Prediction Model for the Differential Diagnosis of Kawasaki Disease and Acute Cervical Lymphadenitis in Patients Initially Presenting with Fever and Cervical Lymphadenitis

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Objectives To distinguish early-stage lymph node first presentation of Kawasaki disease from acute cervical lymphadenitis, we developed an algorithm using sequential laboratory marker levels and radiologic findings.

Study design Data were obtained from pediatric inpatients initially presenting with fever and cervical lymphadenopathy. Discriminative factors for the differential diagnosis of acute cervical lymphadenitis and lymph node first presentation of Kawasaki disease were identified from intergroup comparison or univariate logistic regression analysis. A model for differentiating between lymph node first presentation of Kawasaki disease and acute cervical lymphadenitis was constructed using decision-tree analysis.

Results Patients were divided into 2 cohorts: training (206 patients) and validation (103 patients) cohorts. A decision-tree model developed from the data of the training cohort included 3 determinants: neck computed tomography- or ultrasonography-defined abscess, percentage change in C-reactive protein level, and percentage change in neutrophil count. The prediction power of our decision-tree model for the validation cohort was superior to that of previously known laboratory markers (sensitivity of 89.5%, specificity of 88.9%, positive predictive value of 95.8%, negative predictive value of 75.0%, overall accuracy of 89.3%, and a Youden index of 0.784).

Conclusions A decision-tree model could differentiate lymph node first presentation of Kawasaki disease from acute cervical lymphadenitis with an increased accuracy. External validation based on multicenter data is needed before clinical application. *(J Pediatr 2020;225:30-6)*.

Kawasaki disease is an acute, self-limiting multisystemic vasculitis of unknown etiology first reported by Dr Tomisaku Kawasaki in 1967.[1] Due to lack of definitive diagnostic tests, Kawasaki disease is diagnosed according to its clinical features: (1) unexplained fever lasting for at least 5 days, (2) bilateral nonexudate conjunctivitis, (3) erythema of the lips and oral mucosa, (4) rash, (5) changes in the extremities, and (6) enlargement of the cervical lymph nodes. Cervical lymphadenopathy is the least common of all the features and is present in 50%-70% of patients with Kawasaki disease, whereas other symptoms included in the diagnostic criteria occur in about 90% of cases.[2,3]

However, in clinical practice, clinicians generally prescribe empirical antibiotics for patients with fever and cervical lymphadenopathy to prevent the development of suppurative lymphadenitis. A considerable number of these patients are eventually diagnosed with Kawasaki disease. The delay in Kawasaki disease diagnosis can have a detrimental impact on patients because of an increased risk of coronary artery complications.[4]

Differentiating the early stage of Kawasaki disease with only fever and cervical lymphadenopathy (lymph node first presentation of Kawasaki disease) from acute cervical lymphadenitis by laboratory and imaging characteristics has been suggested in previous studies that identified cut-off values of initial inflammatory markers.[5-7] Unfortunately, the clinical application of these cut-off values for timely differential diagnosis is questionable because they vary even within the same disease category and change substantially during the course of the disease. To overcome the limitations of previous studies, we emphasize the importance of serial laboratory changes rather than values obtained at a single time point.

Generally, empiric intravenous antibiotics are initiated for nearly all patients presenting with fever and cervical lymphadenitis after hospitalization. Focusing on the changing patterns of inflammatory markers after the use of antibiotics within 2-3 days, we aimed to develop an algorithm to facilitate the differential diagnosis of Kawasaki disease in the early stage.

Methods

We retrospectively reviewed the medical records of patients, with cervical lymphadenopathy and fever as the initial presentation, between January 2010 and

CHAID	χ^2 automatic interaction detection
CRP	C-reactive protein
CT	Computed tomography
US	Ultrasonography

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December 2018. This study was designed and conducted using the format recommended by Strengthening the Reporting of Observational Studies in Epidemiology guidelines. The study protocol was approved by the institutional review board of Kangdong Sacred Heart Hospital. The institutional review board waived the need for informed consent for this study.

Study Patients and Grouping

Consecutive hospitalized patients with fever and cervical lymphadenopathy were included after reviewing the medical records (**Figure 1**; available at www.jpeds.com). We excluded the following: patients with Kawasaki disease and development of clinical features followed by initiation of intravenous immunoglobulin before the third hospital day and patients with acute cervical lymphadenitis and surgical drainage or fine-needle aspiration performed before the third hospital day. Not only were they considered definitively diagnosed and enrollment not necessary, but also their laboratory values may have been influenced by previous procedures or intravenous immunoglobulin. Only patients who underwent radiologic studies (either ultrasonography [US] of the neck or contrast-enhanced computed tomography [CT] of the neck) were included. We excluded patients with malignancies, tuberculous infections, subacute or chronic lymphadenitis (defined as lymph node enlargement for over 2 weeks), Epstein–Barr virus infections, cytomegalovirus infections, or afebrile adenopathy. We also excluded patients with incomplete medical records. Through this exclusion process, we intended to include only those patients who were diagnosed with acute cervical lymphadenitis or Kawasaki disease at least 2 days after hospitalization (at least on the third day of hospitalization).

