



# Deep Neck Space Involvement of Kawasaki Disease in the US: A Population-Based Study

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**Objectives** To describe the rate and risk factors of deep neck space involvement of Kawasaki disease.

**Study design** We performed a retrospective analysis using the Kids' Inpatient Database from 2006, 2009, 2012, and 2016. Kawasaki disease and deep neck space involvement cases were identified using *International Classification of Diseases* codes among children aged <12 years. Demographic and outcome data of Kawasaki disease cases with and without deep neck space involvement were compared.

**Results** Of 20 787 patients with Kawasaki disease, 0.6% (130 cases) had deep neck space involvement. On multi-variable analysis, children aged  $\geq 4$  years (OR 8.41; 95% CI 3.79-18.7 in those aged 6-11 years), Asian or Pacific Islanders (OR 3.72; 95% CI 1.90-7.27), non-Hispanic black children (OR 2.39; 95% CI 1.34-4.28), and Northeast hospital region (OR 2.32; 95% CI 1.21-4.46) were associated with deep neck space involvement. Surgical drainage was performed in 21.7% of patients with deep neck space involvement. Deep neck space involvement was associated with longer hospital stay and greater costs.

**Conclusions** Approximately 0.6% of patients with Kawasaki disease present with deep neck space involvement in the US. Deep neck space involvement of Kawasaki disease occurs primarily in older ( $\geq 4$  years old), non-white, non-Hispanic children. Deep neck space involvement is associated with operative procedures for presumed abscess, longer hospital stay, and greater costs. In caring for children with suspected deep neck space abscess, particularly when they are not responding to antibiotics, clinicians should evaluate them for the possibility of Kawasaki disease. (*J Pediatr* 2019;215:118-22).

Deep neck (retropharyngeal and parapharyngeal) space involvement is an unusual presentation of Kawasaki disease.<sup>1,2</sup> Currently, the diagnosis of Kawasaki disease is primarily clinical.<sup>3,4</sup> Because these clinical characteristics are nonspecific, the diagnosis can be missed especially when the presentation is unusual. Patients without all signs of Kawasaki disease (incomplete Kawasaki disease) can develop coronary aneurysms,<sup>5</sup> the most concerning long-term sequelae, particularly when diagnosis and treatment are delayed.<sup>6</sup> Therefore, timely diagnosis is crucial in providing optimal care to the affected children, and clinicians must be familiar with the variety of Kawasaki disease presentations.

Deep neck space involvement of Kawasaki disease has been reported,<sup>7-10</sup> and biopsy results have shown possible vasculitic process in the retropharyngeal lesion.<sup>7</sup> Despite an abundance of case reports, research studies on this particular presentation are scarce. Some of the past studies reported that such patients can present initially with lymphadenopathy ("lymph-node-first presentation").<sup>11,12</sup> Other studies reported that retropharyngeal involvement can be subclinical and may be captured commonly when computed tomography of the neck is performed.<sup>13</sup> Detailed investigation of computed tomography images may be able to distinguish Kawasaki disease-related lesions from bacterial infection.<sup>14,15</sup> In this study, we aimed to describe the rate and characteristics of deep neck space involvement of Kawasaki disease at the US population level.

## Methods

We performed a population-based retrospective analysis of serial cross-sectional datasets using the Kids' Inpatient Database (KID) from 2006, 2009, 2012, and 2016 ([www.hcup-us.ahrq.gov/kidoverview.jsp](http://www.hcup-us.ahrq.gov/kidoverview.jsp)),<sup>16</sup> compiled by the Healthcare Costs and Utilization Project (HCUP) of the Agency for Healthcare Research and Quality. The KID is the largest publicly available all-payer pediatric inpatient database in the US, released every 3 years since 1997 through 2012, and 2016. The data contain a stratified sample of 80% of pediatric non-birth discharges from hospitals in participating states ([https://www.hcup-us.ahrq.gov/db/availability\\_public.jsp](https://www.hcup-us.ahrq.gov/db/availability_public.jsp) for the states included in the KID in each data year). Discharge records in the KID are weighted using poststratification on hospital

HCUP	Healthcare Costs and Utilization Project
ICD-9-CM	<i>International Classification of Diseases, Ninth Revision, Clinical Modification</i>
ICD-10-CM	<i>International Classification of Diseases, Tenth Revision, Clinical Modification</i>
KID	Kids' Inpatient Database

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ownership/control, bed size, teaching status, rural/urban location, and US region, with the addition of a stratum for freestanding children's hospitals in proportion to the total number of newborn or non-newborn discharges.

