A Classification Tool for Differentiation of Kawasaki Disease from Other Febrile Illnesses

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Objective To develop and validate a novel decision tree-based clinical algorithm to differentiate Kawasaki disease (KD) from other pediatric febrile illnesses that share common clinical characteristics.

Study design Using clinical and laboratory data from 801 subjects with acute KD (533 for development, and 268 for validation) and 479 febrile control subjects (318 for development, and 161 for validation), we developed a stepwise KD diagnostic algorithm combining our previously developed linear discriminant analysis (LDA)–based model with a newly developed tree-based algorithm.

Results The primary model (LDA) stratified the 1280 subjects into febrile controls (n = 276), indeterminate (n = 247), and KD (n = 757) subgroups. The subsequent model (decision trees) further classified the indeterminate group into febrile controls (n = 103) and KD (n = 58) subgroups, leaving only 29 of 801 KD (3.6%) and 57 of 479 febrile control (11.9%) subjects indeterminate. The 2-step algorithm had a sensitivity of 96.0% and a specificity of 78.5%, and correctly classified all subjects with KD who later developed coronary artery aneurysms.

Conclusion The addition of a decision tree step increased sensitivity and specificity in the classification of subject with KD and febrile controls over our previously described LDA model. A multicenter trial is needed to prospectively determine its utility as a point of care diagnostic test for KD. *(J Pediatr 2016;176:114-20)*.

More effective methods for the early diagnosis of acute Kawasaki disease (KD) are required to permit timely administration of intravenous immunoglobulin and prevention of adverse outcomes. The classic KD diagnostic criteria adopted by the American Heart Association (AHA) include fever plus ≥4 of 5 principal clinical signs (**Figure 1**).[1] These guidelines, although widely adopted by clinicians, occasionally fail to differentiate KD from other pediatric rash/fever illnesses.[2] Moreover, despite supplementary laboratory criteria to aid in the diagnosis of patients with KD who manifest only 2 or 3 clinical signs, these incomplete cases may still be missed by clinicians.[1] Missing the diagnosis can lead to delayed treatment, thus increasing the risk of developing coronary artery lesions.[3-5]

We previously applied statistical learning using clinical and laboratory test variables, and developed a linear discriminant analysis (LDA)-based scoring system to differentiate KD from febrile controls[6] with a sensitivity of 92%-94% and a specificity of 88%-89%. However, 20%-30% of subjects in either the KD or febrile controls groups remained unclassified, and the algorithm performance on subjects with KD with incomplete clinical criteria was not investigated.[6,7]

In this study, we tested the hypothesis that applying separate tree-based algorithms after the LDA algorithm would improve the classification accuracy in differentiating subjects with KD from febrile control subjects. This novel integrated algorithm was validated with an independent subject cohort.

Methods

Subjects with KD and febrile controls meeting inclusion criteria were identified from the database maintained at the University of California San Diego KD

AHA	American Heart Association
CRP	C-reactive protein
ED	Emergency department
KD	Kawasaki disease
LAD	Left anterior descending
LDA	Linear discriminant analysis
NPV	Negative predictive value
PPV	Positive predictive value
RCA	Right coronary artery

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Supported by the American Heart Association (to H.C. and X.L.), Stanford University Spark Program (H.C. and X.L.), the David Gordon Louis Daniel Foundation (to J.B.), the Mario Batali Foundation (J.B.), the National Institutes of Health, National Heart, Lung, Blood Institute (HL69413 [to J.B.]), the Hartwell Foundation (to A.T.), and the Harold Amos Medical Faculty Development Program/Robert Wood Johnson Foundation (to A.T.). The authors declare no conflicts of interest.

