Multicentre validation of a computer-based tool for differentiation of acute Kawasaki disease from clinically similar febrile illnesses

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ABSTRACT

Background The clinical features of Kawasaki disease (KD) overlap with those of other paediatric febrile illnesses. A missed or delayed diagnosis increases the risk of coronary artery damage. Our computer algorithm for KD and febrile illness differentiation had a sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of 94.8%, 70.8%, 93.7% and 98.3%, respectively, in a single-centre validation study. We sought to determine the performance of this algorithm with febrile children from multiple institutions across the USA.

Methods We used our previously published 18-variable panel that includes illness day, the five KD clinical criteria and readily available laboratory values. We applied this two-step algorithm using a linear discriminant analysis-based clinical model followed by a random forest-based algorithm to a cohort of 1059 acute KD and 282 febrile control patients from five children's hospitals across the USA.

Results The algorithm correctly classified 970 of 1059 patients with KD and 163 of 282 febrile controls resulting in a sensitivity of 91.6%, specificity of 57.8% and PPV and NPV of 95.4% and 93.1%, respectively. The algorithm also correctly identified 218 of the 232 KD patients (94.0%) with abnormal echocardiograms.

Interpretation The expectation is that the predictive accuracy of the algorithm will be reduced in a real-world setting in which patients with KD are rare and febrile controls are common. However, the results of the current analysis suggest that this algorithm warrants a prospective, multicentre study to evaluate its potential utility as a physician support tool.

What is already known on this topic?

► A key objective of research in Kawasaki disease (KD) is to reduce the risk of long-term cardiovascular sequelae by expediting timely diagnosis.
► The major challenge in diagnosing KD is that it shares clinical signs with other childhood febrile illnesses.
► A computer-based algorithm was developed and validated using clinical criteria and laboratory tests to differentiate single-centre patients with KD from those with other febrile illnesses.

What this study adds?

► This is the first blinded, multicentre validation of a computer algorithm for the differentiation of patients with KD from others with clinically similar febrile illnesses.
► The algorithm has sufficient sensitivity and positive predictive value to identify the majority of patients with KD diagnosed at centres across the USA.
► The results suggest a promising approach to the timely diagnosis and treatment of patients with KD to reduce the risk of coronary artery aneurysms.

INTRODUCTION

Kawasaki disease (KD), the most common cause of acquired heart disease in children, is a vasculitis that mostly affects children under 5 years of age but can occur throughout childhood.[1] As treatment with intravenous immunoglobulin (IVIG) reduces the risk of long-term cardiovascular sequelae, KD must be considered in the diagnosis of a febrile child.[2] A delayed diagnosis increases the risk of coronary artery aneurysms, which in some children can lead to myocardial infarction or death.[3–5] The major challenge in diagnosing KD is that it shares clinical signs with other childhood febrile illnesses.[6] To date, there is no diagnostic test for KD, and it remains mostly a clinical diagnosis. While there are supplementary laboratory data as outlined in the American Heart Association (AHA) guidelines that can aid in the diagnosis if only two or three clinical signs are present, the diagnosis of KD is still being missed.[6–8] Thus, a validated and generalisable algorithm that differentiates acute KD from other febrile illnesses is needed to help facilitate timely

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IVIG treatment and, ultimately, to reduce the risk of coronary artery abnormalities.

In 2016, we validated a two-step computer-based algorithm using clinical and laboratory variables to classify an individual as a patient with KD, a febrile control (FC) or indeterminate. In the single-centre validation,[9] the algorithm yielded a sensitivity of 94.8% and a specificity of 70.8%. In this study, we performed a blinded, multicentre validation of the computer algorithm for differentiation of patients with KD from those with other paediatric febrile illnesses. By exploring the classification results of the algorithm in the multicentre study, we aimed to evaluate the performance of the algorithm in a larger, independent cohort.