Weighted analysis permits national estimates with the measures of uncertainty based on the records available from participating states in each data year. The data year up to 2012 used *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM) codes, whereas 2016 data used *International Classification of Diseases, Tenth Revision, Clinical Modification* (ICD-10-CM) codes. HCUP data use agreement training was completed for analyses described herein. Per the institutional review board at the University of Mississippi Medical Center, this study was classified as non-human subjects research.

Patients <12 years of age at the time of hospitalization from January 1 to December 31 in 2006, 2009, 2012, and 2016 were included in the study. We identified cases of Kawasaki disease using ICD-10-CM M30.3 in 2016 data and ICD-9-CM 446.1 in 2006-2012 data in the diagnoses listed in the discharge summary.<sup>17-19</sup> Deep neck space abscesses (retropharyngeal and parapharyngeal abscess) were identified using ICD-10-CM J39.0 and ICD-9-CM 478.24 and 478.22, respectively.<sup>20,21</sup> Cases with both Kawasaki disease and deep neck space abscess diagnoses were considered to have deep neck space involvement of Kawasaki disease in this study.

Demographics (sex, age, race, hospital region, and hospital teaching status) and length of stay information were collected using the variables provided by the database. Using *International Classification of Diseases* codes, we identified coronary artery aneurysm (ICD-9: 414.11, ICD-10: I25.41), and incision and drainage of the pharynx or throat (ICD-9: 28.0, ICD10: 0C9M\*, 0W93\*; procedure codes).

Costs of hospitalization were estimated using the total charge data in the database and the cost/charge ratio provided by the HCUP, which was derived from all-payer inpatient cost/charge ratio when available, or hospital group average all-payer inpatient cost/charge ratio otherwise. Costs were converted to 2016 dollars using the medical care component of the Consumer Price Index to account for inflation.<sup>22</sup> Geometric means of costs were presented to account for the positively skewed nature of cost data, as geometric mean is less influenced by extreme values than arithmetic means.

## Statistical Analyses

Primary outcome of interest was the deep neck space involvement of Kawasaki disease. Secondary outcomes of interest included coronary artery aneurysm diagnosis, requirement for surgical procedure for deep neck space abscess, length of stay, and cost of hospitalization. Primary exposure of interest was the demographic information of the patients. Bivariate analysis of categorical variables was performed using the Pearson  $\chi^2$  test, and that of continuous variables with approximately normal distribution was performed using the Student *t* test. Multivariable analysis of binary outcome variables was performed by developing a logistic regression model including variables that attained statistical

significance on bivariate analysis. Potential effects of the data year on the association between each demographic variable and deep neck space involvement were assessed by fitting models with interaction terms. Race data were missing in 15.7% (SE: 1.5) of the records with Kawasaki disease diagnosis, whereas the rest of the variables had <5% missing values; under an assumption that the values were missing completely at random, we performed complete case analysis in this study.

The rates of Kawasaki disease and deep neck space abscess hospitalizations per 100 000 US children were estimated as the weighted case number divided by the population estimates of children <12 years of age as of July 1 of each study year obtained from the US Census Bureau.<sup>23</sup>

Data were analyzed using R software, version 3.5.0 (R Foundation for Statistical Computing; Vienna, Austria) and Stata software, version 15 (StataCorp; College Station, Texas). Presented values are weighted values accounting for the KID sampling design, unless otherwise specified. We used 2-sided significance level of .05 in all analyses.