Final Diagnosis of Acute Cervical Lymphadenitis and Kawasaki Disease in Our Study Cohort

Patients were diagnosed with Kawasaki disease using the American Heart Association guidelines.[3] Patients with acute cervical lymphadenitis who had 2 or 3 clinical criteria associated with Kawasaki disease were closely assessed based on the "Evaluation of suspected incomplete Kawasaki disease" diagram. Lymph node first presentation of Kawasaki disease was diagnosed when patients finally diagnosed with Kawasaki disease presented with fever and cervical lymphadenopathy at least 2 days before the appearance of other clinical criteria. Two-dimensional echocardiography was performed to assess coronary artery abnormalities, which were defined as having z scores ≥2.5 according to internal diameters of the left anterior descending or right coronary arteries, normalized for body surface area.[8,9] Acute cervical lymphadenitis was diagnosed when patients had a tender cervical neck mass with diameter ≥1.5 cm with fever and was either confirmed by culture or the fever eventually improved after antibiotic therapy.[7]

Routine Protocol in Our Institute

The routine evaluation protocol included taking the patient's medical history (associated symptoms, concurrent viral infections, previous treatment, and animal or travel exposures), assessing the nodes on physical examination (for size, location, fluctuation, color, firmness, tenderness, and duration of lymphadenopathy), and routine laboratory tests. All patients were followed up daily to assess for the appearance of Kawasaki disease diagnostic features. Empiric antibiotics were initially prescribed for all patients (β-lactam agents or clindamycin-cephalosporin combinations). They underwent examination by US or a CT scan of the neck, including patients with lymph node first presentation of Kawasaki disease, in whom treatment with intravenous immunoglobulin (2 g/kg administered over 10-12 hours) together with acetylsalicylic acid was initiated thereafter. Blood samples were collected at hospitalization and on the third hospital day.

Data Collection

Baseline clinical and demographic data were retrieved from the medical records. We compared patients using the initial and subsequent laboratory data of complete blood counts, erythrocyte sedimentation rate, and C-reactive protein (CRP) values. As brain natriuretic peptide levels were not routinely assessed before clinical suspicion of lymph node first presentation of Kawasaki disease, few values were available at initial presentation. Two experienced pediatric radiologists independently reviewed the images (US or CT scan of the neck). They were blinded to the final diagnoses and the original radiographic interpretations. The average value of lymph node sizes measured by both radiologists was used as the data. The presence of an abscess was also assessed and compared by the 2 radiologists to reach consensus.

Statistical Analyses

The patients were divided into 2 groups according to the final diagnosis: patients with acute cervical lymphadenitis and patients with lymph node first presentation of Kawasaki disease (**Table I**). Continuous variables are presented as the mean ± SD and were compared using an independent t test. Categorical variables are presented as the frequency (%) and compared using the Pearson χ^2 test or Fisher exact test.

Discriminative factors for the differential diagnosis between acute cervical lymphadenitis and lymph node first presentation of Kawasaki disease were identified from an intergroup comparison or univariate logistic regression analysis. All significant independent variables ($P < .05$) were further evaluated by the decision-tree method to identify an ideal model for the differential diagnosis between the 2 groups. A decision-tree model was built using a χ^2 automatic interaction detection (CHAID) procedure.

Before the CHAID procedure, simple random sampling without replacement was used to split the entire cohort into a 2:1 ratio training and validation cohort. A decision-tree model built using the CHAID procedure was generated on a training cohort and applied on a validation cohort to

assess generalization errors and resultant overfitting of the model. The performance of our decision-tree model was compared with that of known laboratory markers from previous studies for sensitivity, specificity, positive predictive value, negative predictive value, overall accuracy, and Youden index.[6] Receiver operating characteristic curves were constructed to evaluate areas under the curve with 95% CIs. All statistical analyses were performed using SPSS, version 24, for Windows (IBM Corp, Armonk, New York). Analysis items with $P < .05$ were considered to indicate statistical significance.