MATERIAL AND METHODS
Study design
We previously developed and validated, with data from a single centre, a two-step algorithm that applies a linear discriminant analysis (LDA)-based model followed by a random forest-based algorithm to differentiate patients with KD from children with other febrile illnesses (FCs).[9] Patients who are classified as indeterminate by the LDA-based model are then evaluated by the random-forest algorithm based on the number of KD clinical criteria with which they present. The two-step algorithm was developed with a discovery cohort, and validated with a separate validation cohort, in the single-centre study. We applied the algorithm to a blinded dataset from five paediatric hospitals in the USA. The evaluation was blinded to diagnosis during classification, and then unblinded to calculate performance.

Study population
Patients with acute KD were identified from well-curated databases at five paediatric hospitals in the USA: Boston Children's Hospital, Boston, Massachusetts; Children's Hospital Colorado, Aurora, Colorado; Children's Hospital of Orange County, Orange, California; Nationwide Children's Hospital, Columbus, Ohio; and Rady Children's Hospital, San Diego, California. FCs were identified from Children's Hospital Colorado and Rady Children's Hospital San Diego. The diagnosis of KD was made by KD experts (paediatric infectious disease or paediatric rheumatologists) based on the 2004 AHA guidelines.[10] All FCs had unexplained fever, ≥1 of the five principal clinical criteria for KD, and laboratory evaluation, and came from two of the centres: Rady Children's Hospital San Diego and Children's Hospital Colorado. While the FCs from Rady Children's Hospital San Diego were enrolled through the emergency department, with the diagnosis adjudicated by a paediatric infectious disease specialist and emergency medicine physician, the FCs from Children's Hospital Colorado were diagnosed by paediatric infectious disease consultants. Final FC diagnosis was determined by clinical features, culture or PCR testing.

All patients had fever (≥38.0°C) for no more than 10 days and had complete information for nine clinical or laboratory data points, including the five principal clinical criteria (illness days (ie, days of fever), total white cell count (WCC), percentage of eosinophils and haemoglobin concentration), as we previously demonstrated that these were the most highly weighted variables.[11] Other parameters of the algorithm, including percentages of monocytes, lymphocytes, neutrophils and immature neutrophils (bands), platelet count, levels of C reactive protein (CRP), gamma glutamyl transferase (GGT), alanine aminotransferase (ALT) and erythrocyte sedimentation rate (ESR), were collected if available. Age and sex for all patients, and coronary artery status and Z-score (SD from the mean adjusted for body surface area) for patients with KD, were also recorded. Coronary artery status was classified as normal (right coronary artery (RCA) and left anterior descending (LAD) Z-score always <2.5) or abnormal (RCA and/or LAD Z-score ≥2.5 within the first 6 weeks after diagnosis).

Two-step algorithm for differentiation of KD and FCs
The two-step algorithm uses an LDA-based analysis followed by a random forest-based algorithm. Input variables of the LDA model are illness days, the 5 principal clinical criteria and 12 laboratory test variables. There variables and their corresponding weights in the algorithm are listed in online supplementary appendix 1. Values were imputed with a k-nearest neighbour algorithm. The output of the LDA classifies each individual patient as KD, FC or indeterminate. The cut-off thresholds between the three categories were set in the original algorithm to provide a positive predictive value (PPV) or negative positive value (NPV) of 95%. The indeterminate patients were divided into four subcohorts based on the number of KD criteria present at the time of diagnosis,[9] and separate random forest models were applied to the patients in each sub-cohort to further stratify these patients into KD, FC or indeterminate categories.

Algorithm performance in the multicentre study
The aim of this study was to calculate the algorithm performance on a multicentre cohort. We compared the classifications of patients by the algorithm with the classifications made by the clinical experts who diagnosed the patients. We calculated sensitivity, specificity, PPV, NPV and rates of indeterminate classification of the algorithm when applied to the five-centre population. We then compared these results to those of the single-centre validation cohort to observe any difference in algorithm performance between the multicentre and single-centre cohorts. Performance of the algorithm was evaluated according to age, illness days and coronary artery status. We also performed univariable analysis with each of the 18 variables in subcohorts of patients manifesting 2, 3 or ≥4 clinical criteria for KD. In each subcohort, the distribution of each variable was compared between the patients with KD and FCs, and the differences were measured using Mann-Whitney U test (for continuous variables) or Fisher's exact test (for categorical variables). The distribution of each of the variables was also compared with the results of the single-centre study, in patients with KD and FCs respectively, to explore potential reasons for different performance of the algorithm between the two studies.