## Results

During the study period, the incidence of Kawasaki disease was stable, and was 18.1 to 21.3 per 100 000 children <5 years old and 4.2 to 4.7 per 100 000 children aged 5-11 years. We identified 20 787 (SE: 699) patients with Kawasaki disease, of whom 130 (SE: 16) had deep neck space involvement (**Table I**), corresponding to the prevalence of 0.6% (SE: 0.07%).

Most of the patients with Kawasaki disease were boys (**Table I**). Median age of patients with Kawasaki disease with deep neck space involvement was 5 years (IQR: 3-7), and that of those without was 2 years (IQR: 1-4). By bivariate analysis, we found that deep neck space involvement in Kawasaki disease tended to be diagnosed in individuals who were older, of non-white race, in the Northeast region, and at teaching hospitals (**Table I**). These associations generally remained significant on multivariable analysis, except for the teaching status of the hospitals. The associations were particularly strong in older, non-white non-Hispanic children (**Figure**). We did not identify any support for temporal changes in these associations, as indicated by the lack of interaction with the year variable.

Coronary artery aneurysm occurred in a small proportion of patients with Kawasaki disease with and without deep neck space involvement during the hospitalization (1.1% [SE 1.1] and 3.8% [SE 0.3], respectively) with no statistically significant difference between groups ( $P = .20$ ) (**Table II**). Among patients with Kawasaki disease with deep neck space involvement, 21.7% (SE: 4.5) underwent incision and drainage of the pharynx or throat. Patients with Kawasaki disease with deep neck space involvement had longer hospital stay and greater costs per case than those without (**Table II**).

**Table I. Characteristics of patients with Kawasaki disease with or without deep neck space involvement**

Characteristics	Kawasaki disease, overall (N ± SE = 20 787 ± 699)	Kawasaki disease with deep neck space involvement (N ± SE = 130 ± 16)	Kawasaki disease without deep neck space involvement (N ± SE = 20 657 ± 692)	Bivariate analysis
		N ± SE (% ± SE)	N ± SE (% ± SE)	P value
<b>Patient characteristics</b>				
Male	12 227 ± 429 (59.3% ± 0.5)	88 ± 13 (67.9% ± 4.9)	12 139 ± 424 (59.3% ± 0.5)	.10
Age, y				<.001
0-1	7063 ± 252 (34.0% ± 0.6)	16 ± 5 (12.1% ± 3.6)	7047 ± 251 (34.1% ± 0.6)	
2-3	7034 ± 312 (33.8% ± 0.7)	30 ± 7 (23.2% ± 4.4)	7004 ± 311 (33.9% ± 0.7)	
4-5	3237 ± 128 (15.6% ± 0.5)	34 ± 7 (25.8% ± 5.0)	3203 ± 126 (15.5% ± 0.5)	
6-11	3453 ± 135 (16.6% ± 0.4)	50 ± 10 (38.8% ± 5.3)	3403 ± 132 (16.5% ± 0.4)	
Race*				.007
Non-Hispanic white	7374 ± 292 (42.1% ± 1.1)	32 ± 7 (28.0% ± 5.1)	7342 ± 290 (42.2% ± 1.1)	
Non-Hispanic black	3290 ± 166 (18.8% ± 0.7)	31 ± 7 (27.1% ± 4.8)	3259 ± 164 (18.7% ± 0.7)	
Hispanic	3974 ± 245 (22.7% ± 1.0)	20 ± 6 (17.1% ± 4.4)	3955 ± 244 (22.7% ± 1.0)	
Asian or Pacific Islander	1662 ± 129 (9.5% ± 0.6)	19 ± 6 (16.8% ± 4.2)	1643 ± 128 (9.4% ± 0.6)	
Other	1227 ± 86 (7.0% ± 0.4)	13 ± 4 (11.1% ± 3.7)	1215 ± 86 (7.0% ± 0.4)	
<b>Hospital characteristics</b>				
Hospital region				.003
Northeast	3869 ± 322 (18.6% ± 1.5)	43 ± 10 (33.4% ± 6.2)	3826 ± 317 (18.5% ± 1.5)	
Midwest	4066 ± 374 (19.6% ± 1.8)	16 ± 5 (12.5% ± 3.7)	4050 ± 372 (19.6% ± 1.8)	
South	7245 ± 511 (34.9% ± 2.1)	45 ± 10 (34.5% ± 6.3)	7201 ± 505 (34.9% ± 2.1)	
West	5606 ± 495 (27.0% ± 2.1)	25 ± 6 (19.6% ± 4.6)	5580 ± 493 (27.0% ± 2.1)	
Teaching hospital	16 507 ± 657 (82.5% ± 1.0)	114 ± 15 (91.2% ± 3.1)	16 393 ± 651 (82.5% ± 1.0)	.03
Study year				.29
2006	5404 ± 365 (26.0% ± 1.2)	28 ± 8 (21.3% ± 5.2)	5377 ± 363 (26.0% ± 1.2)	
2009	5292 ± 350 (25.5% ± 1.2)	29 ± 7 (22.4% ± 4.7)	5262 ± 348 (25.5% ± 1.2)	
2012	4820 ± 338 (23.2% ± 1.7)	28 ± 6 (21.8% ± 4.7)	4791 ± 336 (23.2% ± 1.7)	
2016	5271 ± 408 (25.4% ± 1.9)	45 ± 10 (34.4% ± 6.2)	5226 ± 402 (25.3% ± 1.9)	

