ORIGINAL ARTICLE

WILEY

Phenomapping approach to interpreting coronary dimensions in febrile children

Haoxun Tang[1]* | Xin Guo[2]* | Xiaolu Nie[3] | Lin Zheng[4] | Gang Liu[2] | Wilfred Hing-Sang Wong[5] | Yiu-Fai Cheung[5]

[1]Heart Center, Beijing Children's Hospital, Capital Medical University, National Center for Children's Health, Beijing, China
[2]Department of Infectious Disease, Beijing Children's Hospital, Capital Medical University, National Center for Children's Health, Beijing, China
[3]Center for Clinical Epidemiology and Evidence-based Medicine, Beijing Children's Hospital, Capital Medical University, National Center for Children's Health, Beijing, China
[4]Department of Echocardiography, Beijing Children's Hospital, Capital Medical University, National Center for Children's Health, Beijing, China
[5]Department of Paediatrics and Adolescent Medicine, School of Clinical Medicine, The University of Hong Kong, Hong Kong, China

Correspondence
Yiu-fai Cheung, Department of Paediatrics and Adolescent Medicine, Division of Paediatric Cardiology, Hong Kong Children's Hospital, School of Clinical Medicine, LKS Faculty of Medicine, The University of Hong Kong, Hong Kong, China.
Email: xfcheung@hku.hk

*These authors contributed equally to this study.

Received: 6 July 2022
Accepted: 23 November 2022

ABSTRACT

Importance: Coronary artery dilation may occur in febrile children with and without Kawasaki disease (KD).

Objective: We explored the application of unsupervised learning algorithms in the detection of novel patterns of coronary artery phenotypes in febrile children with and without KD.

Methods: A total of 239 febrile children (59 non-KD and 180 KD patients), were recruited. Unsupervised hierarchical clustering analysis of phenotypic data including age, hemoglobin, white cell count, platelet count, C-reactive protein, erythrocyte sedimentation rate, albumin, alanine aminotransferase, aspartate aminotransferase, and coronary artery *z* scores were performed.

Results: Using a cutoff *z* score of 2.5, the specificity was 98.3% and the sensitivity was 22.1% for differentiating non-KD from KD patients. Clustering analysis identified three phenogroups that differed in a clinical, laboratory, and echocardiographic parameters. Compared with phenogroup I, phenogroup III had the highest prevalence of KD (91%), worse inflammatory markers, more deranged liver function, higher coronary artery *z* scores, and lower hematocrit and albumin levels. Abnormal blood parameters in febrile children with *z* scores of coronary artery segments <0.5 and 0.5–1.5 was associated with increased risks of having KD to 8.7 ($P = 0.003$) and 4.4 ($P = 0.002$), respectively.

Interpretation: Phenomapping of febrile children with and without KD identified useful laboratory parameters that aid the diagnosis of KD in febrile children with relatively normal-sized coronary arteries.

KEYWORDS

Coronary artery, Febrile children, Kawasaki disease, Phenomapping

DOI: 10.1002/ped4.12361

INTRODUCTION

Diagnosis of Kawasaki disease (KD) in febrile children can be challenging. Whereas the diagnosis of classical KD is made in the presence of fever for at least 5 days together with at least four of the five principal clinical features that include cervical lymphadenopathy, skin rash, conjunctival injection, erythema, and edema of extremities, and oral changes with crack lips and strawberry tongue, diagnosis of incomplete KD in the presence of fewer than four of the principle clinical features has relied on an algorithm that takes into account of compatible laboratory and echocardiographic findings.[1] In particular, the diagnosis of KD can be considered confirmed in children with prolonged unexplained fever in the presence of echocardiographic findings of coronary artery aneurysm. The finding of coronary artery z scores of ≥ 2.5 for the left anterior descending (LAD) or right coronary artery (RCA) has been reported to have high specificity for the diagnosis.[2]

Nonetheless, coronary artery dilation in febrile children has been reported in conditions other than KD. These include Epstein-Barr virus, adenovirus, *Mycoplasma pneumoniae* and *Rickettsia* infections, osteomyelitis, systemic-onset juvenile idiopathic arthritis, and Henoch-Schonlein purpura.[3–9] To date, there are only two Caucasian studies that have explored coronary artery dilation in febrile children without KD and found that a coronary artery z score of 2.5 or more was either not observed[2] or found in less than 3% of febrile children.[10] Febrile children with KD can, on the other hand, have normal-sized coronary arteries. It is apparent that heterogeneity exists in the coronary artery phenotypes of febrile children.

Recently, phenomapping based on machine learning algorithms has increasingly been applied in the arena of cardiovascular medicine.[11,12] Shah et al.[11] applied unbiased clustering analysis and identified three distinct groups of patients with heart failure and preserved ejection fraction with different clinical characteristics and outcomes. Recently, Katz et al.[12] also reported the use of phenomapping to identify two distinct groups of patients with systemic hypertension that differed in clinical characteristics and myocardial function. Unsupervised learning has the ability to identify patterns in multidimensional data for the identification of novel phenotypic clusters of patients.[11–13] We hypothesized that the application of unsupervised learning algorithms would allow the detection of novel patterns of coronary artery phenotypes in febrile children with and without KD. In the present study, we prospectively investigated the utility of unbiased phenomapping in a cohort of ethnic Chinese children hospitalized for prolonged fever.