Results

Baseline Characteristics of Patients in the Entire Cohort

A total of 309 patients were finally enrolled after we applied the exclusion criteria (Figure 1). The entire cohort was divided into these 2 cohorts: training cohort (206 patients) and validation cohort (103 patients). The mean age of the entire cohort was 4.9 years (range, 1 month to 17 years), and 185 patients (59.9%) were male. The demographic and clinical characteristics of patients in each group of the entire cohort are shown in Table I. In the training cohort, 148 patients were finally diagnosed with acute cervical lymphadenitis and 58 patients with lymph node first presentation of Kawasaki disease. In the validation cohort, 76 patients were eventually diagnosed with acute cervical lymphadenitis and 27 patients with lymph node first presentation of Kawasaki disease.

Characteristics of Disease Profile According to Final Diagnoses within the Training Cohort

The mean age of patients in the training cohort was 4.9 years, and 119 patients (57.8%) were male. Patients with acute cervical lymphadenitis were older than those with lymph node first presentation of Kawasaki disease and had a significantly shorter duration of fever (Table I). Surgical procedures were performed in 24 (16.2%) patients in the acute cervical lymphadenitis group, in which pathogens were identified in 15 patients (62.5%). The isolated organisms were *Staphylococcus aureus* (9/15, 60.0%), *Streptococcus viridans* (3/15, 20.0%), *Streptococcus pyogenes* (2/15, 13.3%), and an anaerobic pathogen (1/15, 6.7%). Overall, 10.8% (16 patients) of the acute cervical lymphadenitis group developed 2 principal clinical features of Kawasaki disease (exanthem in 9 patients and conjunctival injection in 7 patients), including cervical lymphadenopathy. All these suspected patients with incomplete Kawasaki disease were classified into the acute cervical lymphadenitis group after confirmation with an echocardiogram.

At final diagnosis, 79.3% (46/58) of the patients with lymph node first presentation of Kawasaki disease ultimately met the criteria for complete Kawasaki disease. The duration of fever before diagnosis in patients with complete Kawasaki disease was 6.2 ± 1.1 days, which was shorter than that of patients with incomplete Kawasaki disease (7.1 ± 1.3 days) ($P = .015$). Accordingly, patients with complete Kawasaki disease were eventually diagnosed 2.4 ± 1.5 days after admission, which was earlier than that for patients with incomplete Kawasaki disease (3.3 ± 1.6 days) ($P = .036$). In addition, 20.7% (12/58) of the patients with lymph node first presentation of Kawasaki disease met the criteria for incomplete Kawasaki disease, and all of them were evaluated by echocardiograms before the definitive diagnosis. Among them, 83.3% (10/12) had 3 of the 5 principal clinical features. The remaining 2 patients who had 2 clinical features were finally diagnosed based on echocardiograms. The most common features finally identified were conjunctival injection (56/58, 96.6%) and exanthem (56/58, 96.6%), followed by changes in lips or oral cavity (55/58, 94.8%) and changes in extremities (51/58, 87.9%), respectively. Coronary artery abnormalities were observed in 29.3% (17/58), and the rate of immunoglobulin resistance was 19% (11/58) in the lymph node first presentation of Kawasaki disease group.

Comparison of Infection Profiles within the Training Cohort

The initial and follow-up laboratory data and their changes were compared within those of the training cohort. Patients

Table I. Baseline characteristics of patients in the entire cohort

	Training cohort				
Variables	All	Acute cervical lymphadenitis	Lymph node first presentation of Kawasaki disease	*P* value	Validation cohort
Number of cases	206	148	58		103
Age, y	4.9 ± 3.0	5.3 ± 3.1	3.7 ± 2.1	<.001	5.1 ± 3.1
Sex ratio, male:female	119:87 (1.4:1)	84:64 (1.3:1)	35:23 (1.5:1)	.639	66:37 (1.8:1)
Days of fever					
At admission	3.4 ± 2.0	3.2 ± 2.1	3.9 ± 1.7	.022	3.4 ± 2.1
After admission	3.1 ± 2.4	2.7 ± 2.4	4.1 ± 2.3	<.001	2.8 ± 2.1
At diagnosis	4.1 ± 2.4	3.3 ± 2.1	6.5 ± 1.3	<.001	3.8 ± 2.4
Total	6.2 ± 3.0	5.6 ± 3.1	7.6 ± 1.9	<.001	5.9 ± 2.5
Antibiotics duration					
After admission	6.8 ± 4.2	7.6 ± 1.9	4.9 ± 3.1	<.001	6.4 ± 3.9
Surgical procedures, n (%)	25 (12.1)	24 (16.2)	1 (1.7)	.002	11 (10.7)
Total hospital days	7.9 ± 4.1	7.9 ± 4.3	8.0 ± 3.5	.769	7.4 ± 3.6

Data are presented as the mean ± SD.

with lymph node first presentation of Kawasaki disease showed significantly increased values for all inflammatory markers. CT- or US-defined abscesses of the lymph node(s) were observed only among patients with acute cervical lymphadenitis (19.6%, 29/148). After univariate logistic regression analysis, increased risk of lymph node first presentation of Kawasaki disease was associated with younger age (OR 0.788, P = .001) and increased laboratory values of inflammatory markers (**Table II**; available at www.jpeds.com).