\*15.7% ± 1.5 missing.

## Discussion

Deep neck space involvement is well described in Kawasaki disease,<sup>4</sup> but its prevalence had not been previously quantified at the population level. Here we report the rate of 0.6% among the patients who are given a diagnosis of Kawasaki disease in the US. A past US report with single-institution data obtained at a highly experienced center described 344 patients with Kawasaki disease, of whom 57 had lymphadenopathy as the prominent presentation, and 7 had retropharyngeal edema.<sup>12</sup> Our study confirms the relatively rare occurrence of deep neck space involvement using a nationally representative database, including less-experienced institutions.

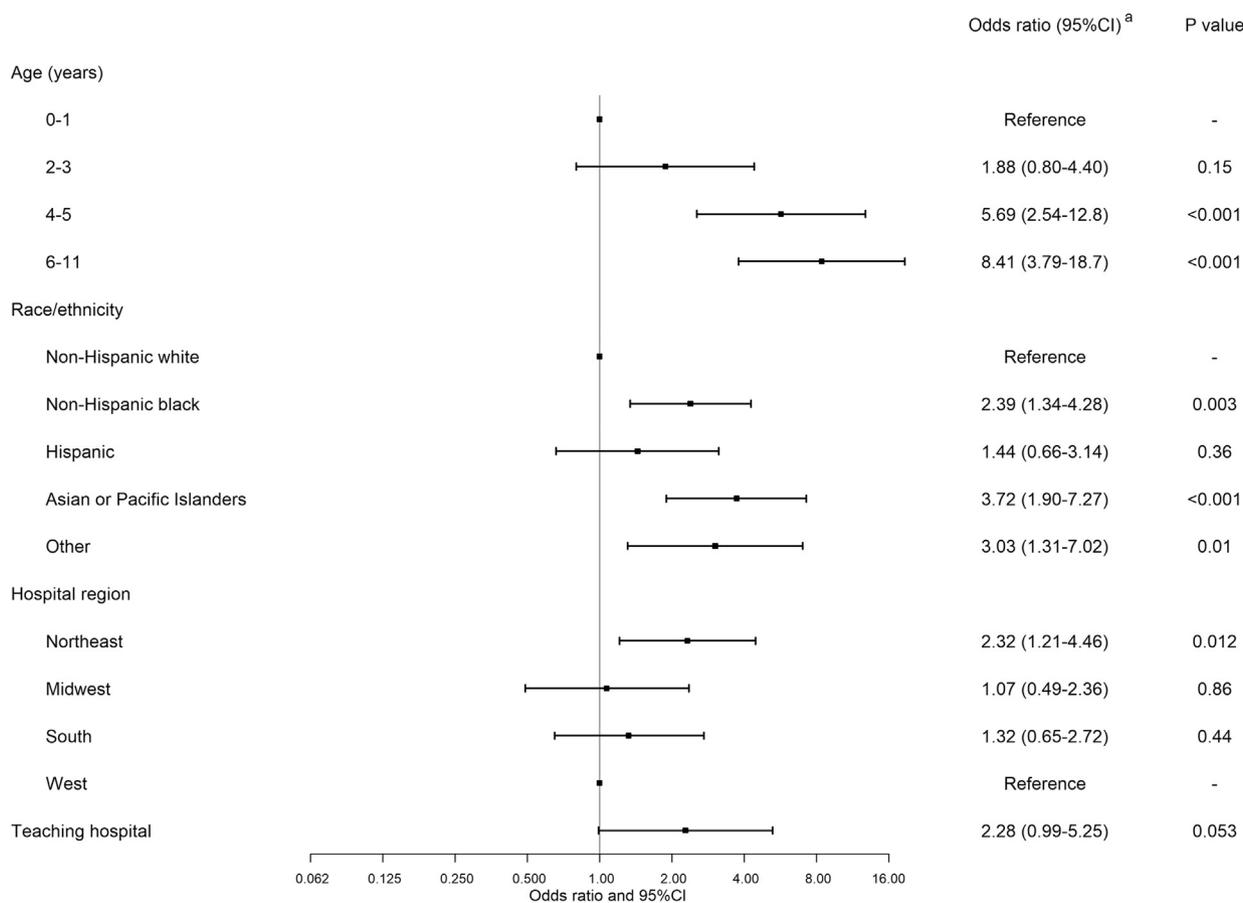
Deep neck space involvement of Kawasaki disease was observed in distinct patient populations. Older age of presentation was reported in a Japanese study, which included 10 patients with retropharyngeal involvement of Kawasaki disease.<sup>11</sup> Our study result adds to these data and shows with a larger sample size that the older presentation age also is observed in the US, which has diverse racial populations. The study that described the lymph-node-first presentation of Kawasaki disease also reported older age of patients,<sup>12</sup> suggesting possibly shared pathogenesis between lymphadenitis and deep neck space involvement of Kawasaki disease.

Racial minorities were particularly more likely to have deep neck space involvement. Asian and Pacific Islander patients are known to be predisposed to Kawasaki disease,<sup>17</sup> but our result indicates that these patients are still more likely to

