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Kawasaki Disease Outcomes and Response to Therapy in a Multiethnic Community: A 10-Year Experience

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Objectives To describe the epidemiology, response to therapy, and outcomes of Kawasaki disease in a multiethnic community with a large Hispanic and Asian population.

Study design We analyzed prospectively collected data from 788 unselected patients with Kawasaki disease diagnosed and treated at a single medical center over a 10-year period.

Results The average incidence of Kawasaki disease in children <5 years in San Diego County over the 10 years from 2006 to 2015 was 25 per 100 000 children, with the greatest incidence (50 per 100 000) for Asian/Pacific Islanders. Compared with other race/ethnicities, Asian/Pacific Islander patients with Kawasaki disease were younger, were diagnosed earlier in the course of their fever, had higher levels of inflammatory markers, and were more likely to develop aneurysms. There was no difference across race/ethnicity groups in response to intravenous immunoglobulin therapy. Filipino children had the highest recurrence rates (9.1%; 95% CI, 3.0%-22.6%) and 12 of 788 patients (1.5%) had a first- or second-degree relative with a history of Kawasaki disease. After correcting for age of onset, sex, and illness day at diagnosis, Asian/Pacific Islander children had an increased risk of developing aneurysms (aOR, 2.37; 95% CI, 1.37-4.11; $P = .002$). Overall, 180 of 788 patients (22.8%) had a maximal Z score of 2.5-10.0 and 14 of the 788 patients (1.8%) had a maximal Z score ≥10.0 despite 84% of these patients being treated within 10 days of fever onset.

Conclusions Our data provide new insights into the natural history of treated Kawasaki disease in a multiethnic population. Patient race/ethnicity influenced susceptibility to Kawasaki disease, timing of diagnosis, coronary artery outcome, and recurrence rates. *(J Pediatr 2018;203:408-15).*

Most of the large epidemiologic and clinical outcome studies of Kawasaki disease have been performed in Japan,[1,2] yet genetic factors are known to influence both susceptibility to Kawasaki disease and disease outcome.[3,4] Thus, a study of Kawasaki disease in a multiethnic population might reveal important differences in susceptibility, response to therapy, and coronary artery outcome. To date, the largest analyses in the US have used administrative databases, which have the advantages of geographic diversity and large numbers and the limitations of the lack of granularity of the data.[5-7] Although Kawasaki disease was first described >50 years ago and intravenous immunoglobulin (IVIG) was established as effective therapy >30 years ago, a subset of our patients with Kawasaki disease continue to suffer significant morbidity. We analyzed a large Kawasaki disease cohort from a single center in a multiethnic community with a large Hispanic and Asian population to gain insight into the influence of race/ethnicity on Kawasaki disease outcomes.

Methods

The Kawasaki Disease Research Center at the University of California San Diego/Rady Children's Hospital San Diego (RCHSD) maintains a database of standardized, prospectively collected data on patients treated for Kawasaki disease at RCHSD, a free-standing children's hospital that is the primary pediatric inpatient facility serving a population of approximately 3.5 million spread over 3 counties. These patients were admitted to a dedicated in-patient team, with 1 of the 2 Kawasaki disease clinicians as the attending physician. All patients were treated according to standardized protocols and were followed in a dedicated Kawasaki disease weekly clinic, where they

AHA	American Heart Association
IVIG	Intravenous immunoglobulin
LAD	Left anterior descending
RCA	Right coronary artery
RCHSD	Rady Children's Hospital San Diego
Z_{max}	Maximal Z score of the LAD or RCA measured at any time point

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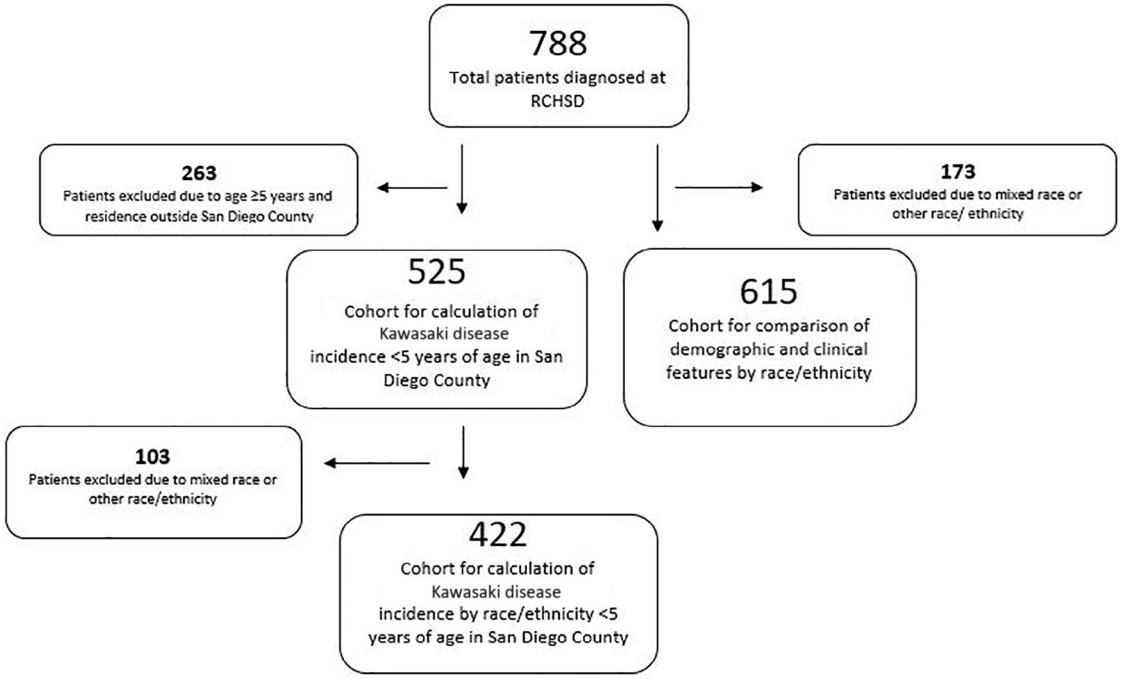

Figure 1. Cohorts used for this study.

were seen after discharge by the 2 Kawasaki disease clinicians at a minimum of 2 weeks, 6 weeks, 1 year, and every 5 years until the late teenage years. All patients diagnosed with Kawasaki disease between January 1, 2006, and December 31, 2015, in our database were included in the current analysis. Prospectively collected data included age at onset, sex, self-reported race/ethnicity of both biologic parents, a family history of Kawasaki disease, Kawasaki disease clinical criteria, therapy, laboratory, echocardiographic data, and subsequent recurrence. Patients were classified as mixed if their parents self-identified as belonging to different race/ethnicity groups. The collection of data was approved by the Institutional Review Board at the University of California San Diego and parents and participants gave signed informed consent or assent as appropriate.