METHODS

Ethical approval

The study was approved by the ethics committee of the Beijing Children's Hospital (ethical approval document number: 2016-56).

Subjects

Ethnic Chinese children were enrolled at the Beijing Children's Hospital, China. For non-KD febrile cohorts, the inclusion criteria for the non-KD febrile cohorts were i) aged 1 month to 18 years, ii) fever $>$ 38 degrees Celsius for more than 5 days, and iii) a defined diagnosis other than KD. Exclusion criteria were i) previously diagnosed congenital or acquired heart conditions, ii) history of underlying chronic disease, iii) systemic hypertension, and iv) weight $>$ 95th or $<$ 5th percentile. For the KD patient cohort, only patients who met the classic diagnostic criteria[1] were included. To further ascertain the validity of the z score based on reported Chinese pediatric data,[14] healthy children were recruited from the health center of Beijing Children's Hospital during routine body check-ups.

Clinical and echocardiographic data collection

The following demographic and laboratory data were collected: age, sex, ethnicity, weight, height, days of fever, hemoglobin (Hb), hematocrit (Hct), total white blood cell, platelet count, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), albumin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), microbiological investigation results including blood culture, viral screening, and mycoplasma antibody.

The echocardiographic assessment was performed using the Philips iE33 ultrasound system (Philips, Andover, MA) for the measurements of the left main coronary artery (LMCA), LAD, and RCA. The average of three measurements at each of the sites was used for the calculation of z scores based on normative data published previously by our group.[14]

Biclustering of phenotypic variables and febrile patients

The following variables were included in the phenotypic domain for subsequent phenomapping: age, Hb, WBC, platelet count, CRP, ESR, albumin, ALT, AST, and z scores of LMCA, LAD, and RCA.

Prior to analysis, missing data were imputed with the group mean value. The percentage of missing values for features ranged from 0% to 5.1%. Eleven continuous phenotypic variables were identified and the phenotype heat map was generated by R (3.5.1) with the function of hierarchical

clustering and heatmap.[15] To determine the optimal number of phenogroups, two-step cluster analysis was used to determine the optimal number of phenogroups. The log-likelihood distance of all continuous variables and the value of the Bayesian information criterion with automatic detection of a number of clusters were used to define the group number. In our implementation, we tried between one and eight clusters.

Statistical analysis

Data are expressed as mean ± standard deviation unless otherwise stated. The demographic and laboratory data of febrile children without KD and KD patients were compared using unpaired Student's *t*-test, Mann-Whitney *U* test, and Fisher's exact test where appropriate. Pearson correlation analysis was performed to assess for associations between coronary artery *z* scores and demographic and laboratory parameters. Once the phenotype groups were defined, we compared differences in demographic, clinical, echocardiographic, and laboratory parameters using the Chi-square exact test for categorical variables and analysis of variance with posthoc Bonferroni correction for normally distributed continuous variables, and Kruskal-Wallis Test with Bonferroni correction for non-normally distributed continuous variables. Sensitivity was calculated as the proportion of patients with KD having coronary artery *z* score above the cutoff of 2.5, while specificity was calculated as the proportion of febrile non-KD patients having a coronary artery *z* score of 2.5 or below. Statistical analyses were performed using SPSS version 25 (SPSS Inc, Chicago, IL, USA) and R package version (3.5.1). A *P*-value of < 0.05 was regarded as statistically significant.

RESULTS

Patient characteristics

A total of 59 patients with febrile conditions not related to KD were recruited. Their diagnosis was bacterial infections ($n = 16$), viral infection syndrome ($n = 16$), Epstein-Barr virus infection ($n = 10$), subacute necrotizing lymphadenitis ($n = 9$), fungal infection ($n = 3$), and juvenile rheumatoid arthritis ($n = 3$), and non-Epstein-Barr virus-related hemophagocytic syndrome ($n = 2$). One hundred and eighty patients with classic KD, aged 2.7 ± 1.9 years, were included in the study.

Clinical and echocardiographic parameters

Table 1 shows the demographic, clinical, and laboratory parameters. Compared with KD patients, febrile non-KD patients were significantly older and had a longer duration of fever (both $P < 0.05$). Furthermore, they had higher body weights and larger body surface areas (both $P < 0.05$). For laboratory parameters, febrile non-KD patients had significantly higher Hb, Hct, and albumin levels but lower WBC, platelet count, CRP, ESR, and ALT levels than KD patients (all $P < 0.05$). However, there was no significant difference in AST levels between the two groups of patients.