have deep neck space involvement. Indeed, a Japanese single institution study including 277 patients with Kawasaki disease reported that 3.6% of patients had retropharyngeal low-density lesion on computed tomography imaging of the neck,<sup>11</sup> which is greater than our reported prevalence. Our study confirms the greater prevalence in this population but adds the comparison with other races.

In addition to the Asians and Pacific Islander patients, we found that black and other non-white non-Hispanic races were more likely to present with deep neck space involvement. Black children are at risk for nonresponse to intravenous immunoglobulin therapy<sup>24,25</sup> and can have a greater incidence of Kawasaki disease than white children according to a study from the United Kingdom,<sup>26</sup> but an association with deep neck space involvement has not been reported previously.

We also observed an increased risk of deep neck space involvement in the Northeast region. The association remained significant after adjusting for other variables, including race/ethnicity and teaching hospital status. In contrast, the association between deep neck space involvement and teaching hospital status was not sustained in multivariable analysis. Although previous studies reported relatively high hospitalization rates of Kawasaki disease in this region,<sup>17,18</sup> an association with deep neck space involvement has not been reported. Increased scanning can result in greater likelihood of detection; however, the use of computed tomography is not more common in the Northeast area.<sup>27</sup> These associations can be a focus of future research if large prospective population-based studies are to be performed,



**Figure.** Multivariable analysis of risk factors for deep neck space involvement of Kawasaki disease. <sup>a</sup>Obtained by multivariable logistic regression.

because identification of populations at risk can help with early diagnosis and thus better care.