Four defined cohorts were used for the analyses (**Figure 1**). For analysis of treatment response and coronary artery outcomes, we included all patients with Kawasaki disease (n = 788) diagnosed at our center regardless of age or county of residence. Population data for children <5 years of age were based on estimates and projections from the 2000 and 2010 US Census obtained from the San Diego Association of Governments (constructed from US Census Bureau's American Community Survey 2006-2015 10-year file). The prevalence of Kawasaki disease was calculated per 100 000 children <5 years of age residing in San Diego County (n = 525) and stratified by self-declared race/ethnicity (n = 422). For analysis of demographic, clinical laboratory data, and disease outcome stratified by race/ethnicity, we included all patients diagnosed at our center and belonging to 1 of the following 4 groups: Asian/Pacific Islander, black, white, and Hispanic (n = 615). The 173 patients of mixed ancestry or belonging to groups with <10 patients (eg, Chaldean, Somali) were excluded from this analysis.

Patients diagnosed with Kawasaki disease at RCHSD were classified as follows: complete Kawasaki disease, fever plus 4 of 5 standard criteria as per the American Heart Association (AHA) guidelines, or incomplete Kawasaki disease, <4 clinical criteria with laboratory or echocardiographic criteria as per the AHA definition of incomplete Kawasaki disease.[8] A minority of patients who met <4 criteria and did not fulfill the AHA criteria for incomplete Kawasaki disease were diagnosed and treated by 1 of 2 expert Kawasaki disease clinicians. Patients were classified as missed Kawasaki disease if they presented at the time of digit peeling after resolution of the acute illness but had a history of fever for ≥5 days and met 4 of the 5 classic criteria by parental history and photographic documentation of clinical signs.

Patients underwent echocardiographic evaluation at the time of diagnosis and at 2 weeks, 6 weeks, 1 year, and 5 years after initial hospitalization or more frequently as clinically indicated. Coronary artery dimensions were described as Z-scores (internal dimension of the coronary artery expressed as SDs from the mean normalized for body surface area).[9] The maximal Z score of the left anterior descending (LAD) or right coronary artery (RCA) measured at any time point (Z_{max}) on any echocardiogram was recorded. Coronary artery Z-scores were classified according to the AHA 2017 guidelines as follows: normal, <2.0; dilated, $2 \geq Z < 2.5$; aneurysm: $2.5 < Z < 10.0$; and giant aneurysm, ≥10.0.

Therapy was stratified into 6 categories: IVIG alone, IVIG plus infliximab for cardiac indications (Z score of ≥2.5 on initial

echocardiogram), IVIG plus infliximab for severe illness, IVIG plus infliximab in a phase III clinical trial,[10] IVIG plus infliximab plus advanced therapies in clinical trials,[11,12] and late treatment (after day 10). IVIG resistance was defined as persistent or recrudescent fever (temperature of ≥38.0°C rectally or orally) ≥36 hours but not >7 days after completion of the first IVIG infusion without other cause. For analysis of IVIG resistance, we included only those patients who received IVIG plus aspirin within the first 10 days after fever onset. The rationale for this was that Kawasaki disease is a self-limited illness and the disappearance of fever after 10 days could be attributed to either a positive response to therapy or the natural history of the illness.

Statistical Analyses

Descriptive summaries were performed for the various cohorts (**Figure 1**). The prevalence of Kawasaki disease among those <5 years of age was calculated as the number of cases divided by the population <5 years of age for each year from 2006 to 2015. Prevalence was also calculated by 4 race/ethnicity groups (Asian/Pacific Islander, black, white, and Hispanic; mixed race and other race were not analyzed) and compared among groups using the proportion test.

To compare the demographic, clinical laboratory data, and disease outcome among the 4 race/ethnicity groups, the Fisher exact test was used for categorical variables and the Kruskal-Wallis test was used for continuous variables for overall difference among the groups. Further pairwise tests were conducted if the overall test was significant. We included all patients from the 4 race/ethnicity groups who were diagnosed at the center (n = 615). For laboratory values that were outside the dynamic range of the test (eg, erythrocyte sedimentation rate of ≥140 mm/hour), the maximal value detected by the assay was used. Multivariable logistic regression was performed to assess the difference in coronary artery aneurysm rate among the different ethnicity groups adjusting for age of onset, sex, and illness days. All statistical analyses were conducted in R version 3.3.2 (R Foundation for Statistical Computing, Vienna, Austria; available at: http://www.R-project.org).

Results

Over the 10-year study period, 788 patients were initially diagnosed at RCHSD with between 60 and 95 new patients with Kawasaki disease per year (**Figure 2**; available at www.jpeds.com). Of the 788, 525 were <5 years old and had their onset and primary residence in San Diego County. Of the 525, 327 (62%) were males; 98 (19%) were Asian/Pacific Islander, 23 (4%) were black, 111 (21%) were white, 190 (36%) were Hispanic, and 103 (20%) were mixed race or other. The prevalence of Kawasaki disease among children <5 years over the 10 years was 25 ± 4.4 per 100 000 (mean ± SD). As has been previously observed, Asian/Pacific Islander children had the highest prevalence (mean ± SD of 50 ± 20/100 000) and were overrepresented in our Kawasaki disease population (**Figure 3** and **Table I**; available at www.jpeds.com). As an example, for 2010, Asian/Pacific Islander children were 9.0% of the <5-year-old population in San Diego County according to the 2010 census, but 17% (11 of 65) of the <5-year-old Kawasaki disease cohort.

Of the 788 patients diagnosed at RCHSD over the 10 years, 130 (16.5%) were Asian/Pacific Islander, 35 (4.4%) black, 178 (22.6%) white, 272 (34.5%) Hispanic, and 173 (22.0%) were mixed race or reported as other. Of the 130 children classified as Asian/Pacific Islander, the largest subset (34%) were of Filipino descent (**Figure 4**; available at www.jpeds.com). Because of the recognized differences in age of onset of Kawasaki disease in Asian and Western populations, we examined the age structure of our cohort by race/ethnicity.[1,13-15] Asian/Pacific Islander and Hispanic patients were younger compared with other groups (**Table II**; median age, 2.4 years for Asian/Pacific Islander vs 3.6 years for white [$P < .001$]; median age, 2.5 years for Hispanic vs 3.6 years for white [$P = .001$] by pairwise Wilcoxon rank-sum test). Another notable demographic difference across the race/ethnicity groups is that Asian/Pacific Islander children were diagnosed earlier (median illness day, 6; IQR 4-7; Asian/Pacific Islander vs white, $P = .03$; Asian/Pacific Islander vs Hispanic, $P < .001$; Asian/Pacific Islander vs black, $P = .055$). Overall, a delayed diagnosis beyond day 10 of illness occurred in 16.8% of the cohort.

Differences were noted across the race/ethnicity strata for several laboratory values related to the severity of inflammation (**Table II**). The white blood cell count was least elevated among black patients (black vs Asian/Pacific Islander, $P = .01$; black vs Hispanic, $P = .03$) and most elevated among Asian/Pacific Islander patients (Asian/Pacific Islander vs white, $P = .008$). Asian/Pacific Islander patients also had a higher erythrocyte sedimentation rate at diagnosis ($P < .001$ vs white; $P = .004$ vs black; and $P = .03$ vs Hispanic). More pronounced normochromic, normocytic anemia was noted in the black and Hispanic populations (Hispanic vs white, $P = .004$; black vs white, $P = .03$). Elevation of the gamma glutamyl transpeptidase was most marked among the Hispanic patients ($P = .002$ vs white).