Development of Decision-Tree Model Using Data from the Training Cohort

All independent variables, identified by intergroup comparison or the univariate logistic regression model, were further evaluated by the decision-tree method to determine an ideal model for the differential diagnosis of acute cervical lymphadenitis and lymph node first presentation of Kawasaki disease. The result of the decision-tree analysis using the CHAID procedure is shown in **Figure 2**. CT- or US-defined abscess of the neck was selected as the first determinant. According to our algorithm, all patients with CT- or US-defined abscess of the neck on initial radiologic evaluation (29 patients) (node 1 in **Figure 2**) were classified as the acute cervical lymphadenitis group, and all of them were finally diagnosed with acute cervical lymphadenitis.

For patients without CT- or US-defined abscess of the neck, the second important determinant was change in the CRP level. According to the algorithm, patients with any increase in the follow-up CRP level (53 patients) (node 3 in **Figure 2**) were classified as the lymph node first presentation of Kawasaki disease group. and 77.4% of them (41 of 53 patients) were finally diagnosed with lymph node first presentation of Kawasaki disease. Patients with more than a 50% decrease in the follow-up CRP level (43 patients) (node 5 in **Figure 2**) were classified into the acute cervical lymphadenitis group, all of whom were actually diagnosed with acute cervical lymphadenitis.

For patients who did not present with a CT- or US-defined abscess of the neck and showed a decrease in CRP level between 0 and 50% (node 4 in **Figure 2**), the third determinant for further classification was change in the neutrophil percentage. Among them, patients with more than a 13% increase in neutrophil percentage were classified as lymph node first presentation of patients with Kawasaki disease according to our algorithm (node 6 in **Figure 2**), and 52.2% of them (12 of 23 patients) were finally diagnosed with lymph node first presentation of Kawasaki disease. In contrast, patients with a less than 13% increase or any decrease in neutrophil percentage were classified as patients with acute cervical lymphadenitis (node 7 in **Figure 2**) and 91.4% of them (53 of 58 patients) were finally diagnosed with acute cervical lymphadenitis.

Comparison of Prediction Power in the Validation Cohort: Internal Validation of the Decision-Tree Model

To evaluate the generalizability of our model developed using the training cohort, the prediction power of our model was estimated in the validation cohort and compared with those of 3 known discriminatory laboratory values selected from previous studies.[6,7,10] including neutrophil count (>10 000/μL), aspartate aminotransferase level (≥30 IU/L), and CRP level (>7 mg/dL). Compared with these 3 laboratory cut-off values, our decision-tree model showed better prediction power including sensitivity, negative predictive value, overall accuracy, and a more reliable Youden index (**Table III**).

Discussion

In the present study, a decision-tree model for differentiating between patients with lymph node first presentation of Kawasaki disease and those with acute cervical lymphadenitis was established based on radiologic findings and sequential laboratory data. The sensitivity, specificity, and accuracy of our model for diagnosing lymph node first presentation of Kawasaki disease were 89.5%, 88.9%, and 89.3%, respectively, in our validation cohort. Compared with previous studies, it is expected to be useful as a diagnostic algorithm for differentiating patients with lymph node first presentation of Kawasaki disease and acute cervical lymphadenitis. Immunoglobulin resistance in lymph node first presentation of patients with Kawasaki disease (11/58, 19%) was similar to that reported in other studies.[11,12] The incidence of coronary artery lesions during the acute phase among patients with lymph node first presentation of Kawasaki disease (17/58, 29.3%) was similar to that reported in previous studies.[7,13]

In our study cohort, 28.1% of patients who initially presented with only fever and cervical lymphadenopathy were finally diagnosed with lymph node first presentation of Kawasaki disease. In total 9%-23% of patients with Kawasaki disease were reported to present initially with lymph node first presentation of Kawasaki disease.[7,14,15] Timely treatment with intravenous immunoglobulin reduces the incidence of coronary lesions, and thus, initial differential diagnosis between lymph node first presentation of Kawasaki disease and acute cervical lymphadenitis is a prerequisite. However, despite this clinical importance, there have been limited studies on the differential diagnosis of these 2 disease entities. Previous studies have suggested cut-off values for several individual inflammatory markers including neutrophil count, aspartate aminotransferase level, and CRP level.[6,7,10,16] Unfortunately, despite the significant differences in the individual inflammatory markers between the 2 groups, the range of the individual laboratory values overlaps between the 2 groups, and their single point cut-off values (binary) were not clinically useful for the differential diagnosis (**Table III**). In addition, individual laboratory values are highly linearly related, and multivariate analysis using multiple laboratory values was theoretically impossible