We did not identify any increased risk of coronary artery aneurysm in the setting of Kawasaki disease complicated by deep neck space involvement, at least during the hospitalization. This finding is consistent with the aforementioned Japanese study,<sup>11</sup> and the US study of lymph-node-first presentation,<sup>12</sup> although our study was not able to evaluate follow up echocardiogram results. At this time, there is no ev-

idence that deep neck space involvement is associated with increased risk of coronary artery aneurysm.

Long hospital stay and high costs in the setting of deep neck space involvement may reflect the fact that such presentation hinders the clinicians from arriving at the diagnosis of Kawasaki disease. This is well illustrated in case reports, where delayed diagnosis is quite common.<sup>9</sup> Although overall healthcare burden may not be substantial, given its rarity, 21.7% of such patients underwent incision and drainage,

**Table II.** Complications and healthcare use of patients with Kawasaki disease with or without deep neck space involvement

Complications/healthcare utilization variables	Kawasaki disease with deep neck space involvement (N ± SE = 130 ± 16)	Kawasaki disease without deep neck space involvement (N ± SE = 20 657 ± 692)	P value
Coronary artery aneurysm, N ± SE (% ± SE)	<10* (1.1% ± 1.1)	782 ± 71 (3.8% ± 0.3)	.20 <sup>†</sup>
Incision and drainage, N ± SE (% ± SE)	28 ± 6 (21.7% ± 4.5)	N/A	-
Length of stay, median days (IQR)	7 (5-9)	3 (2-4)	-
Cost of hospitalization in 2016 dollars, <sup>‡</sup> geometric mean (SE)	19 773 (1443)	8645 (140)	<.001 <sup>§</sup>

N/A, not available.

\*Cells with <10 observations were included in analysis but omitted from presentation following the recommendation by the HCUP.

<sup>†</sup>P value obtained by  $\chi^2$  test.

<sup>‡</sup>Costs were converted to 2016 US dollars.

<sup>§</sup>P value obtained by Student *t* test on log-transformed cost, which was approximately normally distributed.

which is invasive and yet may not benefit them in the setting of Kawasaki disease. This underscores the importance of maintaining the awareness of such presentation.

This study had important limitations. First, we relied solely on accurate *International Classification of Diseases* coding for identification of cases, as in the case of any research using administrative data. To address this limitation, we used diagnostic codes that have been used in the past studies,<sup>17-21</sup> although bias cannot be excluded. Second, the coding system employed by the KID changed from ICD-9-CM to ICD-10-CM between 2012 and 2016. Kawasaki disease ICD-9-CM code 446.1 transitioned to ICD-10-CM M30.3, and retropharyngeal abscess and parapharyngeal abscess ICD-9-CM codes 478.24 and 478.22, respectively, were merged to ICD-10-CM code J39.0, indicating no major changes. In addition, the incidence of Kawasaki disease did not show temporal changes. Therefore, the changes in the coding systems likely did not affect our conclusion, but this is a possible source of bias.

Third, although the KID covers a large number of pediatric hospitalizations and allows for obtaining national estimates by using sampling weight, it does not contain records from all states in the US. Its large sample size likely mitigates this limitation, but selection bias remains a possibility. Fourth, this study included serial cross-sectional data, 4 years' worth from an 11-year period. There is a chance that the findings cannot be extrapolated to the years not included in the study, although we addressed this concern by ensuring that the associations between deep neck space involvement of Kawasaki disease and demographic characteristics did not change over time. Fifth, the race variable was missing 15.7% of the cases. We believe it was reasonable to assume that the values were missing completely at random, but bias cannot be excluded. Sixth, because of the lack of radiology data in the database, we were not able to tell whether greater risks for deep neck space involvement were secondary to the greater incidence or increased number of tests in particular populations. In caring for children with suspected deep neck space abscess, particularly when they are not responding to antibiotics, clinicians should evaluate them for the possibility of Kawasaki disease. ■

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