There was no difference across the race/ethnicity strata in response to IVIG therapy with 62 of the 394 (15.7%) treated within the first 10 days after fever onset classified as IVIG resistant (**Table II**). Of the 615 patients, 66 (10.7%) had dilated coronary arteries (Z_{max} of ≥2.0 and <2.5), 142 patients (23.1%) developed aneurysms (Z_{max} of ≥2.5 and <10.0), and 12 patients (2.0%) developed giant aneurysms (Z_{max} of ≥10). Despite earlier diagnosis and treatment among our Asian/Pacific Islander population, this group had worse coronary artery outcomes with higher rates of aneurysms ($P = .004$ vs Hispanic; $P < .001$ vs white). Of the 124 Asian/Pacific Islander children treated within the first 10 days after fever onset, 50 (40.3%) developed aneurysms (Z_{max} of ≥2.5). After adjusting for age of onset, sex, and illness day at diagnosis, Asian/Pacific Islander children had an increased risk of developing aneurysms (aOR, 2.37; 95% CI, 1.37-4.11; $P = .002$). This finding is consistent with this group's higher values for pretreatment markers of inflammation.

Of the entire cohort of 788 patients, 44 (5.6%) were not treated because they presented beyond the 10th day of illness when clinical signs and inflammation had resolved and the

Table II. Comparison of demographic and clinical characteristics, response to therapy, and outcome among 615 patients with Kawasaki disease stratified by race/ethnicity group

	Asian/Pacific Islander	Black	White	Hispanic	Total	*P* value*
	(n = 130)	(n = 35)	(n = 178)	(n = 272)	(n = 615)	
Age at onset, y	2.4 (1.1 to 4.1)	3.1 (0.9 to 4.8)	3.6 (1.9 to 5.3)	2.5 (1.4 to 4.5)	2.8 (1.4 to 4.7)	.001
Sex						
Male	70 (53.8)	23 (65.7)	120 (67.4)	160 (58.8)	373 (60.7)	.082
Illness, day at diagnosis						
≤10 d	124 (95.4)	26 (74.3)	142 (79.8)	220 (80.9)	512 (83.3)	<.001
>10 d	6 (4.6)	9 (25.7)	36 (20.2)	52 (19.1)	103 (16.8)	
White blood cell count						.008
$\times 10^3$	14.45 (10.8 to 18.0)	10.7 (8.3 to 15.1)	12.35 (9.6 to 16.1)	13.5 (10.4 to 17.7)	13.3 (10.1 to 17.3)	
n	128	33	172	263	596	
zHgb	−1.29 (−2.2 to −0.3)	−1.5 (−2.4 to −0.7)	−1 (−2 to 0)	−1.33 (−2.3 to −0.5)	−1.22 (−2.2 to −0.3)	.014
n	128	33	172	263	596	
Platelet count						.458
$\times 10^3$	395 (283 to 483)	378 (292 to 478)	342 (266 to 466)	361 (285 to 455)	364 (282 to 465)	
n	128	32	172	263	595	
ESR						<.001
mm/h	62 (46 to 83)	48 (23 to 63)	48 (33 to 67)	58 (39 to 73)	56 (35 to 73)	
n	118	33	166	259	576	
CRP						.122
mg/dL	7.1 (4.1 to 15.7)	6.6 (4.1 to 14.7)	5.5 (3.2 to 12.6)	7 (3.6 to 14.9)	6.5 (3.6 to 14.9)	
n	127	33	171	260	591	
ALT						.027
IU/L	31 (18 to 87)	26 (18 to 79)	36 (23 to 105)	49 (26 to 114)	39 (22 to 107)	
n	121	31	160	240	552	
GGT						.018
IU/L	37 (17 to 104)	45 (20 to 153)	29 (15 to 108)	55 (20 to 134)	42 (17 to 122)	
n	119	31	158	240	548	
Albumin						.209
mg/dL	4 (3.6 to 4.2)	3.9 (3.5 to 4.2)	3.9 (3.5 to 4.2)	3.8 (3.5 to 4.2)	3.9 (3.5 to 4.2)	
n	109	26	136	207	478	
IVIG response†						
IVIG resistant	14 (15.9)	4 (21.0)	18 (15.8)	26 (15.0)	62 (15.7)	.925
IVIG responsive	74 (84.1)	15 (79.0)	96 (84.2)	147 (85.0)	332 (84.3)	
n	88	19	114	173	394	
Overall coronary artery outcome (Z_{max})						
Z < 2.0	62 (47.7)	22 (62.9)	128 (71.9)	183 (67.3)	395 (64.2)	.002
Z (2-2.5)	17 (13.1)	6 (17.1)	15 (8.4)	28 (10.3)	66 (10.7)	
Z (2.5-10.0)	48 (36.9)	7 (20.0)	31 (17.4)	56 (20.6)	142 (23.1)	
Z ≥ 10.0	3 (2.3)	0 (0.0)	4 (2.3)	5 (1.8)	12 (2.0)	
Coronary artery outcome among diagnosed ≤ 10 days						
Z < 2.0	57 (46.0)	16 (61.6)	99 (69.7)	141 (64.0)	313 (61.1)	.016
Z (2-2.5)	17 (13.7)	5 (19.2)	13 (9.2)	23 (10.5)	58 (11.3)	
Z (2.5-10.0)	48 (38.7)	5 (19.2)	28 (19.7)	51 (23.2)	132 (25.8)	
Z ≥ 10.0	2 (1.6)	0 (0.0)	2 (1.4)	5 (2.3)	9 (1.8)	
n	124	26	142	220	512	

ALT, Alanine aminotransferase; *CRP*, C-reactive protein; *ESR*, erythrocyte sedimentation rate; *GGT*, gamma glutamyl transpeptidase; *zHgb*, hemoglobin concentration normalized for age.
Values are median (IQR) or n (%) unless otherwise noted.
**P* value from the Kruskal-Wallis test for continuous variables to compare overall difference among the 4 groups. Further pairwise tests were conducted if the overall test *P* value was significant and the pairwise test *P* values are reported in the text; Fisher exact test for categorical variables.
†Therapy response evaluated only for those who received IVIG alone as their first treatment (n = 394).

echocardiogram was normal. Of the 744 remaining patients, 514 (69.1%) were treated initially with only a single dose of IVIG (**Figure 5**). Of these, 431 (83.8%) responded to a single infusion and required no additional therapy. Of the 83 (16.1%) classified as IVIG resistant, 33 (39.7%) received a second IVIG and 50 (60.2%) received infliximab. The choice of second therapy varied over the 10-year period with greater use of infliximab for IVIG resistance in the later years after the publication of a phase III clinical trial.[10] Of the 33 patients who received a second IVIG infusion, 12 (36.4%) required further therapy because of persistent fever at 24 hours after completion of the second IVIG infusion as compared with 10 of 50 patients (20.0%) who received infliximab ($P = .13$). Patients who presented with either abnormal coronary artery dimensions on the initial echocardiogram (n = 72) or severe illness including Kawasaki disease shock syndrome (n = 9) received infliximab immediately after their IVIG infusion. An additional 69 patients received infliximab before IVIG infusion as part of a phase III clinical trial[10] and 22 patients with coronary artery abnormalities received infliximab plus advanced therapies in ongoing clinical trials of atorvastatin and anakinra (NCT 1431105 and NCT 2179853, respectively).[11,16,17] A total of 232 patients received infliximab (either 5 or 10 mg/kg intravenously) as part of their treatment for acute Kawasaki disease.