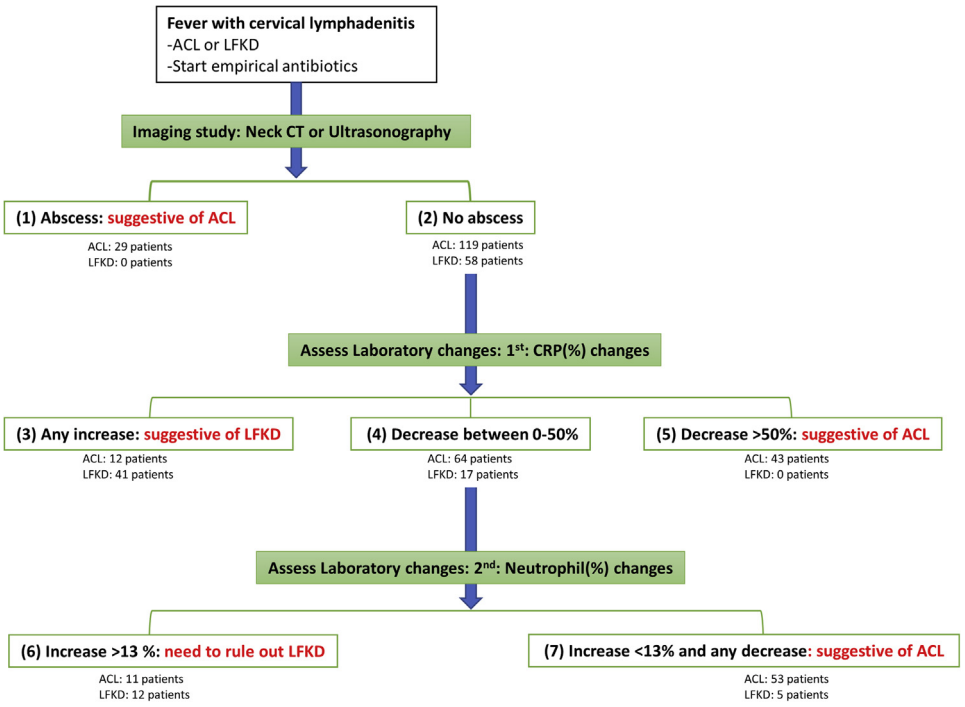

Figure 2. Steps for the differential diagnosis of acute cervical lymphadenitis and lymph node first presentation of Kawasaki disease in patients with fever and cervical lymphadenitis. *Numbers in parenthesis* were sequentially applied according to the decision-tree analysis steps.

because of multicollinearity. Therefore, we tried to overcome such statistical problems using a decision-tree model with the CHAID procedure, which can build nonbinary trees (each tree can be split into more than 2 branches) (Figure 2). As a result, our model successfully classified our study cohort into 2 groups with better performance than the previously identified binary cut-off values of inflammatory markers (Table III). Three determinants for differential diagnosis in our decision-tree model were CT- or US-defined abscess of the neck, changes in CRP level, and changes in neutrophil percentage.

The first step in the algorithm, radiologic evaluation to investigate the cause of resistance to antibiotic therapy, would enable the differentiation of most cases of suppurative lymphadenitis. After exclusion of suppurative lymphadenitis, which represents the most severe form of acute cervical lymphadenitis, assessing serial laboratory changes would be valuable for differentiating nonsuppurative acute cervical lymphadenitis and Kawasaki disease.

Neutrophil count and CRP are well-known variables included in the predictive model for the assessment of unresponsiveness to intravenous immunoglobulin therapy.[17-19]

Table III. Comparison between decision tree analysis and previous markers for the differential diagnosis of lymph node first presentation of Kawasaki disease

Types of cohorts	Cut-off point	*P* value	AUC (95% CI)	Sensitivity	Specificity	Positive predictive value	Negative predictive value	Overall accuracy	Youden index
Training cohort (n = 206)									
Decision tree analysis		<.001	0.878 (0.824-0.933)	84.5%	91.2%	96.2%	69.3%	86.3%	0.757
Neutrophil count, $10^3/\mu L$	10	.186	0.559 (0.472-0.647)	60.1%	51.7%	76.1%	33.7%	57.8%	0.119
AST, IU/L	30	.501	0.587 (0.501-0.673)	55.4%	62.1%	78.8%	35.3%	57.3%	0.175
CRP, mg/L	7	.348	0.542 (0.457-0.627)	10.1%	98.3%	93.8%	30.0%	35.0%	0.084
Validation cohort (n = 103)									
Decision tree analysis		.024	0.854 (0.759-0.948)	89.5%	88.9%	95.8%	75.0%	89.3%	0.784
Neutrophil count, $10^3/\mu L$	10	.065	0.551 (0.423-0.679)	65.8%	44.4%	76.9%	31.6%	60.2%	0.102
AST, IU/L	30	.064	0.573 (0.447-0.698)	55.3%	59.3%	79.2%	32.0%	56.3%	0.145
CRP, mg/L	7	.062	0.553 (0.432-0.673)	10.5%	100.0%	100.0%	28.4%	34.0%	0.105

AST, aspartate aminotransferase; *AUC*, area under the curve.