TABLE 1 Demographic, clinical, and laboratory parameters of the patients

Variables	Febrile non-KD patients ($n = 59$)	KD patients ($n = 180$)	*P*-Value
Female	27 (45.8)	57 (31.7)	0.059
Age (year)	6.4 ± 4.8	2.7 ± 1.9	<0.001
Weight (kg)	24.6 ± 17.6	14.0 ± 5.9	<0.001
Body surface area (m^2)	0.87 ± 0.44	0.56 ± 0.15	<0.001
Days of fever	23.6 ± 18.3	6.7 ± 3.0	<0.001
WBC count ($\times 10^9$/L)	9.9 ± 6.3	14.7 ± 5.6	<0.001
Hb (g/L)	117 ± 19	111 ± 14	0.025
Hct (%)	34.6 ± 5.3	31.3 ± 3.6	<0.001
Platelet ($\times 10^9$/L)	294.9 ± 152.9	349.4 ± 150.4	0.017
CRP (mg/L)	8.0 (8.0, 48.0)	38.0 (10.0, 86.5)	<0.001
ESR (mm/h)	22 (11, 38)	58 (39, 84)	<0.001
Albumin (g/L)	37.2 ± 5.4	34.1 ± 4.3	0.001
ALT (U/L)	16.5 (11.2, 34.2)	22.8 (13.7, 63.8)	0.010
AST (U/L)	28.3 (19.6, 48.2)	28.8 (22.3, 40.5)	0.902

Data are presented as *n*(%), mean ± standard deviation, or median (interquartile range).
Abbreviations: ALT, alanine aminotransaminase; AST, aspartate aminotransaminase; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; Hb, hemoglobin; Hct, hematocrit; KD, Kawasaki disease; WBC, white blood cell.

The LMCA, LAD, and RCA *z* scores of febrile non-KD patients, KD patients, and healthy children are shown in Figure 1.

For the 281 healthy children, the *z* scores of the three coronary artery segments were normally distributed within the range of −2 to +2, which attests to the validity of our previously reported normative Chinese pediatric data.[14]

For the febrile non-KD patients, the z scores of LMCA were −0.04 ± 0.83 ($P = 0.721$) and RCA was 0.00 ± 0.78 ($P = 0.993$), which were not statistically different from a mean *z* score 0. On the other hand, the *z* score of LAD was 0.30 ± 0.91, which was significantly greater than a mean *z* score of 0 ($P = 0.014$). Only 2 of these 59 (3.3%) patients had a *z* score > 2. One patient is a 42-day-infant with cytomegalovirus infection having a LAD *z* score of 2.4 and the other is a 73-day-infant with bacterial meningitis having a LAD *z* score of 2.5. Hence, none of the febrile

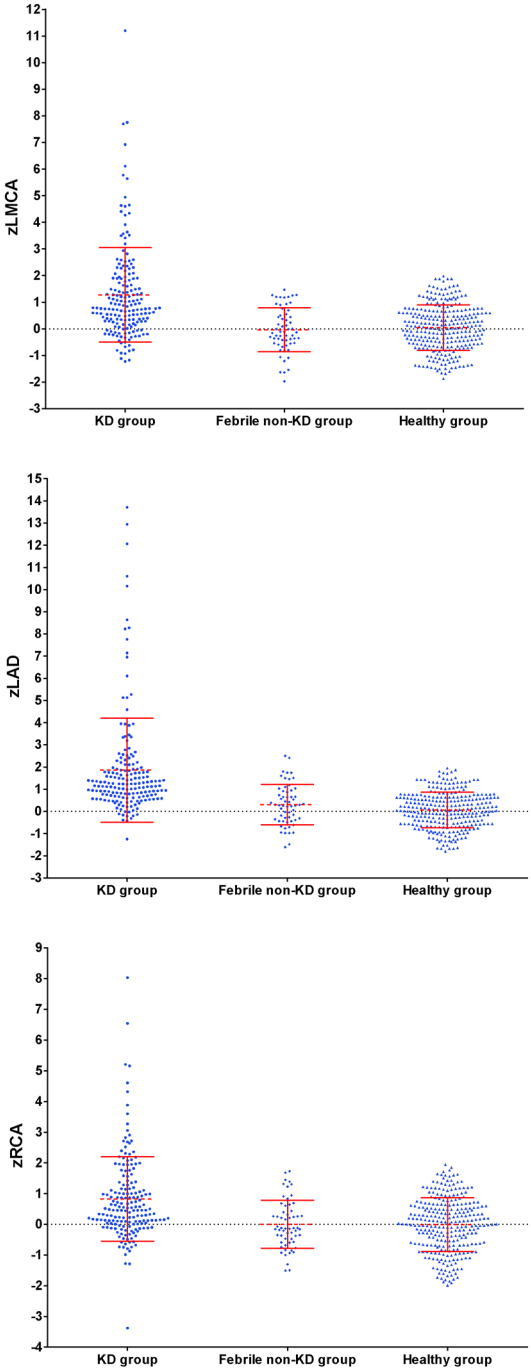

FIGURE 1 Distribution of z scores of the score of left main coronary artery (LMCA), left anterior descending branch (LAD), and right coronary artery (RCA) in febrile children with and with Kawasaki disease (KD) and healthy children. The error bars represent mean ± standard deviation.

non-KD patients had a z score of any of the three coronary artery segments > 2.5.