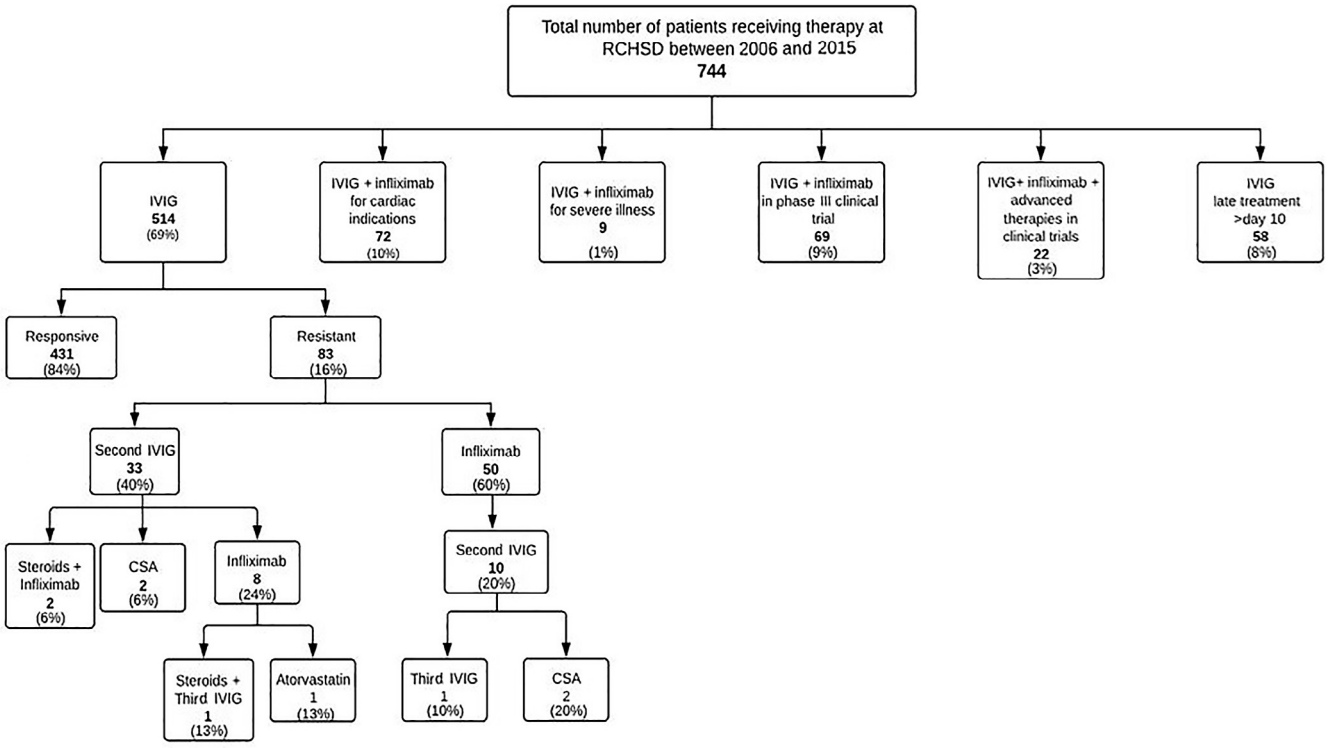

Figure 5. Initial and subsequent treatments administered to 744 patients with acute Kawasaki disease at a single tertiary care pediatric center. The 44 of 788 patients (5.6%) who presented late and were not treated were excluded from this analysis. Additional therapies are shown only for patients who were IVIG resistant. *CSA*, Cyclosporine.

There were no complications or adverse events associated with infliximab therapy. Treatment with IVIG beyond the 10th day of fever was administered to 58 patients who had either fever or evidence of persistent inflammation on laboratory studies at the time of their delayed presentation.

Of the 788 patients, coronary artery outcomes defined by Z_{max} for the LAD and RCA were distributed as follows: normal (Z_{max} of <2.0), 504 (64.0%); dilated, 90 (11.4%); aneurysm, 180 (22.8%); and giant aneurysm, 14 (1.8%; **Figure 6**). Of the 194 patients with aneurysms (Z_{max} of ≥2.5), 175 (90.2%) were diagnosed and treated within the first 10 days after fever onset and 83 (42.8%) were treated within the first 5 days after fever onset (**Figure 7**; available at www.jpeds.com). Despite timely treatment, aneurysms persisted at illness day 21 in 35 of 83 patients (42.2%) treated within the first 5 days and 43 of 92 patients (46.7%) treated by 6-10 days of illness (**Figure 8**). Of the 116 diagnosed and treated at ≤5 days, 83 (42.8%) had a Z score of ≥2.5 on their first echocardiogram. Thus, 90.2% of patients who developed aneurysms had received IVIG in a timely manner as outlined by current AHA guidelines. Of the 194 patients with aneurysms, 99 (51.0%) had normalized their Z score by the time of their first outpatient visit within a window of 7-21 days. Predicting which patients are at risk for developing aneurysms has become a subject of great interest now that there are several adjunctive therapies under study. In this series, of the 194 patients with a Z_{max} of ≥2.5, 146 (75.2%) had a Z score for either the RCA or LAD of ≥2.5 on their first echocardiogram at the time of diagnosis. Patients with aneurysms tended to be younger (median age, 1.9 years; IQR, 0.73-3.50) compared with patients without aneurysms (median age, 3.1 years; IQR, 1.74-5.14; $P < .001$). There were no deaths during this study period.

Of the 788 patients, 618 (78.4%) were classified as complete Kawasaki disease; 137 of those 618 (61.7%) developed aneurysms and 12 (5.4%) developed giant aneurysms (**Figure 6**). Of the 126 (16.0%) patients with incomplete Kawasaki disease, 47 (37%) were diagnosed by echocardiogram and 57 (45%) were diagnosed by AHA clinical and laboratory criteria for incomplete Kawasaki disease.[8] A third category of incomplete Kawasaki disease included 22 patients (18%) who failed to meet the AHA criteria for incomplete Kawasaki disease but who had a fever for >5 days and met the Kawasaki disease criteria of oropharyngeal changes, conjunctival injection, and rash. All had an elevated erythrocyte sedimentation rate and C-reactive protein, but lacked the minimum 3 of the 5 ancillary laboratory criteria required for the AHA algorithm. All patients were treated with IVIG and had a dramatic resolution of their clinical signs and symptoms. Of these 22 patients, 1 subsequently developed transient coronary dilation and 1 developed aneurysms.