RESULTS
Patient characteristics
From the five centres, 1059 patients with KD and 282 FCs were evaluated in the study. Patients with KD were more likely to be male than FCs (61.9% (649 of 1048 KDs in whom sex was available) vs 53.8% (98 of 182 FCs in whom sex was available), p=0.04). The FCs had a higher median age than the patients with KD (3.7 vs 2.8 years, p<0.0001). The FCs most common final diagnosis was a viral illness (online supplementary appendix 2). Echocardiography, performed in 27.3% (77 of 282) of the FCs for evaluation of suspected KD, revealed normal Z-scores of the LAD and RCA in all of these patients.

Classification results and comparison with the single-centre study validation results
In this multicentre study, the algorithm had a sensitivity of 91.6% (970 of 1059; 918 (86.7%) were identified by the LDA and 52
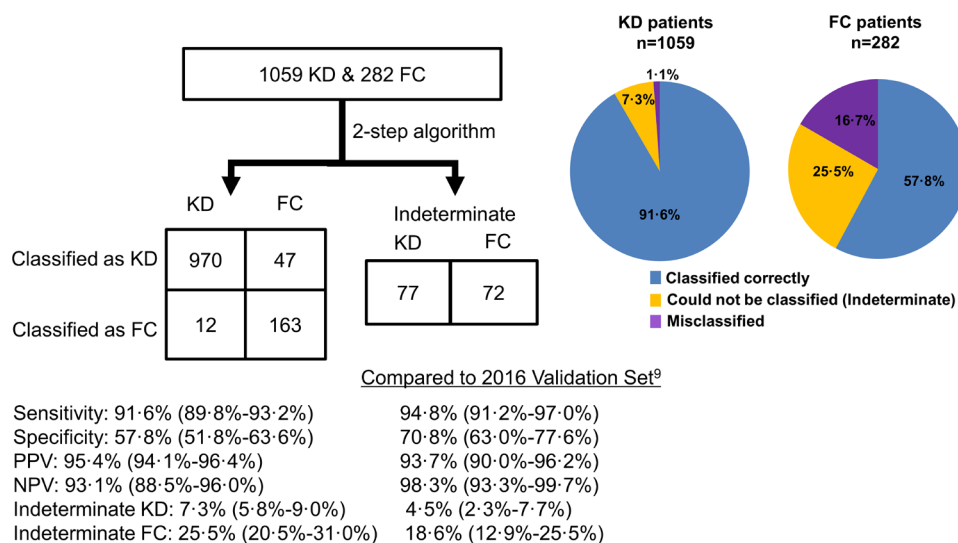
Figure 1 Performance of the two-step algorithm for classification of patients with KD and FCs. Left: a 2×2 table compared with single-centre validation results in 2016. Right: percentages of correctly classified, misclassified and indeterminate patients. FCs, febrile controls; KD, Kawasaki disease; NPV, negative positive value; PPV, positive predictive value.