Considering that nonresponse may reflect the severity of ongoing inflammation, they are anticipated to increase despite antibiotic treatment in our study population (nodes 3 and 6 in **Figure 2**). Increases in neutrophil count reflect an accelerated inflammatory response. The increased number of neutrophils is enhanced with the markedly increased production of oxygen intermediate, leading to endothelial cell injury, which is involved in the pathogenesis of Kawasaki disease.[20,21]

Although sequential change in CRP level or neutrophil count are predictors of lymph node first presentation of Kawasaki disease, some patients in the acute cervical lymphadenitis group, who have slow response to antibiotics or underwent testing in the early stage before the CRP level reaches its peak at 24-48 hours,[22] might show an increase in secondary CRP level. However, these patients are expected to be differentiated by the stepwise manner of the decision-tree, in which suppurative cervical lymphadenitis is ruled out from imaging studies in the first step (node 1 in **Figure 2**).

Accurate diagnosis would reduce unnecessary exposure to prolonged antibiotics and prevent invasive procedures such as fine-needle aspiration. However, pathologic findings of lymph nodes in Kawasaki disease are known to be nonspecific and include multiple foci of necrosis and fibrin thrombi within the microvasculature.[23] Therefore, not only are cervical lymph node biopsies usually unnecessary, but also definite diagnosis of lymph node first presentation of Kawasaki disease would not be feasible even through lymph node biopsy. In these circumstances, our decision-tree model using widely available laboratory markers and imaging studies can provide a rapid and reasonable tool for helping to differentiate between lymph node first presentation of Kawasaki disease and acute cervical lymphadenitis in hospitals with limited resources.

The main limitation of our study is its retrospective design based on a limited number of inpatients from a single center. Although our decision-tree model showed a better performance for the differential diagnosis of acute cervical lymphadenitis and lymph node first presentation of Kawasaki disease in both the training and internal validation cohorts, external validation of our decision-tree model based on multicenter data is required to reduce the risk of model overfitting and prevent generalization errors before clinical application. Second, misclassification of the final diagnoses might exist. Although clinical features used to diagnose these 2 diseases were evident at the time of final diagnoses as mentioned previously, we could not avoid the possibility of symptom underreporting and misclassification because of our retrospective design. Therefore, it is possible that patients with acute cervical lymphadenitis who had any associated clinical features of Kawasaki disease may have truly had incomplete Kawasaki disease. Interestingly, among 16 patients with acute cervical lymphadenitis who were eventually excluded from the lymph node first presentation of Kawasaki disease group due to incomplete clinical features, 87.5% (14/16) were successfully classified into the acute cervical lymphadenitis group by our model. Finally, because of the variability in disease course, our criteria for enrollment may have left out some patients in the late phase of lymph node first presentation of Kawasaki disease who presented to the hospital with classic Kawasaki disease.

In conclusion, our decision-tree model was able to successfully differentiate lymph node first presentation of Kawasaki disease from acute cervical lymphadenitis using 3 determinants: CT- or US-defined abscess of the neck, sequential changes of CRP, and sequential changes of neutrophils. Without a "gold standard" for diagnosis, patients with cervical lymphadenopathy and fever with a possible diagnosis of LKFD could benefit from our decision-tree model before the onset of other features of Kawasaki disease. ■

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50 Years Ago in *THE JOURNAL OF PEDIATRICS*

Magnesium Supplementation in Protein-Energy Malnutrition: The Current Practice

Rosen EU, Campbell PG, Moosa GM. Hypomagnesemia and magnesium protein-calorie malnutrition. J Pediatr 1970;77:709.

There was no consensus on magnesium therapy and thus a persistent dilemma regarding routine supplementation of magnesium in severe protein-energy malnutrition (PEM). In 1970, Rosen et al published this trial in *The Journal* on parenteral magnesium therapy in children suffering from severe PEM. Serum magnesium levels were low at admission in most of these children. However, clinical features clearly attributed to hypomagnesemia were not identified. They concluded that magnesium therapy did not produce any therapeutic response in treated children compared with untreated children.