The 44 missed and not treated patients with Kawasaki disease presented beyond the 10th day of illness (range, 10-131 days) and at a point in time when all systemic indicators of acute inflammation had resolved. Of the 44 patients, 41 (93.2%) were ascertained and referred to our clinic because of periungual

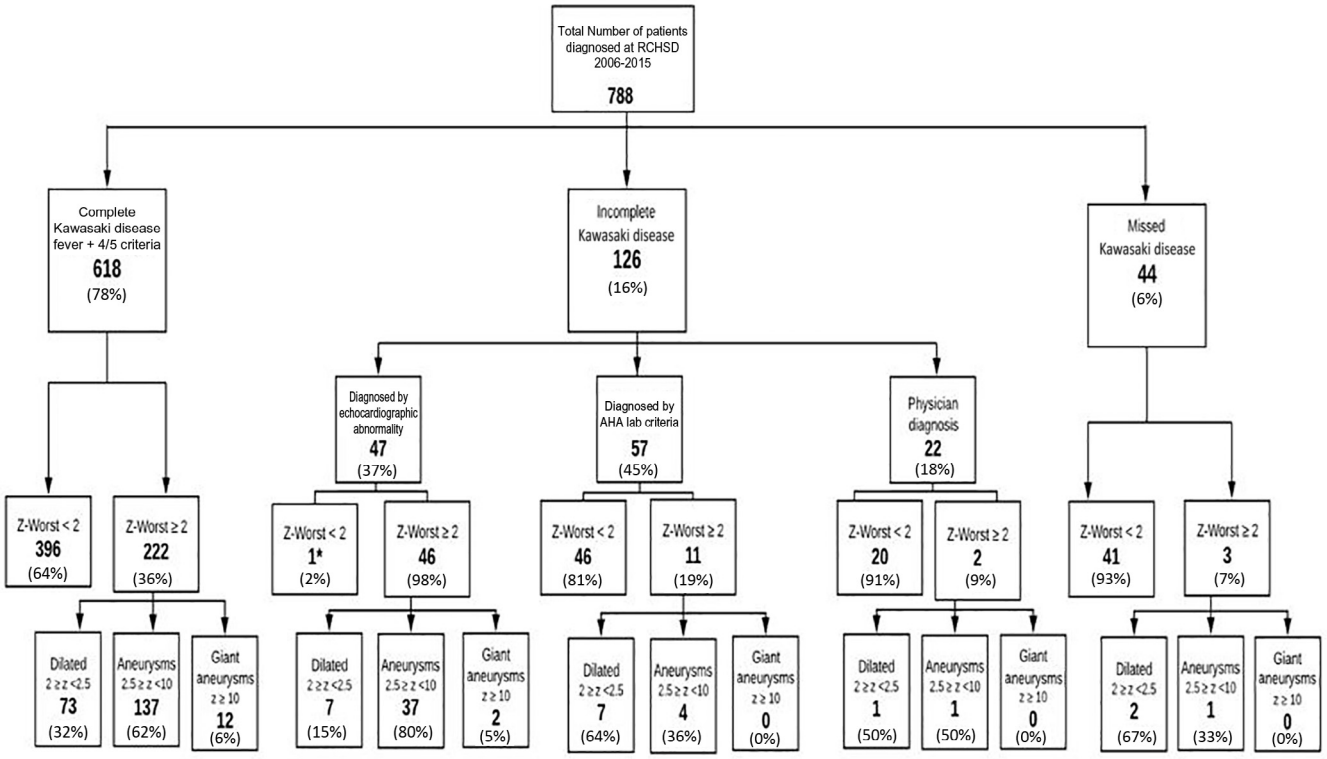

Figure 6. Cardiac outcomes in 788 patients with Kawasaki disease diagnosed at a single tertiary care pediatric center. *Patient diagnosed owing to abnormal LMCA.

desquamation after a febrile illness compatible with acute Kawasaki disease. The 3 patients with dilated coronary arteries (maximum Z scores, 2.00, 2.31, and 2.67) presented 1-2 months after the onset of fever and were not treated because they were well with normal laboratory studies at the time of their delayed Kawasaki disease diagnosis.

All recurrent Kawasaki disease cases were diagnosed and managed by the 2 Kawasaki disease clinicians for both their initial and recurrent Kawasaki disease episodes. The median interval between the first and recurrent Kawasaki disease episodes was 1.3 years (range, 0.1-5.1 years; **Table III**; available at www.jpeds.com). Recurrent Kawasaki disease occurred in 11 of 788 patients (1.4%) with the highest recurrence rate among Filipino children (4 of 44, 9.0%; 95% CI, 3.3%-20.4%) compared with 2 of 86 (2.3%; 95% CI, 0.4%-8.9%) for non-Filipino Asian/Pacific Islander children, although the difference was not statistically significant. The recurrence rate among children with both Hispanic parents was 2 of 272 (0.7%). There were no recurrences among children with both parents classified as white. Of the recurrent cases, 2 patients were discordant in their response to IVIG and 1 patient was not treated for the second episode that was retrospectively diagnosed at a point when the inflammation had subsided. Only 2 patients had a worse Z_{max} associated with the second episode of Kawasaki disease and most patients remained normal or had less coronary artery dilation with the second episode.

Susceptibility to Kawasaki disease is determined by genetic factors and 12 of 788 patients (1.5%) had a first- or second-degree relative with a history of Kawasaki disease (**Figure 9**; available at www.jpeds.com). Among these, there were 3 sibling cases, 1 uncle case, 1 grandfather case, and 7 first or second cousin cases.

Discussion

Several themes emerge from this analysis of prospectively collected data over a 10-year period at a single center in the US with a diverse, multiethnic population. First, and not surprisingly, children of Asian/Pacific Islander descent were over-represented in the cohort. Compared with other race/ethnicities, the Asian/Pacific Islander patients with Kawasaki disease were younger, were diagnosed earlier in the course of their fever, had higher levels of inflammatory markers, and were more likely to develop aneurysms. These features are likely inter-related; one might expect worse outcomes in children with higher levels of inflammation. The increased severity of disease and less favorable coronary artery outcomes in our Asian/Pacific Islander patients may be related, at least in part, to the high percentage of Filipino children (34%) who were previously reported to have a more severe disease course compared with other groups.[18] The small numbers of patients, however, precluded a meaningful subgroup analysis of the different Asian populations (**Figure 3**). Despite the less favorable outcome, Asian/Pacific Islander patients did not have a higher rate of IVIG resistance compared with other racial/ethnic groups. Data from this observational study