(4.9%) were identified by the random forest), a specificity of 57.8% (163 of 282; 129 (45.7%) were identified by LDA and 34 (12.1%) by the random forest), a PPV of 95.4% (970 of 1017; 918 of 942 (97.5%) for the LDA and 52 of 75 (69.3%) for the random forest) and a NPV of 93.1% (163 of 175; 129 of 135 (95.6%) for the LDA and 34 of 40 (85.0%) for the random forest); 7.3% (77 of 1059) of the patients with KD and 25.5% (72 of 282) FCs were classified as indeterminate (figure 1). Overall, 1.1% (12 of 1059) of the patients with KD and 16.7% (47 of 282) of FCs were misclassified by the algorithm (online supplementary appendix 3). Compared with the results of the single-centre study where the PPV, NPV, sensitivity, specificity, indeterminate KD and indeterminate FC were 93.7% (254 of 271), 98.3% (114 of 116), 94.8% (254 of 268), 70.8% (114 of 161), 4.5% (12 of 268) and 18.6% (30 of 161), respectively, the PPV, NPV and sensitivity did not change significantly (PPV: p=0.3; NPV: p=0.052; sensitivity: p=0.1; Fisher's exact test), while the specificity decreased (Fisher's exact test p=0.008). Of the 1059 patients with KD, 184 were infants younger than 1 year and 90.8% (167 of 184) were classified correctly, 1.1% (2 of 184) were misclassified and 8.2% (15 of 184) were indeterminate (online supplementary appendix 4). Of patients with KD ≥1 year, 91.8% (803 of 875) were classified correctly, 1.1% (10 of 875) were misclassified and 7.1% (62 of 875) were indeterminate. The algorithm did not show significantly different performance between patients with KD in the two age groups (Fisher's exact test p=0.9). The performance of the algorithm by age for the patients with KD for this multicentre study was similar to that in the single-centre study (95.9% of the infants (47 of 49; Fisher's exact test p=0.7) and 94.5% of the patients ≥1 year (207 of 219; Fisher's exact p=0.4) were classified correctly).

The algorithm performance was also examined in subgroups with different illness days (online supplementary appendix 4). The overall performance of the algorithm was worse for patients having 8–10 days of illness compared with those with <8 days of illness. Statistically significantly lower specificity was observed (Fisher's exact test p<0.0001) while sensitivity, PPV and NPV were similar. This may in part be due to the fact that inflammatory markers in patients with KD were more similar (ratio of median was getting closer to 1) to those of FCs at 8–10 days of illness as compared with those with <8 days of illness (online supplementary appendix 5).

There were 306 patients with KD who presented with three or less clinical criteria. Compared with its performance in KD patients with four or five clinical criteria, the algorithm had a lower sensitivity (72.2% vs 99.5%; Fisher's exact test p<0.0001) and higher rate of misclassification (2.6% vs 0.5%; Fisher's exact test p=0.007) in KD patients with three or fewer clinical criteria.

One or more variables had missing values for 630 of 1059 (59.5%) patients with KD and 110 of 282 (39.0%) FCs. The algorithm was less sensitive in identifying KD patients with one or more missing variables as compared with patients with complete data. Sensitivity dropped from 94.7% to 89.5% (p=0.003), and the indeterminate rate of KD increased from 4.4% to 9.2% (p=0.004).

Classification of KD patients with coronary artery abnormalities

Coronary artery abnormalities were documented in 232 of the 1059 patients with KD (21.9%). Of these, 13 (5.6%) were classified as indeterminate and 1 (0.4%) was misclassified (table 1). The misclassified patient had a maximum Z-score of 2.8 that resolved by 8 weeks after treatment. Of the 13 indeterminate patients, 11 met the AHA criteria for incomplete KD.[6] The two remaining patients classified as indeterminate with abnormal

Table 1 Performance of the two-step algorithm in relation to echocardiogram results

Coronary artery status by echocardiogram, n (%)	KD, correctly classified, n=970	KD, indeterminate, n=77	KD, misclassified, n=12
Normal, n=827	752 (90.9)	64 (7.7)	11 (1.3)
Abnormal, n=232*	218 (94.0)	13 (5.6)	1 (0.4)