For KD patients, 28 (15.6%) had LMCA z score > 2.5, 32 (17.8%) had LAD z score > 2.5, and 17 (9.4%) had RCA z score > 2.5. Using a cutoff z score of 2.5 for any of the

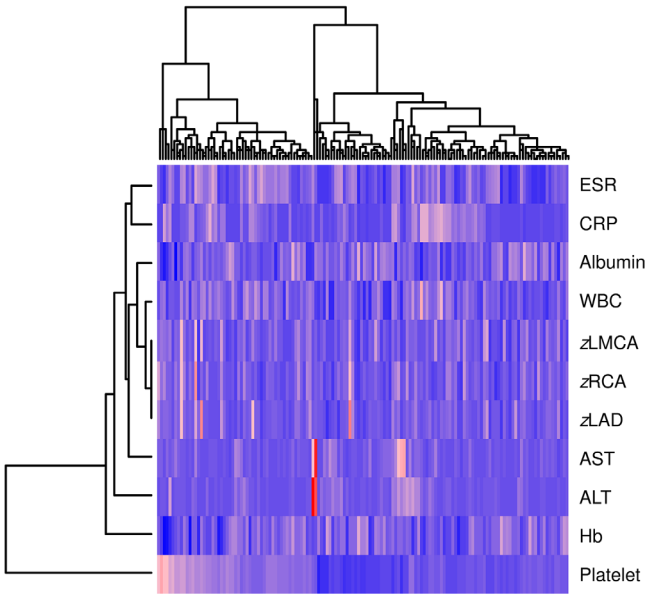

FIGURE 2 Phenotype heat map of febrile children with and with Kawasaki disease. Columns represent individual patents, and rows represent individual phenotypes. ALT, albumin, alanine aminotransferase; AST, aspartate aminotransferase; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate, Hb, hemoglobin; Hct, hematocrit; WBC, white blood cell; zLAD, z score of the left anterior descending branch; zLMCA, z score of left main coronary artery; zRCA, z score of the right coronary artery.

coronary artery segments, the specificity was 98.3% (95% CI, 95.0% to 100.0%) and the sensitivity was 22.1% (95% CI, 16.1%–38.3%) for differentiation of febrile non-KD patients from KD patients.

Phenotyping overlapping-based coronary artery z score between febrile children with and without KD was evident and further explored by unsupervised clustering analysis.

Heterogeneity and classification of the febrile patient cohort

Figure 2 shows the phenotype heat map created for febrile children, including non-KD and KD patients, by hierarchical clustering. This heat map demonstrated heterogeneity among subjects. In the heat map, clusters of individuals with shared characteristics, as shown by hotspots, can be highlighted, corresponding in part to elevated activity of various laboratory and echocardiographic parameters. These traits appeared to occur in varying patterns. For example, relatively normal coronary artery z scores can occur in association with normal liver enzyme levels in some patients and increased liver enzyme levels in others.

We then grouped patients into a minimal group of clusters that reflected the phenotypic variability using model-based clustering. The analysis arrived at three as the optimal number of clusters (Figure 3).

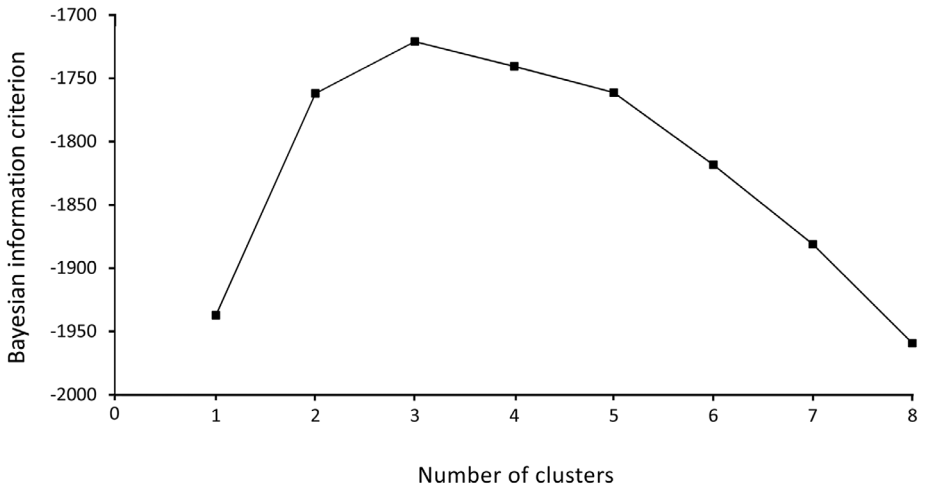

FIGURE 3 Bayesian information criterion analysis for defining the optimal number of phenogroups.