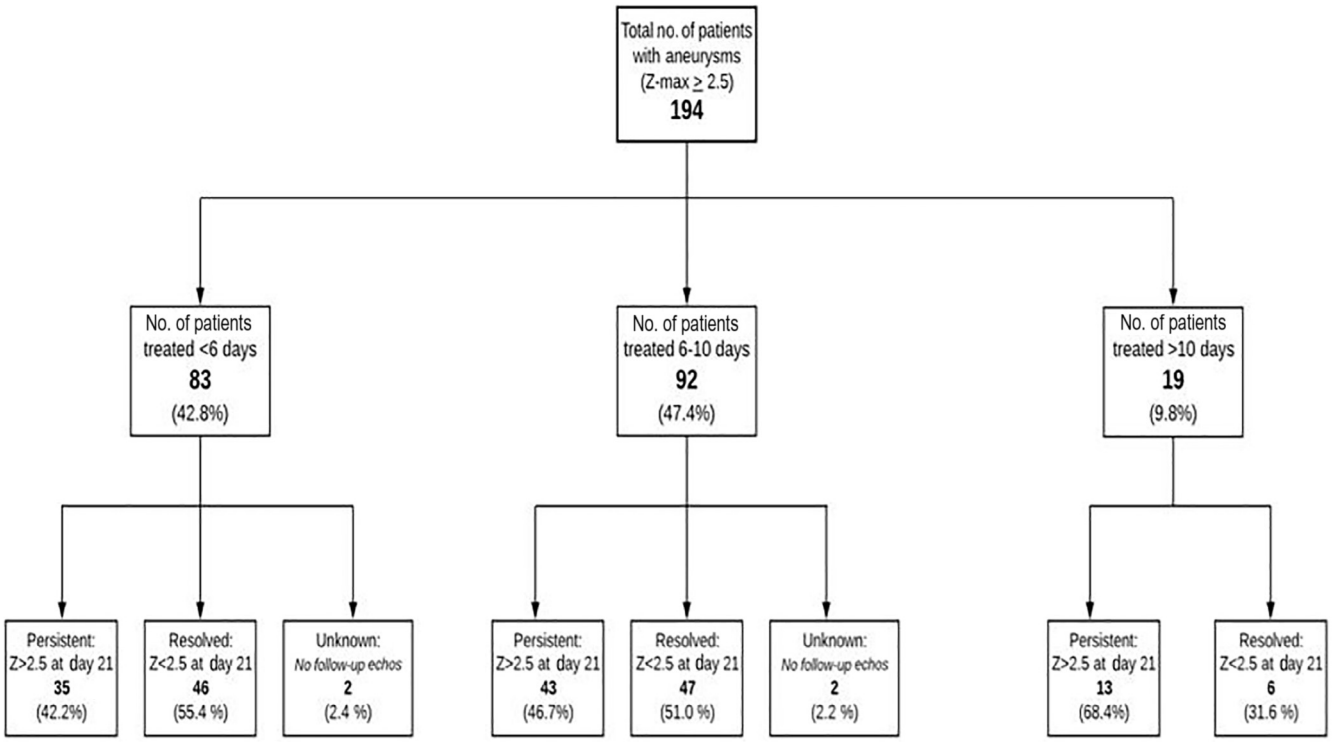

Figure 8. Illness day at diagnosis and persistence of aneurysms at day 21. *echos*, echocardiographs.

suggest that future clinical trials may need to consider randomization schemes to achieve balance of Asian/Pacific Islander children in the treatment arms given the apparent greater severity of Kawasaki disease in this group.

With respect to coronary artery outcomes, several points should be highlighted. One important message is that aneurysms are occurring despite timely treatment with IVIG. The new definition of an aneurysm as a Z score for the LAD or RCA of ≥2.5 resulted in a surprisingly high aneurysm rate (194 of 788 [24.6%]) in our study population, which is likely related to the lower Z score threshold for aneurysm rather than any specific characteristic of our study population. Of the 194 patients who developed aneurysms, 60% received IVIG within the first 5 days after fever onset and 43% already had coronary artery abnormalities at the time of diagnosis. Overall, 75% had a Z score of ≥2.5 on their first echocardiogram. Thus, aneurysms were present at the time of diagnosis and developed despite early administration of IVIG. This finding suggests that patients with Kawasaki disease with an abnormal first echocardiogram would be logical candidates for clinical trials of intensification of initial treatment with adjunctive therapies. Steroids would be a potential therapy, but the benchmark clinical trial studying methylprednisolone for intensification of initial treatment specifically excluded patients with an abnormal baseline echocardiogram.[19] A phase III trial of intensification of initial therapy with infliximab included patients with an abnormal first echocardiograph and showed a modest but significant reduction in LAD Z score in the patients who received IVIG plus infliximab compared with those who received IVIG plus placebo in this double-blind, placebo-controlled trial, although the study was underpowered for this outcome.[10] Intensification of initial therapy for patients with abnormal Z scores on their first echocardiogram is encouraged in the 2017 AHA guidelines, although no specific recommendation is given for which treatment should be added. We chose infliximab as our first-line treatment for intensification of initial therapy based on the suggestive, but not conclusive, results of our randomized trial.

This study supports the use of the AHA algorithm for complete and incomplete Kawasaki disease.[8] Of the 57 patients with incomplete Kawasaki disease diagnosed by laboratory criteria specified in the algorithm, all were treated with IVIG and 11 (19.3%) went on to develop an abnormal echocardiogram (7 dilated, 4 aneurysm). Of the 22 patients who failed to meet criteria for incomplete Kawasaki disease but were nonetheless diagnosed and treated by experienced clinicians, 1 developed coronary artery dilation and 1 developed an aneurysm. Thus, by strictly applying the AHA diagnostic criteria, only 1 of the 194 patients (0.5%) who developed aneurysms would have been missed.

This study also highlights the dilemma regarding the choice of second treatment when fever recurs after the initial IVIG infusion. For patients who were IVIG resistant who received a second IVIG infusion, 36.4% went on to require additional therapy for persistent fever compared with 20% of the patients who received infliximab. To inform best clinical practice, a 30-site comparative effectiveness trial (the KawasakI Disease CompaRative Effectiveness trial [KIDCARE],

NCT03065244) is currently enrolling patients who are IVIG resistant who are randomized to either a second IVIG infusion or infliximab (10 mg/kg). Of the 788 patients reported, 232 received infliximab at a dose of either 5 or 10 mg/kg with no adverse events, thus, supporting the safety of this treatment across the different ethnicities in the patient population.

