
Initial hospital visit on ≥7 d of illness (delayed hospital visit)	250 (21)	407 (16)	<0.001
Sibling case of KD (+)	33 (3)	68 (3)	0.831
Parental history of KD (+)	16 (1)	37 (1)	0.812

KD indicates Kawasaki disease.
*Mann–Whitney *U* tests for median age and median day of illness at initial hospital visit; Chi-square tests for other categorical variables.

describing a U-shape trend. Finally, patients with 3 or 4 principal KD signs were independently associated with CAL detection at initial echocardiography. These patients were significantly more likely to be aged <12 months but were not associated with delayed hospital visit. Rather, younger patients visited a hospital at earlier days of illness. Because IVIG initiation before the fifth day of illness could lead to improved 30-day–post-onset CALs among patients with CALs detected at initial echocardiography,[28] timely diagnosis and treatment could be particularly beneficial for patients with 3 or 4 principal KD signs and delayed hospital visit. Although an algorithm from the American Heart Association[5] recommends evaluating suspected patients with KD at 5 days of illness, waiting for ≥5 days before initiation of treatment might risk CAL development in at least 3% of patients with KD.

Previous studies have reported relatively high CAL prevalence at initial echocardiography (range, 22%–44%)[19,20,24] By contrast, our findings were much lower than these previous reports. There are several possible reasons for the large differences in prevalence between

Table 4. Factors Associated With Patients With Coronary Artery Lesions Detected at Initial Echocardiography (n=103 222)

Characteristics	Unadjusted ORs (95% CIs)	*P* Value	Adjusted ORs (95% CIs)*	*P* Value
Male sex	1.60 (1.49–1.72)	<0.001	1.59 (1.48–1.70)	<0.001
Age group, mo				
<12	1.33 (1.23–1.44)	<0.001	1.28 (1.18–1.39)	<0.001
12–59	1 [Reference]	NA	1 [Reference]	NA
≥60†	1.43 (1.30–1.57)	<0.001	1.32 (1.20–1.45)	<0.001
Day of illness at initial hospital visit				
1–4	1 [Reference]	NA	1 [Reference]	NA
5–6	1.02 (0.94–1.10)	0.707	1.05 (0.97–1.14)	0.195
7–8	1.88 (1.67–2.12)	<0.001	1.84 (1.63–2.08)	<0.001
9–10	4.52 (3.78–5.41)	<0.001	4.30 (3.58–5.15)	<0.001
≥11	10.09 (8.47–12.03)	<0.001	9.12 (7.63–10.90)	<0.001
No. of principal signs of KD				
5 or 6 signs	1 [Reference]	NA	1 [Reference]	NA
3 or 4 signs	1.92 (1.79–2.06)	<0.001	1.75 (1.63–1.88)	<0.001
Sibling case of KD (+)	1.10 (0.90–1.34)	0.365	1.11 (0.91–1.37)	0.301
Parental history of KD (+)	1.22 (0.92–1.60)	0.169	1.25 (0.95–1.66)	0.116

KD, Kawasaki disease; NA, not applicable; and OR, odds ratio.
*Adjusted for all the variables listed in this table.
†Excluding patients aged ≥18 years.

studies. First, patients in our study initially visited a hospital earlier than in previous studies; median day of illness at initial echocardiography was day 4 in our study versus days 6 to 8 in previous studies, which could impact the results. Second, previous studies included small numbers of selected participants (n=100–621) from limited medical facilities, resulting in a large selection bias. By contrast, we analyzed large-scale data obtained from a general population of patients with KD. Third, our results might underestimate the prevalence of CALs because we used the Japanese criteria as the definition of CAL,[36,37] instead of evaluation using Z-scores,[38–40] by which the previous studies measured CALs.[19,20,24] Use of the Z-score criteria might result in increased recognition of CALs.[15,41]

The finding that patients aged <12 months were more likely than other aged patients to have 3 or 4 principal KD signs, with a higher prevalence of CALs detected at initial echocardiography, is consistent with results from previous studies. A meta-analysis previously indicated that the association between the presence of ≤4 principal KD signs and an increased risk of CALs was more prominent in patients younger than 12 months.[21] Furthermore, infants with KD have a higher prevalence of CALs with a more severe form than older children, requiring prompt echocardiographic examination for the diagnosis as well as careful long-term monitoring for the complications.[23–25] Our results showed infants with CALs visited a hospital earlier from disease onset regardless of the number of principal KD signs compared with older patients, indicating that abnormal change in coronary arteries due to systemic rapid inflammation might begin extremely early in the KD illness, possibly at the afebrile stage among the young population.