*Coronary artery status was classified as normal (right coronary artery (RCA) and left anterior descending (LAD) Z-score always <2.5) or abnormal (RCA and/or LAD Z-score ≥2.5 within the first 6 weeks after diagnosis).
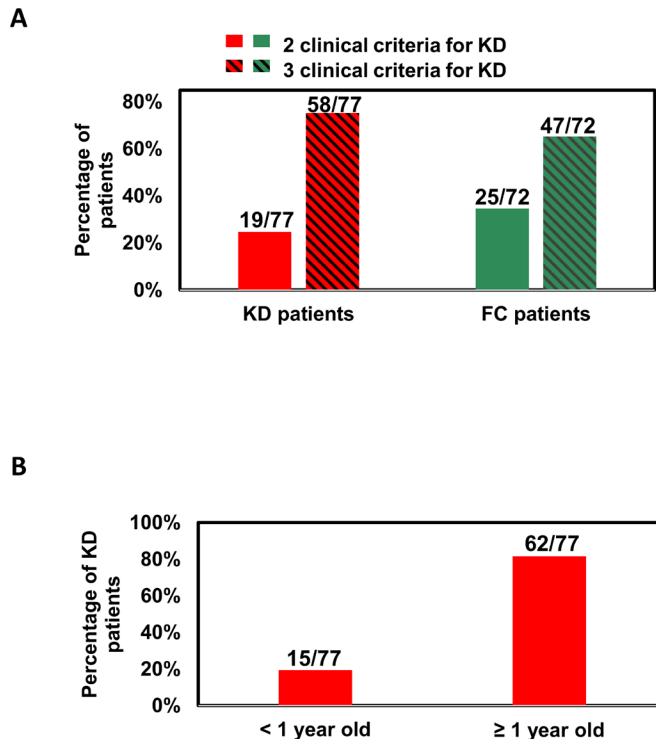KD, Kawasaki disease.

Figure 2 Percentage of KD and FC patients classified as indeterminate (A) stratified by the number of clinical criteria for KD and (B) stratified by less than or greater than 1 year. Age distribution was measured for patients with KD only. FC, febrile control; KD, Kawasaki disease.

echocardiograms had a maximum Z-score of 3.9 that resolved 6 weeks after treatment and a maximum Z-score of 2.14.

Characteristics of the patients classified as indeterminate

All subjects (77 KD and 72 FCs) classified as indeterminate by the algorithm had two or three clinical criteria (figure 2). Of the 77 patients with KD, 15 were <1 year of age. The algorithm performed equally well in both age groups (p=0.9): 15 of 184 (8.2%) of the patients with KD <1 year and 62 of 875 (7.1%) of the patients ≥1 year were classified as indeterminate.

Univariable analysis of clinical and laboratory test variables

The majority of the patients with KD (753 of 1059, 71.1%) had four or five principal clinical criteria, and more than half (187 of 282, 66.3%) of FCs had one or two principal clinical criteria (table 2). Most of the laboratory test variables except illness day,

ALT and immature neutrophils differed significantly between patients with KD and FCs in all three subcohorts (table 3).

Comparison of clinical and laboratory data between single-centre and multicentre study

The frequencies of the five principal criteria were similar to those in the single-centre validation dataset of the algorithm except for rash and conjunctival injection (online supplementary appendix 6). Distribution of illness days and immature neutrophils was significantly different in this multicentre cohort compared with the single-centre cohort for both KD subjects and FCs. Neutrophils, lymphocytes, monocytes, CRP and GGT were significantly different for patients with KD, and platelet count and ALT were significantly different for FCs between the two studies (online supplementary appendix 7).

FCs misclassified as KD in this study had many variables that were significantly different from the FCs in the single-centre study. In a comparison of the misclassified FCs in this study, 4 of 6 clinical signs and 8 of 12 laboratory values were significantly increased or decreased (p<0.05) as compared with FCs in the single-centre study (online supplementary appendix 8 and 9).

DISCUSSION

It is essential to diagnose KD early in the acute phase as early intervention with anti-inflammatory therapies can reduce the risk of developing coronary artery aneurysms.[12] However, the diagnosis of KD remains difficult as the clinical signs overlap with those of other paediatric febrile illnesses. In this study, we validated a previously developed algorithm for differentiation of acute KD from other febrile illnesses using a blinded, multicentre cohort. The algorithm had a sensitivity of 91.6%, a specificity of 57.8%, a PPV of 95.4% and a NPV of 93.1%. Given that the true KD-to-FC ratio in a paediatric emergency department is estimated to be 1:10, the algorithm will certainly have a lower sensitivity and specificity in a real-world setting. Recognising this limitation, the algorithm still merits prospective testing in a setting in which patients with KD are rare and FCs are common to evaluate its potential utility as a physician support tool.