Two novel aspects of our analysis were the ability to track recurrent cases and familial occurrence of Kawasaki disease across the different racial/ethnic groups. The analysis of recurrent cases represents the lower bound of this occurrence because families had different durations of observation depending on the year of Kawasaki disease onset and some families were lost to follow-up or moved from the area. The high rate of recurrence among our Filipino families (9.0%) is of note and should be considered when counseling Filipino families about the possibility of recurrence. A detailed study of recurrence rates in Ontario, Canada, found 2.9 recurrences per 1000 observation-years, but no data were available regarding race/ethnicity.[20] Recurrence rates have been reported for Japan (3%-4%) and Korea (4.7%), but no data are available from the Philippines.[1,14,21] The lack of recurrence among our patients of European descent emphasizes that recurrence is rare in this genetic background. Familial occurrence of Kawasaki disease in first- and second-degree relatives was noted for 1.5% of our population. This finding was identical to the familial occurrence of Kawasaki disease noted in the Canadian study.[20]

We recognize both strengths and limitations to our descriptive study. Because of the detailed, prospectively collected data, we were able to address Kawasaki disease presentation and outcomes stratified by race/ethnicity. Our estimates of Kawasaki disease incidence do not include San Diego County residents who were treated at either of 2 regional hospitals serving a health maintenance organization population and military personnel and dependents. However, previous studies from our group suggest that our tertiary care pediatric center captures >94% of the patients with Kawasaki disease diagnosed in our region.[22] Our estimates of recurrence rates and familial occurrence also represent a lower bound because some families were lost to follow-up or moved from the area.

Asian/Pacific Islander patients with Kawasaki disease, of whom 34% were Filipino, were younger, diagnosed earlier in the course of their fever, had higher levels of inflammatory markers, and were more likely to develop aneurysms. Development of aneurysms despite timely treatment with IVIG underscores the inadequacy of current standard therapy for this subset of patients with Kawasaki disease. ■

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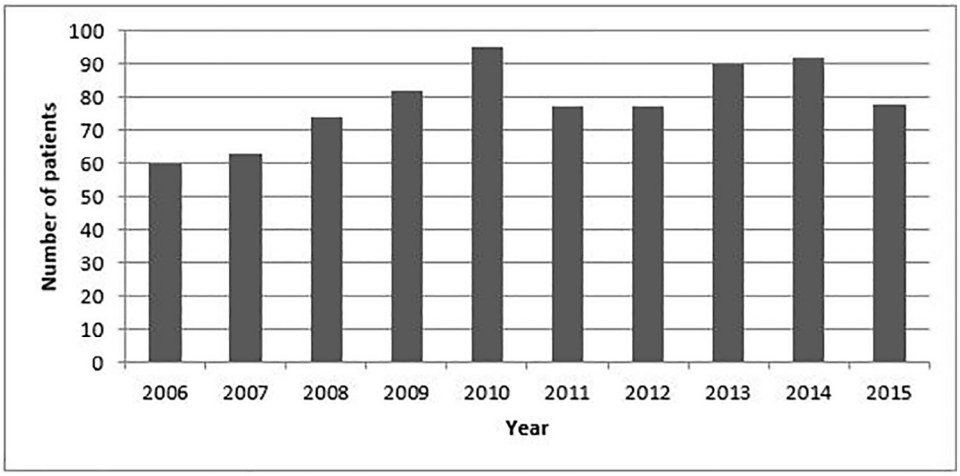

Figure 2. Patients with Kawasaki disease diagnosed at a single tertiary care pediatric center by year, 2006-2015.

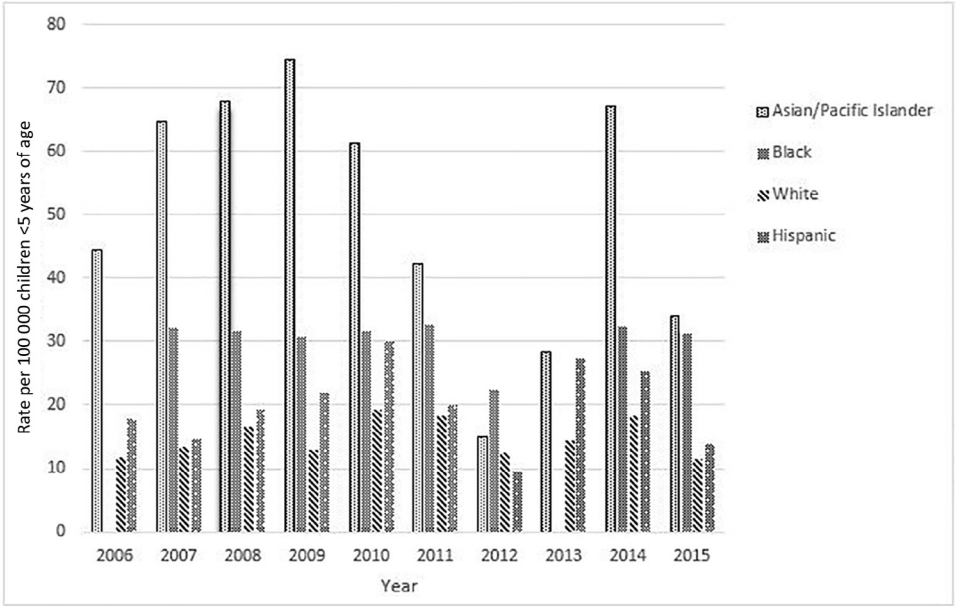

Figure 3. Incidence of Kawasaki disease in San Diego County per 100 000 children <5 years of age residing in San Diego County, stratified by race/ethnicity.

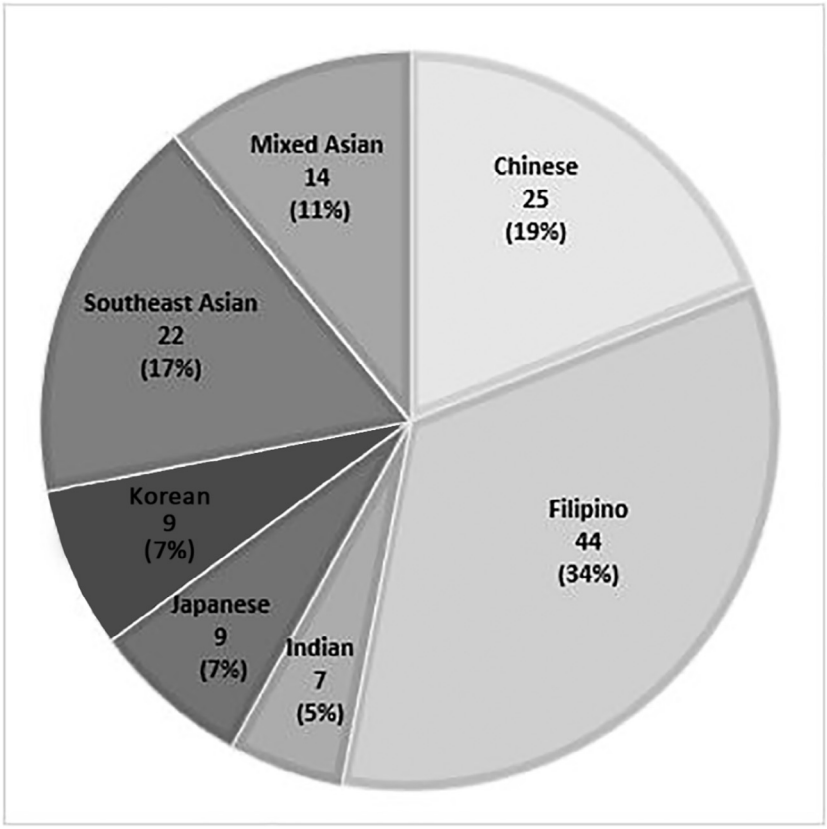

Figure 4. Subsets of Asian/Pacific Islander patients with Kawasaki disease (n = 130) diagnosed at a single tertiary care pediatric center.