The landmark study of Caddell et al on magnesium therapy in malnourished children must be mentioned.[1] Muscle biopsies and plasma were deficient in magnesium, clinical features compatible with magnesium deficiency were documented, and it was concluded that magnesium therapy hastened recovery and decreased mortality in children with PEM. This work appeared 3 years earlier than the Rosen paper, but has stood the test of time. Low magnesium levels in blood, muscle biopsy, and the cerebrospinal fluid, now an established finding in PEM, may be due to inadequate intake, malabsorption, recurrent diarrhea, or infections. Various neuromuscular manifestations and electrocardiogram changes in PEM are attributed to magnesium deficiency. Nicholas et al concluded that magnesium supplementation accelerated recovery in PEM by 2 weeks and recommended oral supplementation.[2] Currently, the World Health Organization recommends routine supplementation of all severely malnourished children with magnesium.[3] On day one, 50% magnesium sulfate (2 mmol/L) should be administered intramuscularly (0.3 mL/kg, maximum 2 mL) followed by daily oral magnesium (0.2-0.3 mL/kg/day) mixed with feeds for the next 2 weeks. This can be done by the addition of an electrolyte/mineral mix or solution containing magnesium to the feeds. In case of nonavailability of mineral mix or an inability to prepare the mineral solution, it is recommended to add injection magnesium sulphate to feeds. The last 50 years have witnessed a paradigm shift in our understanding of magnesium—from being an innocent bystander to an active player in the pathogenesis and therapy of severe acute malnutrition—the current avatar of severe PEM.

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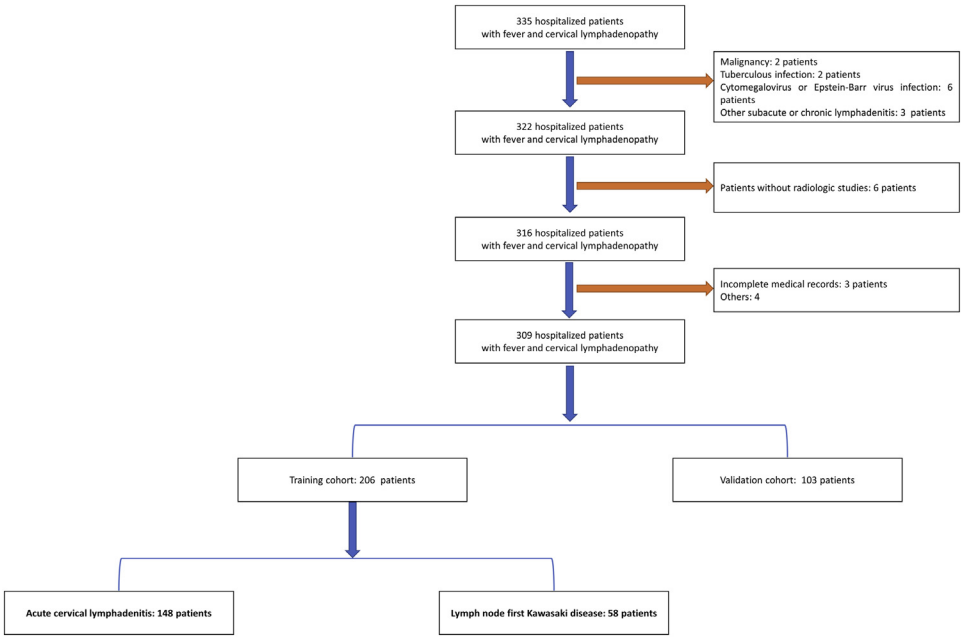

Figure 1. Flow diagram of the study process.

Table II. Comparison of laboratory profiles within the training cohort: Univariate logistic regression analysis