TABLE 2 Demographic, clinical laboratory, and echocardiographic parameters stratified by the three cluster groups

Variables	Group I ($n = 51$)	Group II ($n = 165$)	Group III ($n = 23$)	*P*-Value
Age (year)	6.1 ± 4.3	2.8 ± 2.5[†]	3.8 ± 3.2[‡]	<0.001
Female	18 (35.3)	63 (38.2)	3 (13.0)	0.061
Patient status				<0.001
Febrile non-KD	35 (68.6)	22 (13.3)	2 (8.7)	
KD	16 (31.4)	143 (86.7)	21 (91.3)	
Hb (g/L)	128 ± 13	108 ± 14[†]	111 ± 11[‡]	<0.001
Hct (%)	36.6 ± 3.7	30.9 ± 3.8[†]	31.3 ± 2.7[‡]	<0.001
WBC ($\times 10^9$/L)	10.4 ± 5.1	14.4 ± 6.0[†]	14.0 ± 7.0	<0.001
Platelet ($\times 10^9$/L)	261.9 ± 102.8	356.8 ± 156.8[†]	350.2 ± 168.0	<0.001
CRP (mg/L)	8.0 (8.0, 12.0)	50 (13.0, 97.0)[†,§]	25.0 (9.0, 43.0)	<0.001
ESR (mm/h)	16 (11, 36)	57 (40, 83)[†]	69 (38, 93)[‡]	<0.001
Albumin (g/L)	39.8 ± 3.1	33.5 ± 4.3[†]	33.8 ± 4.2[‡]	<0.001
ALT (U/L)	17.0 (12.0, 35.2)	21.0 (13.1, 46.3)[§]	74.6 (22.9, 217.0)[‡]	<0.001
AST (U/L)	28.4 (20.4, 44.0)	27.9 (21.9, 37.8)[§]	77.3 (29.5, 179.0)[‡]	<0.001
LMCA *z* score	−0.22 ± 0.77	0.94 ± 1.09[†,§]	3.58 ± 3.20[‡]	<0.001
LAD *z* score	0.13 ± 0.77	1.30 ± 1.03[†,§]	5.68 ± 4.46[‡]	<0.001
RCA *z* score	−0.20 ± 0.75	0.62 ± 0.94[†,§]	2.43 ± 2.36[‡]	<0.001

Data are presented as *n* (%), mean ± standard deviation, or median (interquartile range).
Abbreviations: ALT, alanine aminotransaminase; AST, aspartate aminotransaminase; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; Hb, hemoglobin; Hct, hematocrit; KD, Kawasaki disease; LAD, left anterior descending artery; LMCA, Left main coronary artery; RCA, right coronary artery; WBC, white blood cell.
[†]Group II *vs*. I Bonferroni adjusted $P < 0.05$.
[‡]Group III *vs*. I Bonferroni adjusted $P < 0.05$.
[§]Group II *vs*. III Bonferroni adjusted $P < 0.05$.

Comparison of clinical, laboratory, and echocardiographic parameters among phenogroups

The three phenogroups differed significantly in terms of the clinical, laboratory, and echocardiographic parameters (Table 2).

Phenogroup I had the lowest prevalence of KD (31.4%), significantly lower ESR and *z* scores of all three coronary artery segments, and significantly higher Hct and albumin levels compared with phenogroups II and III. The CRP and platelet counts were lower in phenogroup I compared

with phenogroup II. The liver enzymes were also lower in phenogroup I compared with phenogroup III.

Phenogroup III, by contrast, had the highest prevalence of KD (91.3%), significantly higher ESR, worse liver dysfunction, greater z scores of all three coronary artery segments, and significantly lower Hct and albumin levels compared with phenogroup I.

Phenogroup II, on the other hand, was characterized by a relatively high prevalence of KD (86.7%), but with patients having less impairment of liver function and smaller z scores of the three coronary artery segments compared with phenogroup III (all $P < 0.05$).

Across the three phenogroups, there is a trend of progressive increase in the prevalence of KD and z scores of all three coronary artery segments.

Interactions between coronary artery z score phenotype and blood investigation results

Across the phenogroups, the range of mean z scores of the coronary artery segments increases from −0.22 to 0.13 for phenogroup I, 0.62 to 1.30 for phenogroup II, and to 2.43–5.68 for phenogroup III. We further explored potential interactions between coronary artery z scores and abnormal blood results in determining the odds of febrile children having KD (Figure 4).

For z score of coronary artery segments < 0.5, the presence of abnormal blood test results as defined by increased ESR, CRP, ALT, AST, and /or platelet count in febrile children is associated with increased risks of having KD to 8.7 ($P = 0.003$) for LCA, 2.5 ($P = 0.097$) for LAD, and 5.1 ($P < 0.001$) for RCA measurements. For z score of coronary artery segments between 0.5 and 1.5, the presence of abnormal blood test results in febrile children is associated with an increased risk of having KD to 4.4 ($P = 0.002$) for LAD measurement. On the other hand, with the z score of coronary artery segments > 1.5, the majority of our patients were having KD regardless of the blood test results.

