Point-of-Care Differentiation of Kawasaki Disease from Other Febrile Illnesses

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Objective To test whether statistical learning on clinical and laboratory test patterns would lead to an algorithm for Kawasaki disease (KD) diagnosis that could aid clinicians.

Study design Demographic, clinical, and laboratory data were prospectively collected for subjects with KD and febrile controls (FCs) using a standardized data collection form.

Results Our multivariate models were trained with a cohort of 276 patients with KD and 243 FCs (who shared some features of KD) and validated with a cohort of 136 patients with KD and 121 FCs using either clinical data, laboratory test results, or their combination. Our KD scoring method stratified the subjects into subgroups with low (FC diagnosis, negative predictive value >95%), intermediate, and high (KD diagnosis, positive predictive value >95%) scores. Combining both clinical and laboratory test results, the algorithm diagnosed 81.2% of all training and 74.3% of all testing of patients with KD in the high score group and 67.5% of all training and 62.8% of all testing FCs in the low score group.

Conclusions Our KD scoring metric and the associated data system with online (http://translationalmedicine.stanford.edu/cgi-bin/KD/kd.pl) and smartphone applications are easily accessible, inexpensive tools to improve the differentiation of most children with KD from FCs with other pediatric illnesses. *(J Pediatr 2013;162:183-8)*.

In the absence of a specific diagnostic test, the diagnosis of Kawasaki disease (KD) is currently based on clinical criteria.[1] Nonspecific laboratory testing can help to support the diagnosis.[2] If not treated promptly, patients with KD may develop coronary artery dilatation or aneurysms. The cardiovascular damage can be largely prevented by timely administration of intravenous immunoglobulin.[3] Thus, there is a need for a sensitive and specific diagnostic test that can facilitate diagnosis and permit timely treatment.

We postulated that quantitative analyses of KD-associated patterns of clinical and laboratory data could synergistically improve diagnostic accuracy. We used statistical learning methods to develop and validate KD diagnostic algorithms, which can be applied to existing and evolving information technologies to create novel and inexpensive point-of-care tools for the diagnosis of acute KD.

Methods

Inclusion criteria for subjects with KD were based on the American Heart Association guidelines.[1] We included all subjects with KD diagnosed within the first 10 days after fever onset who had fever for at least 3 days and 4 of 5 classic criteria or 3 or fewer criteria with coronary artery abnormalities documented by echocardiogram. Febrile controls (FCs) were children evaluated in the emergency department who had fever for at least 3 days accompanied by at least 1 of the KD criteria (rash, conjunctival injection, oral mucosal changes, extremity changes, enlarged cervical lymph node). Febrile children with prominent respiratory or gastrointestinal symptoms were specifically excluded so the majority of the controls had KD in the differential diagnosis of their condition. Informed consent was obtained from the parents of all subjects and assent from all subjects ≥7 years of age. This study was approved by the Human Subjects Protection Programs at the University of California San Diego and Stanford University.

AUC	Area under the curve
EMR	Electronic medical record
FC	Febrile control
Hgb	Hemoglobin
KD	Kawasaki disease
LDA	Linear discriminant analysis
NPV	Negative predictive value
PPV	Positive predictive value
ROC	Receiver operating characteristics

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De-identified clinical and laboratory data were extracted from the University of California San Diego KD electronic database for multivariate analysis. FCs had a clinically determined or culture-proved etiology for their febrile illness (Table I; available at www.jpeds.com). Possible viral infection was defined as a febrile illness that resolved without specific treatment within 3 days of obtaining the clinical samples. All subjects underwent evaluation for their febrile illnesses at Rady Children's Hospital San Diego and had complete historical, physical examination, and laboratory data required for multivariate analysis. Subjects were randomized (R random sampling method) into 2 cohorts: 276 patients with KD and 243 FCs for model training analysis; 136 patients with KD and 121 FCs for model testing analysis. Demographic data were analyzed using R epicalc package (The R Project for Statistical Computing; http://r-project.org).

Clinical data included 7 variables: (1) fever (temperature ≥38.0°C) in the emergency department or by history in the past 24 hours; (2) conjunctival injection; (3) extremity changes including red, swollen, or peeling hands or feet; (4) oropharyngeal changes including red pharynx, red, fissured lips, or strawberry tongue; (5) cervical lymph node of at least 1.5 cm; (6) rash; and (7) number of days of illness (first day of fever = illness day 1). Laboratory data obtained prior to administration of intravenous immunoglobulin included 12 variables: total white blood cell count; percentages of monocytes, lymphocytes, eosinophils, neutrophils, and immature neutrophils (bands); platelet count; hemoglobin (Hgb) concentration normalized for age; C-reactive protein; gamma-glutamyl transferase; alanine aminotransferase; and erythrocyte sedimentation rate. Logistic regression computation using the training data yielded both the adjusted ORs and the likelihood ratio test *P* value.