Variables	Total	Acute cervical lymphadenitis	Lymph node first presentation of Kawasaki disease	OR	95% CI	*P* value
Number of cases	206	148	58			
Age	4.9 ± 3.0	5.3 ± 3.1	3.7 ± 2.1	0.788	0.688-0.903	.001
Sex ratio, male:female	119:87 (1.4:1)	84:64 (1.3:1)	35:23 (1.5:1)	1.159	0.625-2.152	.639
Hb, g/dL	11.9 ± 1.0	12.1 ± 1.1	11.6 ± 0.9	0.649	0.475-0.888	.007
Anemia for age	26 (12.6%)	15 (10.1%)	11 (19.0%)	2.075	0.890-4.836	.091
WBC $\times 10^3/\mu L$						
Initial	15.1 ± 0.7	14.8 ± 0.7	15.6 ± 0.6	1.000	1.000-1.000	.440
Follow-up	11.8 ± 0.5	10.8 ± 0.5	14.4 ± 0.5	1.000	1.000-1.000	<.001
Percentage difference, %	17.53 ± 27.9	23.4 ± 23.8	2.6 ± 32.1	0.031	0.006-0.162	<.001
Neutrophils, %						
Initial	65.1 ± 19.2	61.4 ± 20.1	74.7 ± 12.2	1.050	1.026-1.074	<.001
Follow-up	56.3 ± 19.2	50.2 ± 17.9	72.1 ± 12.5	1.115	1.077-1.155	<.001
Percentage difference, %	13.1 ± 28.1	17.2 ± 30.3	2.4 ± 17.8	0.111	0.024-0.518	.005
Lymphocytes, %						
Initial	24.4 ± 16.1	27.5 ± 17.1	16.3 ± 9.7	0.942	0.916-0.969	<.001
Follow-up	32.9 ± 17.0	38.2 ± 15.5	18.5 ± 10.6	0.871	0.835-0.909	<.001
Percentage difference, %	(−) 64.8 ± 106.1	(−) 74.9 ± 106.2	(−) 38.9 ± 102.3	1.566	1.037-2.366	.033
Neutrophil-lymphocyte ratio						
Initial	5.4 ± 6.5	4.5 ± 5.8	7.8 ± 7.7	1.078	1.024-1.134	.004
Follow-up	3.1 ± 4.0	1.8 ± 1.6	6.4 ± 6.0	1.896	1.500-2.396	<.001
Percentage difference, %	24.6 ± 80.3	38.1 ± 56.7	(−) 6.5 ± 114.8	0.367	0.195-0.690	.002
Platelets, $10^3/\mu L$						
Initial	329.2 ± 123.4	324.4 ± 129.9	341.3 ± 104.8	1.001	0.999-1.004	.378
Follow-up	356.3 ± 150.1	344.1 ± 160.4	387.0 ± 116.2	1.002	1.000-1.004	.067
Percentage difference, %	(−) 11.3 ± 45.4	(−) 9.6 ± 50.9	(−) 15.9 ± 26.9	0.745	0.390-1.424	.373
ESR, mm/h						
Initial	46.3 ± 26.1	42.7 ± 25.5	55.5 ± 25.7	1.019	1.007-1.031	.002
Follow-up	48.4 ± 28.8	42.1 ± 27.9	63.6 ± 25.2	1.027	1.015-1.039	<.001
Percentage difference, %	(−) 9.2 ± 82.9	1.5 ± 73.8	(−) 3.7 ± 98.3	0.558	0.367-0.848	.006
CRP, mg/L						
Initial	71.9 ± 72.2	60.5 ± 67.3	101.5 ± 76.4	1.007	1.003-1.012	.001
Follow-up	55.4 ± 65.2	37.8 ± 50.3	100.0 ± 76.7	1.017	0.011-1.024	<.001
Percentage difference, %	23.7 ± 64.8	36.8 ± 58.5	(−) 10.6 ± 68.2	0.182	0.076-0.433	<.001
Albumin, g/dL, initial	4.0 ± 0.4	4.0 ± 0.5	3.9 ± 0.4	0.591	0.294-1.187	.139
Na, initial	136.6 ± 9.9	137.6 ± 3.0	133.8 ± 18.0	0.819	0.725-0.925	.001
AST, IU/L, initial	60.2 ± 108.2	36.4 ± 29.0	120.8 ± 185.8	1.012	1.006-1.019	<.001
ALT, IU/L, initial	48.6 ± 101.1	30.0 ± 56.1	96.8 ± 159.3	1.007	1.003-1.011	.001
LDH, IU/L, initial	329.1 ± 117.9	325.6 ± 108.0	337.9 ± 140.6	1.001	0.998-1.003	.497
Total bilirubin, mg/dL, initial	0.7 ± 0.6	0.6 ± 0.3	0.9 ± 0.9	2.464	1.385-4.382	.002
Urine WBC, initial	30 (14.6%)	15 (10.4%)	15 (25.9%)	3.093	1.398-6.842	.005
BNP, pg/mL, follow-up	103.4 ± 126.9	39.2 ± 29.9	136.8 ± 144.5	1.026	1.009-1.042	.002
Size of lymph node	3.08 ± 0.95	3.14 ± 1.01	2.90 ± 0.75	0.745	0.561-0.990	.042
CT or US-defined abscess of the neck	29 (14.0%)	29 (19.6%)	0 (0%)	<0.001	–	<.001

ALT, alanine aminotransferase; *BNP*, brain natriuretic peptide; *ESR*, erythrocyte sedimentation rate; *LDH*, lactate dehydrogenase; *WBC*, white blood cell.
Data are presented as the mean ± SD.