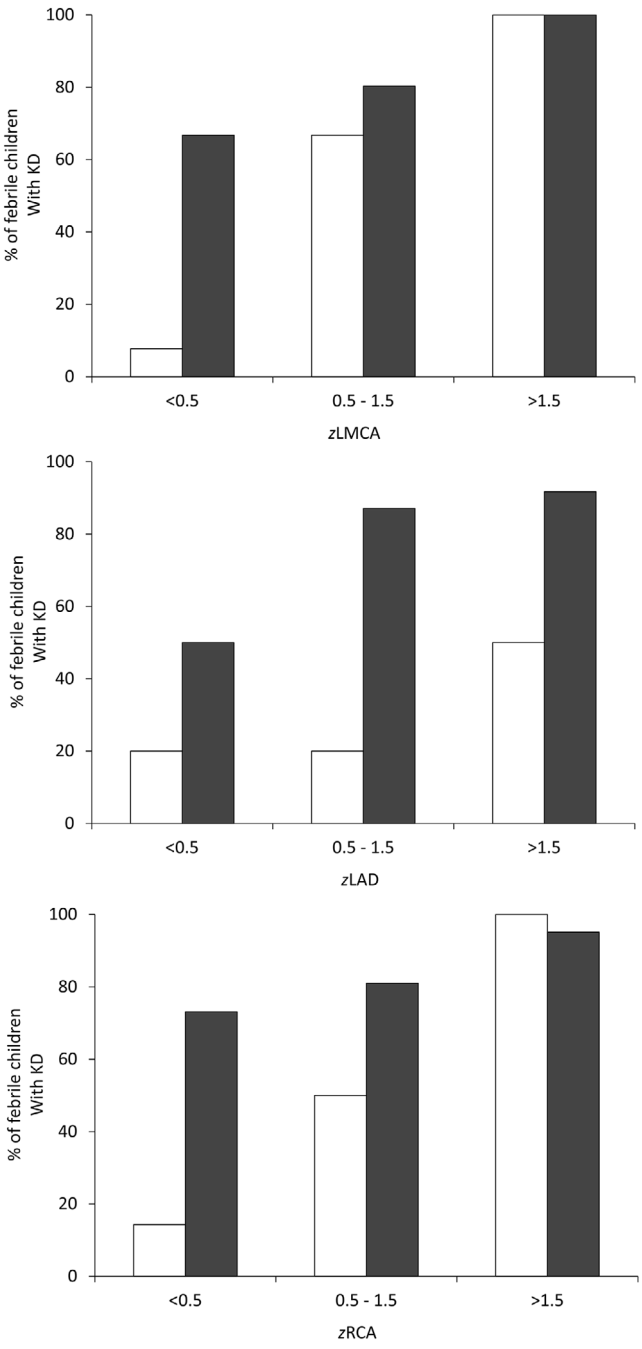

FIGURE 4 Bar charts showing the prevalence of febrile patients with Kawasaki disease stratified by normal (white bars) and abnormal (black bars) blood results and z score of the three coronary artery segments. KD, Kawasaki disease; zLAD, z score of the left anterior descending branch; zLMCA, z score of left main coronary artery; zRCA, z score of the right coronary artery.

DISCUSSION

In this study, we used an unsupervised learning algorithm to explore novel patterns of coronary artery phenotypes in febrile children with and without KD. To our knowledge, this is the first study to adopt this approach to unveil different groups of febrile children with varying degrees of coronary artery dilation. Indeed, we found that among febrile children with and without KD, three phenotypes could be identified and distinguished by the varying size of the coronary artery segments and abnormal blood results. This is of clinical relevance given the reported coronary artery dilation in febrile children without KD and the difficulties in diagnosing children having normal-sized coronary arteries with suspected incomplete KD.

Increased myocardial oxygen demand in the setting of fever has been hypothesized to explain the mild dilation of the

coronary arteries.[2] Two Caucasian studies have explored previously coronary artery dilation in febrile children without KD.[2,10] Bratincsak et al.[2] found that of the 45 febrile children having various types of infections, none had coronary artery z scores $\geq$ 2.5. In another study by Muniz et al.,[10] of the 43 febrile children without KD studied, two (5%) had coronary artery z score $>$ 2, of whom one (3%) had a coronary artery z score $>$2.5. In the latter study, using a maximum coronary artery z score cutoff of 2.5, there is a specificity of 98% and a sensitivity of 20% in distinguishing non-KD febrile children from KD patients. Our study in ethnic Chinese children, reveals similar findings with none of our febrile non-KD patients having a z score of any of the three coronary artery segments $>$ 2.5. Using a cutoff z score of 2.5 for any of the coronary artery segments, we similarly found a specificity of 98% and a sensitivity of 22% to differentiate febrile non-KD patients from KD patients.