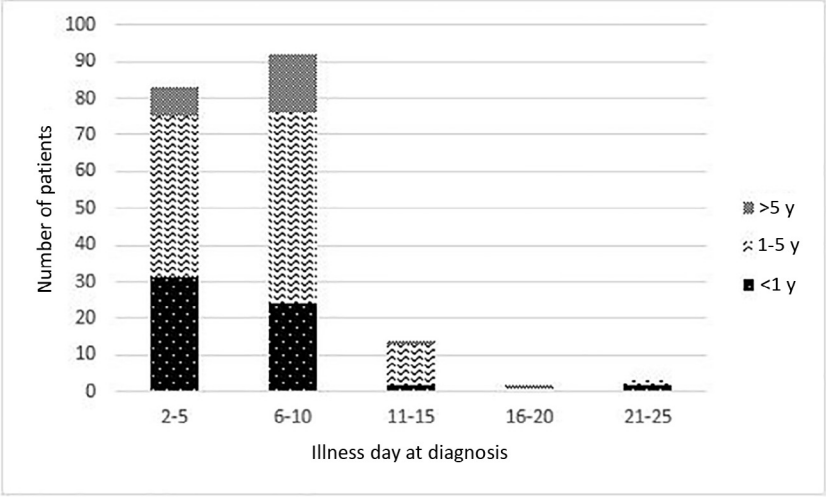

Figure 7. Age strata and illness day at diagnosis for patients with aneurysms ($Z_{max} \geq 2.5$; n = 194).

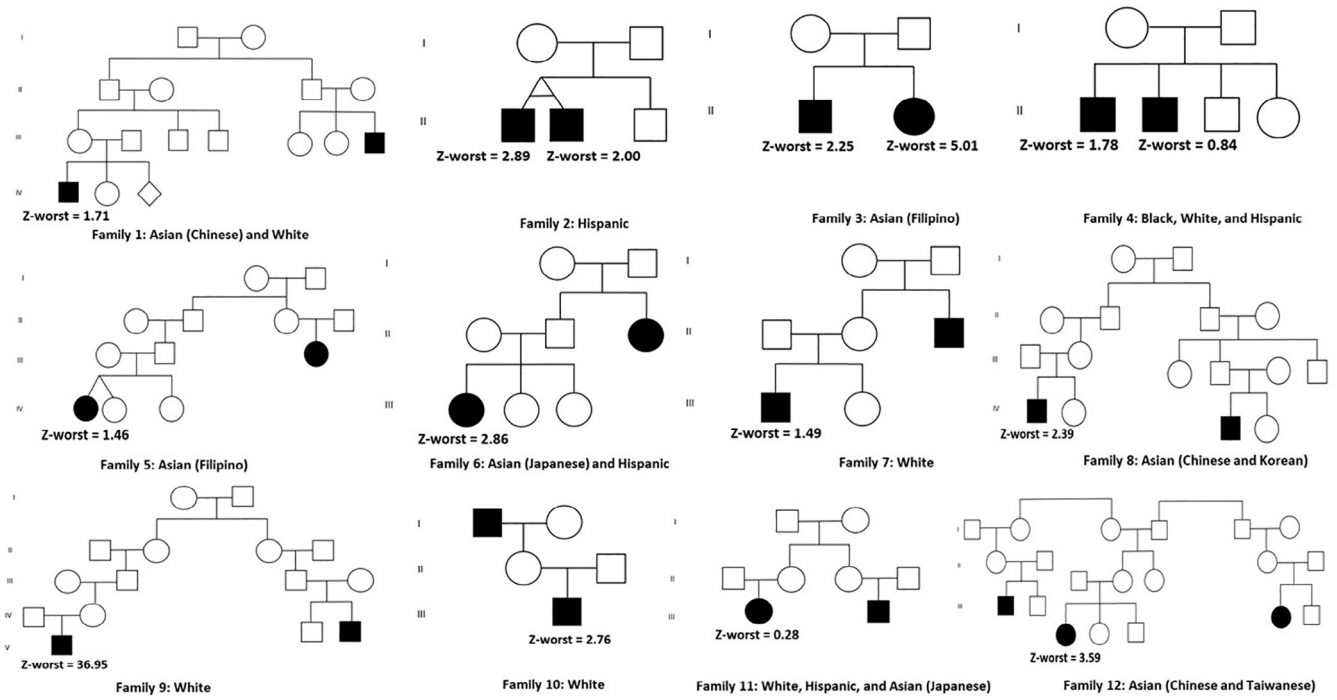

Figure 9. Pedigrees of 12 families with ≥2 patients with Kawasaki disease.

Table I. Incidence of Kawasaki disease among children in San Diego County stratified by race/ethnicity during the period 2006-2015

Categories	No. (%)	Incidence per 100 000 children <5 y ± SD
All children <5 y of age residing in San Diego County and diagnosed with Kawasaki disease at Rady Children's Hospital	525 (100)	25.0 ± 4.4
Sex		
Male	327 (62)	30.4 ± 5.9
Female	198 (38)	19.3 ± 6.4
Race/ethnicity (n = 422; 103 mixed and other race excluded)		
Asian/Pacific Islander	98 (19)	50.0 ± 20.0
Black	23 (4)	24.5 ± 13.3
White	111 (21)	14.9 ± 3.0
Hispanic	190 (36)	20.0 ± 6.4

Table III. Clinical details of 11 patients with a recurrent episode of Kawasaki disease

Ethnicities	Age of onset	Interval between the first and second episodes (y)	Treatment response	Z_{max}
Filipino	2.1	0.1	IVIG resistant	4.1
	2.2		IVIG responsive	4.8
Filipino	1.4	5.0	IVIG responsive	2.3
	6.5		IVIG responsive	3.0
Filipino	1.2	2.8	IVIG responsive	6.7
	3.9		IVIG responsive	2.8
Filipino	2.4	1.7	IVIG responsive	3.0
	4.1		IVIG responsive	0.8
Korean	1.8	1.8	IVIG resistant	3.2
	3.6		Not treated	2.4
Korean + white	1.9	1.6	IVIG resistant	4.5
	3.5		IVIG responsive	1.4
Vietnamese	1.4	0.6	IVIG responsive	2.2
	2.0		IVIG responsive	1.7
Black + white	0.3	0.0	IVIG resistant	2.8
	0.4		IVIG responsive	0.0
Hispanic	1.0	0.5	IVIG responsive	2.4
	1.5		IVIG responsive	2.4
Hispanic	4.0	1.3	IVIG responsive	1.8
	5.2		IVIG responsive	2.0
Hispanic + white	4.5	0.3	IVIG responsive	2.0
	4.8		IVIG responsive	2.0