Using the past survey data, Sudo et al[42] previously reported an association between CALs and ≤4 principal signs of KD. They reported that patients with ≤4 KD signs received initial IVIG treatment significantly later with higher occurrence of CALs than complete patients with KD, suggesting that timely diagnosis and treatment of those with ≤4 KD signs could further prevent CAL development.[42] While consistent with our findings, specific information regarding CALs at initial echocardiography was not available for their study, which assessed CALs detected ≤30 days from onset as outcomes; 2863 (10.3%) of 27 906 patients had detectable CALs.[42] Addressing their study limitation, we focused on 3707 (3.6%) of 103 222 patients with CALs detected at initial echocardiography.

Delayed hospital visit was an independent predictor of CALs detected at initial echocardiography, consistent with the concept that earlier admission may increase the likelihood of KD treatment preventing CALs.[5,28] However, our results also indicate that 57% of the patients with CALs initially detected visited a hospital at 1 to 4 days from disease onset. Although some studies previously reported that patients receiving early IVIG treatment (at 1–4 days from KD onset) were at higher risk for CAL development,[43–46] such patients are most likely to experience an initial rapid and severe form of disease and therefore should be treated as early as possible.[47–49] Recent studies indicated that patients with CALs at diagnosis were likely to result in progression of CALs even after standard treatment.[26,28] Intensification of primary IVIG treatment might be required for such patients.[29–35]

Our study has some limitations. First, the data set did not include information for specific types of principal KD signs; only the number of signs was available. Previous studies reported that CAL occurrence might differ related to combinations of specific principal KD signs manifesting in patients with ≤4 KD signs.[20,50] Second, the data set also did not include information regarding initial principal sign or when in the course of illness each sign appeared. Fever may not have always been present at illness onset; a previous study reported afebrile patients with KD[51] who were diagnosed based on the Japanese criteria[52] but not the American Heart Association criteria.[5] Third, our results might underestimate the true prevalence of CALs because we lacked information on Z-score evaluation; to an unknown extent, the use of Z-score criteria could have resulted in increased detection of CALs.[15,41] Finally, the assessment of echocardiogram findings was not standardized or centralized. Although our study has the above limitations, it benefits from access to 8 years of data from the Japanese nationwide KD survey, which includes records on a vast number of patients with KD diagnosed in Japan and is the largest source of data on patients with KD worldwide.

CONCLUSIONS

We evaluated the prevalence of CALs detected at initial echocardiography in patients with KD, and associated risk factors, using a large epidemiologic data set. Among all patients with KD with at least 3 principal signs, those who had CALs at initial echocardiography were associated with hospital visit after the fifth day of illness and the presence of only 3 or 4 principal signs. While timely diagnosis and treatment could be beneficial for patients with delayed hospital visit, patients with 3 or 4 principal signs, especially those <12 months of age, are at higher risk of having CALs detected even when the hospital visit occurs early in the course of illness.

ARTICLE INFORMATION

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Affiliations

From the Division of High–Consequence Pathogens and Pathology, National Center for Emerging and Zoonotic Infectious Diseases, Centers for Disease Control and Prevention, Atlanta, GA (R.A., R.A.M., J.Y.A., L.B.S., E.D.B.); Division of Public Health, Center for Community Medicine (R.A., Y.N., M.K., N.M., K.K., Y.M., T.S.) and Department of Pediatrics, Jichi Medical University, Tochigi, Japan (D.M.).

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Disclosures

None.

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