The algorithm identified 94.0% of patients with KD who developed coronary artery abnormalities, and only misclassified as FC one patient with a maximal Z-score of 2.8 whose coronary arteries remodelled within 8 weeks of diagnosis. The majority of patients with coronary artery abnormalities classified as indeterminate by the two-step algorithm would have been identified by the 2017 AHA algorithm for incomplete KD. Thus, our two-step algorithm and the AHA algorithm for incomplete KD could be useful if applied sequentially. Patients classified as indeterminate

Table 2 Distribution of the clinical signs among KD and FC patients in subcohorts manifesting 1, 2, 3 or ≥4 clinical criteria for KD

| | Clinical criteria* | | | | | | | | | | | |
| | 1 | 2 | | | | 3 | | | ≥4 | | |
Clinical signs, n (%)	KD, n=1	FC, n=71	KD, n=64	FC, n=116	P value†	KD, n=241	FC, n=80	P value†	KD, n=753	FC, n=15	P value†
Cervical lymph node >1.5 cm	0 (0)	10 (14)	3 (5)	19 (16.4)	0.03	41 (17.0)	16 (20)	0.6	305 (40.5)	10 (67)	0.06
Rash	1 (100)‡	45 (63)	36 (56)	75 (64.7)	0.3	189 (78.4)	66 (83)	0.5	736 (97.7)	14 (93)	0.3
Conjunctival injection	0 (0)	10 (14)	45 (70)	75 (64.7)	0.5	203 (84.2)	66 (83)	0.7	743 (98.7)	15 (100)	1
Extremity changes	0 (0)	1 (1)	13 (20)	13 (11.2)	0.1	102 (42.3)	30 (38)	0.5	697 (92.6)	10 (67)	0.004
Oropharyngeal changes	0 (0)	5 (7)	31 (48)	50 (43.1)	0.5	188 (78.0)	62 (78)	1	737 (97.9)	15 (100)	1

*Column totals exceed the number of patients because each feature is counted for each patient.
†Fisher's exact test.
‡six-month male patient with dilated coronary arteries.
FC, febrile control; KD, Kawasaki disease.

Table 3 Univariable analysis of clinical and laboratory test variables in patients with KD and FCS who had two, three and at least four clinical criteria