In this study, we have further taken advantage of deep phenotyping of the entire febrile pediatric cohort to explore potential unique patterns of associations among various phenotypic variables, with a particular focus on coronary artery size. Children in these three phenogroups, all having the shared feature of fever, differed significantly in terms of other characteristics and blood results (Table 2). It is obvious that these phenotypes represent three clinical subtypes of febrile children: i) febrile children who are less likely to have KD, who have normal-sized coronary arteries and who mostly have normal liver enzymes and milder elevation of CRP and ESR, ii) febrile children who are more likely to have KD with increased in inflammatory markers and greater coronary artery z scores, albeit with an average still within the normal range, and iii) febrile children who are mostly KD patients with the highest levels of inflammatory markers and liver enzymes and significantly greater coronary artery z score with mean $>$ 2.5.

While the high specificity of coronary artery z scores of $\geq$2.5 in diagnosing KD is acknowledged,[1,2] differentiation between febrile children with KD and those without significant coronary artery dilation and insufficient KD criteria may pose difficulties. Based on the significant blood parameters found to be different among phenogroups, we further examined the additive role of these as markers in increasing the odds of diagnosing KD. Indeed, as shown in Figure 3, in children having relatively normal-sized coronary arteries, with mean z scores $<$ 0.5 or between 0.5 to 1.5, the addition of the consideration of abnormal blood results defined by increased ESR, CRP, ALT, AST, and /or platelet count, significantly increases the odds of diagnosing of KD among febrile children. Indeed, these abnormal laboratory results have been incorporated into the AHA algorithm for diagnosis of incomplete KD.[1] Using the data-mining approach, Tremoulet et al.[16] have found the usefulness of ESR, CRP, ALT, and platelet, together with other four panel markers (absolute neutrophil count, gamma-glutamyl transferase, alpha-1-antitrypsin, and fibrinogen), in the recognition of KD.

While the present study did not focus on the phenotyping of KD patients, there is a suggestion from Table 2 that their clinical phenotypes differ, in particular in terms of the occurrence of liver dysfunction. The mechanism of liver dysfunction in KD is unclear. Proposed causes include generalized inflammation, vasculitis, and congestion related to heart failure.[17–19] Importantly, the elevation of liver enzymes have been associated with resistance to intravenous immunoglobulin treatment.[19–21] Further studies on KD can harness the power of deep phenotyping for the identification of new patient subgroups that might differ in clinical characteristics, risks and outcomes, risk stratification, and response to trials of new therapeutic regimens.

The strength of the present study is the inclusion of a homogeneous population of ethnic Chinese classic KD patients and febrile children with defined diagnoses, a large cohort of healthy children to confirm the distribution of the reported dimensions of the coronary arteries, and the application of novel unsupervised learning algorithms in phenogrouping the febrile cohort as a whole. There are, however, two important limitations. First, we have not validated the distinctiveness of our phenogroups with the prospective recruitment of new patients. Further studies are undoubtedly required to provide additional data in this regard. Second, this is a cross-sectional study that fails to provide longitudinal data in terms of treatment and long-term outcomes of KD patients. Further focused deep phenotyping of KD patients may shed more light on the clinical usefulness of this approach.

In conclusion, the present study shows that in ethnic Chinese children, none of the febrile non-KD patients had a z score of any of the three coronary artery segments $>$ 2.5. The application of a new unbiased phenomapping approach to our febrile non-KD and KD patient cohorts has further enabled the identification of useful laboratory markers for diagnosing KD in febrile children with relatively normal-sized coronary arteries.

CONFLICT OF INTEREST

Gang Liu is a member of the *Pediatric Investigation* editorial board.

REFERENCES

1. McCrindle BW, Rowley AH, Newburger JW, Burns JC, Bolger AF, Gewitz M, et al. Diagnosis, treatment, and long-term management of Kawasaki disease: a scientific statement for health professionals from the American Heart