We used linear discriminant analysis (LDA) to classify individual subjects based on clinical variables alone, laboratory test variables alone, or the combined data sets. R library MASS function "lda" was used. Coefficients of linear discriminants, which are the associated weights with the first linear discriminant function, were calculated as a measure of the association of each variable with the final diagnosis (Table II). We performed receiver operating characteristic (ROC) analyses of the diagnostic performance of the clinical, laboratory, and combined LDA models for binary classification of subjects with KD from FCs in the training/testing cohort and compared their area under the curve (AUC).

The projection value onto the first canonical (LDA) was designated as the KD score, allowing the clinical variables to be collectively interpreted on a scale, rather than a strict binary discrimination. Three different types of KD scores were computed based on clinical findings, laboratory test results, and their combination for all subjects and were used to stratify subjects into subgroups with low, intermediate, and high scores. The low and high groups had a negative predictive value (NPV, FC diagnosis) >95% and a positive predictive value (PPV, KD diagnosis) >95%, respectively.

With a model view controller design, we applied a previously developed server-based biocomputational framework[4] to allow physicians remote access to our KD diagnostic algorithm. The algorithm and associated Web application were implemented using R and PERL, respectively. The iPhone application was developed in the integrated development environment Xcode 3.2.4 and iOS SDK 4.1 using Objective C. Later it was tested using iPhone Simulator 4.1 and was supported by iOS 4.1 or higher versions. The Google phone application, enabled by the Android Application Framework, was developed on the Google Android platform (Ver. 2.3, which is used by 57% of all current Android developers),

Table II. KD predictive features and multivariate modeling to discriminate KD from FC using training cohort

				LDA		
Twelve parameters	**Feature**	**OR (95% CI)**	***P***	**Clinical (LD1)**	**Laboratory (LD1)**	**Combined (LD1)**
Clinical parameters	Conjunctival injection	7.95 (3.41-18.53)	<.001	1.114157471		0.928053276
	Extremity changes	6.97 (3.4-14.3)	<.001	1.429549527		1.0550829
	Oropharyngeal changes	5.21 (2.22-12.2)	<.001	0.930626782		0.770919996
	Rash	2.43 (0.86-6.84)	.088	0.368589847		0.383400509
	Cervical lymph node >1.5 cm	1.51 (0.68-3.37)	.304	0.344090925		0.185409544
	Days of illness	1.12 (0.97-1.29)	.12	0.072792981		0.05634683
	Fever, temperature ≥38.0°C	0.05 (0.01-0.25)	<.001	−1.034326504		−0.952150912
Laboratory tests	Eosinophils, %	1.06 (0.95-1.19)	.293		0.068841219	0.028443882
	C-reactive protein, mg/dL	1.04 (0.98-1.11)	.172		0.021868585	0.015627459
	ESR, mm/h	1.03 (1.01-1.05)	<.001		0.014970912	0.008380854
	WBC, 10^3/mm^3	1.03 (0.97-1.1)	.364		0.011353403	0.016912331
	Monocytes, %	1.02 (0.93-1.13)	.634		−0.046919896	−0.00169595
	Gamma-glutamyl transferase, IU/L	1.0074 (0.9995-1.0153)	.054		0.004634134	0.002988495
	Platelets, %	1.0055 (1.0021-1.009)	.001		0.004126564	0.002753319
	Alanine aminotransferase, IU/L	1.0052 (0.9985-1.0119)	.089		0.001249501	0.001066656
	Neutrophils, %	0.97 (0.93-1.02)	.259		−0.004545484	−0.010462242
	Immature neutrophils, %	0.98 (0.93-1.03)	.452		−0.000422233	−0.006581996
	Lymphocytes, %	0.96 (0.91-1.01)	.155		−0.013016002	−0.013392125
	Hgb normalized for age, mg/dL	0.57 (0.41-0.79)	<.001		−0.28002571	−0.219374457

ESR, erythrocyte sedimentation rate; *LD1*, variable coefficient of the first linear discriminant; *WBC*, white blood cell count.