Variable, median, IQR*	Two clinical criteria			Three clinical criteria			≥4 clinical criteria		
	KD (n=64)	FC† (n=116)	P value‡	KD (n=241)	FC (n=80)	P value‡	KD (n=753)	FC (n=15)	P value‡
Days of illness	7 (6,8)	5 (4,7)	<0.0001	6 (5,8)	5 (4,7.3)	0.0006	6 (5,7)	5 (4,7)	0.3
Alanine aminotransferase, IU/L	36 (22,77.5)	34 (23,45.5)	0.4	33 (19,67)	30 (24.5,38.5)	0.4	50.5 (24,120.5)	33 (23,45)	0.2
C reactive protein, mg/dL	8.7 (4.8,16.1)	3.4 (1.5,6.9)	<0.0001	9.23 (4.8,16.3)	3.1 (1.6,6.2)	<0.0001	8.1 (4.9,16)	3.6 (1.5,9)	<0.0001
Eosinophils, %	2 (1,5.7)	0.6 (0,2)	<0.0001	2.1 (1,4)	0.05 (0,1.2)	<0.0001	2 (1,5)	1 (0,2)	0.008
Erythrocyte sedimentation rate, mm/hour	61 (47.5,88)	30 (12.5,52)	<0.0001	62 (43.5,89)	30 (15.8,52)	<0.0001	57 (42,79)	29 (11.5,47)	0.0002
Gamma-glutamyl transferase, IU/L	30.5 (18,127.8)	16 (12,22)	0.001	35 (17,111)	16 (12.8,19.3)	<0.0001	57 (20,136)	12 (10,16)	<0.0001
Haemoglobin concentration, g/dL	10.8 (10.2,11.4)	12.1 (11.3,12.7)	<0.0001	10.9 (10,11.7)	12 (11.4,12.8)	<0.0001	11.2 (10.4,12)	12.4 (12.15,12.9)	<0.0001
Immature neutrophils, %	5 (0.3,8.8)	3 (1,9)	0.6	4 (0,12)	3 (0,8)	0.7	7 (0,17)	6.5 (0.3,11.8)	0.7
Lymphocytes, %	22 (12.5,32.3)	29 (18,42.5)	0.003	22 (15,33)	32.5 (18.8,48)	0.0001	18 (10,29)	30 (19,39)	0.01
Monocytes, %	5.1 (3.9,8.5)	8 (4.1,10.3)	0.02	6 (3,8.7)	8 (5.8,12)	0.0001	5 (3,7)	8 (6.5,11)	0.004
Neutrophils, %	63 (51.8,73.2)	52.5 (35.3,66.2)	0.0007	60.5 (50.5,70.8)	47.2 (33.5,64.3)	<0.0001	65 (52.6,75)	55 (32,65.7)	0.006
Platelet count, $10^3/mm^3$	413 (323.5,495)	248 (187,301.5)	<0.0001	356.5 (267.8,446.5)	252 (182,347.5)	<0.0001	349 (278,429)	179.5 (100.8,281.3)	<0.0001
White cell count, $10^3/mm^3$	12.9 (10.1,16.4)	9.4 (6.9,13.5)	<0.0001	13.1 (10.3,16.9)	10.4 (7,13.5)	<0.0001	13.5 (10.3,17.3)	7.8 (4.3,11.2)	<0.0001

Distribution of each variable was compared between the patients with KD and FC. Mann–Whitney U test was used to calculated p values.
*interquartile range.
†febrile controls.
‡Mann–Whitney U test.
KD, Kawasaki disease.

could be referred for evaluation by a specialist with expertise in KD. Future versions of the algorithm could aid the clinician by assigning a probability of KD rather than rendering categorical classifications.

The performance of the algorithm was similar to that of the single-centre validation study in terms of sensitivity, PPV and NPV, as well as in subgroups divided by age and illness days. However, the specificity decreased significantly for patients having 8–10 days of fever at presentation, in part due to laboratory values becoming more similar between KD and FC patients. Since an important goal of the algorithm is to enable IVIG administration in the early phase of the disease, the fact that the algorithm had better performance in patients with fewer illness days makes it a potentially more useful tool to ensure missing fewer patients earlier in the course of illness.[10]

We recognise both strengths and weaknesses in this study. The algorithm performed well with FCs who shared many clinical characteristics with our patients with KD, thus demonstrating its potential clinical utility across a broad range of similar appearing illnesses. However, in this multicentre study, the specificity dropped to 57.8% from 70.8% in the single-centre study, in part due to a higher percentage of FCs with many clinical and laboratory variables that were more similar to patients with acute KD. Some of these variables had large weights in the algorithm, including extremity changes, conjunctival injection, oropharyngeal changes, days of illness and WCC. Application of machine learning in future versions of the algorithm may improve the specificity and reduce the number of patients classified as indeterminate. Information on race was not collected, and FCs were only available from two participating sites, which limited our ability to assess patient characteristics and their association with algorithm performance. In this multicentre study, we had a larger number of patients with KD than FCs, and the frequency of KD patients in a prospective study in the emergency department setting will be much lower, which will undoubtedly worsen the performance of this algorithm. The actual ratio of KD-to-FC patients who would be screened for KD is not known. We are planning a multicentre study in the emergency room setting to assess the prevalence of KD and prospectively evaluate the utility of this algorithm.

CONCLUSIONS
We assessed the performance of our two-step algorithm in a blinded, multicentre study. This work provides further support for moving forward with an adequately powered, multicentre study in the emergency department setting to assess if this algorithm will be a useful clinical support tool.

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