Association. *Circulation.* 2017;135:e927-e999. DOI: 10.1161/CIR.0000000000000484
2. Bratincsak A, Reddy VD, Purohit PJ, Tremoulet AH, Molkara DP, Frazer JR, et al. Coronary artery dilation in acute Kawasaki disease and acute illnesses associated with fever. *Pediatr Infect Dis J.* 2012;31:924-926. DOI: 10.1097/INF.0b013e31826252b3
3. Barone SR, Pontrelli LR, Krilov LR. The differentiation of classic Kawasaki disease, atypical Kawasaki disease, and acute adenoviral infection: use of clinical features and a rapid direct fluorescent antigen test. *Arch Pediatr Adolesc Med.* 2000;154:453-456. DOI: 10.1001/archpedi.154.5.453
4. Burns JC, Mason WH, Glode MP, Shulman ST, Melish ME, Meissner C, et al. Clinical and epidemiologic characteristics of patients referred for evaluation of possible Kawasaki disease. United States multicenter Kawasaki disease study group. *J Pediatr.* 1991;118:680-686. DOI: 10.1016/s0022-3476(05)80026-5
5. Komatsu H, Tateno A. Failure to distinguish systemic-onset juvenile idiopathic arthritis from incomplete Kawasaki disease in an infant. *J Paediatr Child Health.* 2007;43:707-709. DOI: 10.1111/j.1440-1754.2007.01189.x
6. Binstadt BA, Levine JC, Nigrovic PA, Gauvreau K, Dedeoglu F, Fuhlbrigge RC, et al. Coronary artery dilation among patients presenting with systemic-onset juvenile idiopathic arthritis. *Pediatrics.* 2005;116:e89-e93. DOI: 10.1542/peds.2004-2190
7. Kikuta H, Taguchi Y, Tomizawa K, Kojima K, Kawamura N, Ishizaka A, et al. Epstein-Barr virus genome-positive T lymphocytes in a boy with chronic active EBV infection associated with Kawasaki-like disease. *Nature.* 1988;333:455-457. DOI: 10.1038/333455a0
8. van Doorn HR, Lo-A-Njoe SM, Ottenkamp J, Pajkrt D. Widened coronary arteries in a feverish child. *Pediatr Cardiol.* 2006;27:515-518. DOI: 10.1007/s00246-006-1324-1
9. Bloom JL, Darst JR, Prok L, Soep JB. A case of Henoch-Schonlein purpura with dilated coronary arteries. *Pediatr Rheumatol Online J.* 2018;16:54. DOI: 10.1186/s12969-018-0270-9
10. Muniz JC, Dummer K, Gauvreau K, Colan SD, Fulton DR, Newburger JW. Coronary artery dimensions in febrile children without Kawasaki disease. *Circ Cardiovasc Imaging.* 2013;6:239-244. DOI: 10.1161/CIRCIMAGING.112.000159
11. Shah SJ, Katz DH, Selvaraj S, Burke MA, Yancy CW, Gheorghiade M, et al. Phenomapping for novel classification of heart failure with preserved ejection fraction. *Circulation.* 2015;131:269-279. DOI: 10.1161/CIRCULATIONAHA.114.010637
12. Katz DH, Deo RC, Aguilar FG, Selvaraj S, Martinez EE, Beussink-Nelson L, et al. Phenomapping for the identification of hypertensive patients with the myocardial substrate for heart failure with preserved ejection fraction. *J Cardiovasc Transl Res.* 2017;10:275-284. DOI: 10.1007/s12265-017-9739-z
13. Hinton GE, Salakhutdinov RR. Reducing the dimensionality of data with neural networks. *Science.* 2006;313:504-507. DOI: 10.1126/science.1127647
14. Zheng L, Du ZD, Jin LZ, Wang FY, Ma GQ, Wei HY, et al. Evaluation of coronary artery diameter in normal children by echocardiography and its clinical significance. *Chin J Pediatr.* 2013;51:371-376. DOI: 10.3760/cma.j.issn.0578-1310.2013.05.011 (in Chinese)
15. Gehlenborg N, Wong B. Points of view: heat maps. *Nat Methods.* 2012;9:213. DOI: 10.1038/nmeth.1902
16. Tremoulet AH, Dutkowski J, Sato Y, Kanegaye JT, Ling XB, Burns JC. Novel data-mining approach identifies biomarkers for diagnosis of Kawasaki disease. *Pediatr Res.* 2015;78:547-553. DOI: 10.1038/pr.2015.137
17. Ting EC, Capparelli EV, Billman GF, Lavine JE, Matsubara T, Burns JC. Elevated gamma-glutamyltransferase concentrations in patients with acute Kawasaki disease. *Pediatr Infect Dis J.* 1998;17:431-432. DOI: 10.1097/00006454-199805000-00020
18. Ohshio G, Furukawa F, Fujiwara H, Hamashima Y. Hepatomegaly and splenomegaly in Kawasaki disease. *Pediatr Pathol.* 1985;4:257-264. DOI: 10.3109/15513818509026899
19. Sano T, Kurotobi S, Matsuzaki K, Yamamoto T, Maki I, Miki K, et al. Prediction of non-responsiveness to standard high-dose gamma-globulin therapy in patients with acute Kawasaki disease before starting initial treatment. *Eur J Pediatr.* 2007;166:131-137. DOI: 10.1007/s00431-006-0223-z
20. Kobayashi T, Inoue Y, Takeuchi K, Okada Y, Tamura K, Tomomasa T, et al. Prediction of intravenous immunoglobulin unresponsiveness in patients with Kawasaki disease. *Circulation.* 2006;113:2606-2612. DOI: 10.1161/CIRCULATIONAHA.105.592865
21. Egami K, Muta H, Ishii M, Suda K, Sugahara Y, Iemura M, et al. Prediction of resistance to intravenous immunoglobulin treatment in patients with Kawasaki disease. *J Pediatr.* 2006;149:237-240. DOI: 10.1016/j.jpeds.2006.03.050

How to cite this article: Tang H, Guo X, Nie X, Zheng L, Liu G, Wong WHS, et al. Phenomapping approach to interpreting coronary dimensions in febrile children. *Pediatr Investig*. 2022;6:233–240. https://doi.org/10.1002/ped4.12361