http://dx.doi.org/10.1016/j.jpeds.2016.05.060

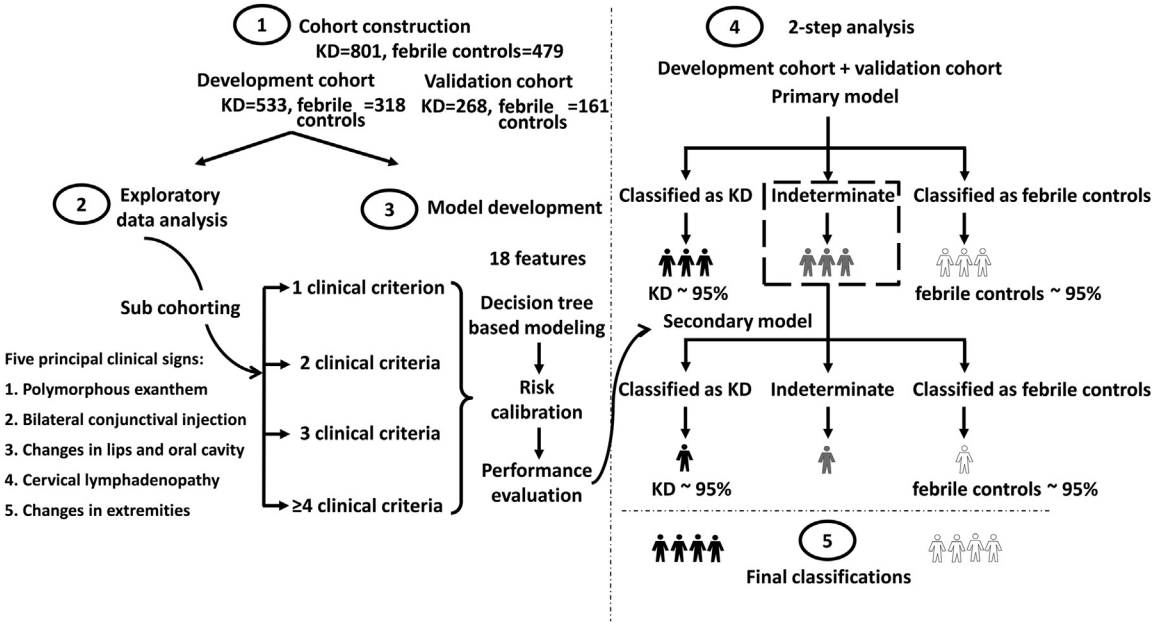

Figure 1. Workflow to create a 2-step statistical algorithm for distinguishing subjects with KD and febrile control subjects. LDA- and decision-tree–based models developed based on clinical and laboratory test variables were applied in sequence to construct a 2-step algorithm, partitioning the subjects into 3 diagnostic classifications (febrile controls, KD, and indeterminate). PPV and NPV of 95% were achieved at each step.

Research Center. Complete demographic and clinical data were collected prospectively on all subjects with KD and febrile controls. A total of 1280 subjects (801 with KD and 479 febrile controls) were included in this study (**Figure 2**; available at www.jpeds.com). Subjects with KD in this study were (a) patients with fever (≥38.0°C rectally or orally) for no more than 10 days plus ≥4 of the 5 principal clinical criteria, (b) patients meeting fewer criteria but with coronary artery abnormalities (*Z*-score ≥ 2.5 for left anterior descending [LAD] and/or right coronary arteries [RCA]) documented by echocardiography, and (c) patients meeting <4 criteria but meeting the AHA criteria for incomplete KD by laboratory criteria.[1] A concomitant viral infection by reverse transcriptase polymerase chain reaction did not disqualify the patient as a KD subject. Every subject was evaluated clinically by 1 of 2 expert KD clinicians and the final assignment of a KD diagnosis was based on the opinion of these 2 experts. Febrile control subjects were recruited from the emergency department (ED) at Rady Children's Hospital San Diego. All febrile control subjects had unexplained fever, ≥1 of the 5 principal clinical criteria for KD, and had laboratory tests performed including those commonly ordered for evaluation of KD, which included a complete blood count with manual differential, erythrocyte sedimentation rate, and levels of C-reactive protein (CRP), alanine aminotransferase, and gamma glutamyl transferase. All patients referred to the ED for evaluation of possible KD (approximately 50% of the febrile control cohort) were offered enrollment as febrile control subjects in our study. We enrolled the remaining febrile controls from children in the ED presenting with fever and ≥1 of the clinical signs of KD, and excluded patients who had an obvious respiratory or gastrointestinal infection because KD would be unlikely to present in this manner. The final diagnoses of the febrile controls were determined by chart review by 2 expert clinicians from prospectively collected clinical and laboratory data and from review of microbiologic and serologic results and subsequent clinical encounters. Only 3.8% of the febrile controls (18 of 479) underwent echocardiography to evaluate for possible KD.

Signed consent or assent forms were obtained from the parents of all subjects and from all subjects >6 years of age. The study was approved by the institutional review boards of the University of California San Diego and Stanford University.

For each subject, we collected the 18 clinical and laboratory test variables retained in the final model of the LDA-based algorithm.[6] Clinical data included 6 clinical signs associated with KD: illness days (temperature ≥38.0°C); cervical lymph node of ≥1.5 cm; rash; conjunctival injection; extremity changes including red, swollen, or peeling hands or feet; and oropharyngeal changes including red pharynx, red, fissured lips, or strawberry tongue. Laboratory test data (obtained prior to administration of intravenous immunoglobulin for subjects with KD) included total white blood cell