Development of a score for early identification of children with Kawasaki disease requiring second-line treatment in multi-ethnic populations in Europe: A multicentre retrospective cohort study

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Summary

Background Early identification of high-risk patients is essential to stratify treatment algorithms of Kawasaki disease (KD) and to appropriately select patients at risk for complicated disease who would benefit from intensified first-line treatment. Several scores have been developed and validated in Asian populations but have shown low sensitivity in predicting intravenous immunoglobulin (IVIG) resistance in non-Asian populations. We sought methods to predict the need for secondary treatment after initial IVIG in non-Asian populations.

Methods We conducted a retrospective, multicenter study including consecutive patients with KD admitted to two tertiary pediatric hospitals in France and Italy from 2005 to 2019. We evaluated the performance of the Kawanet-score and compared it with the performances of initial echocardiography findings, and of a newly proposed score combining the Kawanet-score and initial echocardiography findings. For each score, we assessed the AUC, sensitivity and specificity for predicting the need for second-line treatment.

Findings We included 363 children with KD, 186 from France and 177 from Italy, of whom 57 (16%) required second-line therapy after the first IVIG dose. The Kawanet score, coronary artery dilation or aneurysm with maximal Z-score ≥2.0 at baseline, and abnormal initial echocardiography had a sensitivity of 43%, 55% and 65% and a specificity of 73%, 78%, 73%, respectively, for predicting the need for second-line treatment. The Kawanet-score was significantly improved by combining it with initial echocardiography findings. The best predictive performance (Sensitivity 76%, Specificity 54%) was obtained by combining the Kawanet-score with abnormal initial echocardiography, defined by the presence of either coronary artery maximal Z-score ≥2.0, pericarditis, myocarditis and/or ventricular dysfunction. This score predicted the need for second-line treatment in European, African/Afro-Caribbean

The Lancet Regional Health - Europe 2022;22: 100481
Published online xxx
https://doi.org/10.1016/j.lanepe.2022.100481

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and Asian ethnicity with a sensitivity of 80%, 65% and 100%, respectively, and a specificity of 56%, 51% and 61%, respectively.

Interpretation Our study proposes a score that we named the Kawanet-echo score, which allows early identification of children with KD who require a second-line treatment in multi-ethnic populations in Europe.

Funding None.

Keywords: Kawasaki disease; Vasculitis; Pediatric rheumatology; Coronary artery; Echocardiography; Severity score; Clinical scoring

Research in context

Evidence before this study

We searched in Pubmed articles using the terms "Kawasaki Disease" AND "scoring system" or "prognosis" or "risk factors". We identified more than 20 articles assessing the performance of several scores to identify patients at high risk of resistance to intravenous immunoglobulins (IVIG), first line of treatment in Kawasaki Disease. These scores have mainly been developed and validated in Asian populations, but have shown low sensitivity to predict IVIG resistance in other populations, including multi-ethnic populations in European countries. Thus, there is a need for new methods to predict the need for secondary treatment after initial IVIG in non-Asian populations. Recently, a score called the Kawanet score was developed in an European population.

Added value of this study

Based on data from two independent cohorts of consecutive patients hospitalized at tertiary centers in France and Italy, we describe a scoring system that can predict patients requiring second-line treatment after the first dose of IVIG with a sensitivity of 76% and specificity of 54%. This scoring system combines the clinical and laboratory parameters of the previously published Kawanet-score and findings from the initial echocardiography.

Implications of all the available evidence

If validated in other populations, this scoring system could be a useful tool to identify at-risk patients in multi-ethnic populations in European countries who might benefit from intensive first-line treatment strategies.

Introduction

Kawasaki disease (KD) is the leading cause of acquired heart disease in childhood in developed countries.[1] Coronary artery aneurysms (CAA) determine the prognosis of KD. The cardiac prognosis has been dramatically improved by treatment with acetylsalicylic acid (ASA) and intravenous infusion of 2g/kg of human immunoglobulin (IVIG).[1] However, 11-20% of patients are resistant to a first line of IVIG and show a higher rate of risk of coronary artery abnormalities (CAAs).[1,2] These patients require secondary treatments.[1,3] Recent studies have shown the use of intensified first-line treatments, such as adding glucocorticoids[4,5] or ciclosporine[6] to IVIG and ASA, may be beneficial, particularly for patients at high risk for developing coronary aneurysms.

Early identification of high-risk patients is essential to stratify treatment algorithms of KD and appropriately select patients at risk for severe disease who would benefit from the intensification of first-line treatments. Several scores have been developed to identify patients at high risk of resistance to IVIG or coronary disease.[7–9] Most of them have been developed and validated in Japan, but have shown low sensitivity to predict IVIG resistance in other non-Asian populations, including multi-ethnic populations in Europe.[10–16] A current challenge is therefore to establish new methods for early identification for severe KD and predict the need for secondary treatment after initial IVIG in non-Asian populations.

In non-Asian populations, a scoring system called Kawanet-score that takes into account laboratory and clinical findings has recently been proposed to predict patients requiring second-line treatment.[17] This score includes ALT level > 30 IU/L, hepatomegaly, lymphocyte count < 2400/mm^3 and time to treatment < 5 days, with 1 point per variable and cut-off ≥ 2 points.[17] Echocardiography, the imaging modality of choice for the detection of coronary artery abnormalities and assessment of myocardial function,[18] is not included in the Kawanet score. However, it has also been proposed to be useful in the risk stratification of patients with KD.[15,19–22] Recent studies have proposed that abnormal findings on initial echocardiography may be associated with resistance to IVIG[15,19] in European populations

and a baseline coronary artery maximal Z-score ≥ 2.0 in children is predictive of subsequent CAA development in Asian[22] and North American[20] populations.

The objective of this study was to evaluate the performance of the Kawanet-score in two KD independent cohorts from two European countries and to assess whether its performance can be improved by incorporating initial echocardiographic findings.

Methods

Study design

We conducted a retrospective, multicenter study including two cohorts of consecutive KD patients admitted from January 2005 to December 2019 (before the outbreak of the SARS-CoV-2 pandemics in Europe) to either of the following two pediatric tertiary hospitals, Robert-Debré University Hospital, in Paris, France and Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico in Milan, Italy. We included all patients diagnosed with KD according to AHA diagnostic criteria[1] before 18 years of age. Exclusion criteria were: i) another diagnosis confirmed during the follow-up, ii) first echocardiography performed >10 days after disease onset, iii) first echocardiography performed >48h hours after first treatment with immunoglobulins, iv) Patients previously included in the Kawanet cohort. For each patient we recorded demographic, clinical and echocardiographic data. All collected data were anonymous. This study followed national ethic guidelines and has been approved by data protection authorities and ethic committees (CNIL/No.2014908 & No1980120, CE Milano Area 2 No 2018/0802).

Definitions. Initial dilatation or aneurysm was defined according to the AHA criteria: dilation in presence of a maximal Z score of 2 to <2.5; aneurysm in presence of a maximal Z-score ≥ 2.5.[1] Z-scores were measured using Dallaire and Dahdah method from Montreal,[23] which is a rigorous scoring system, that has been developed based on larger populations and with careful statistical modeling. It uses a square root function of the body surface area and has the advantage of also providing normative data for the left circumflex branch.[1] Abnormal initial echocardiography was defined as presence of one or more of the following findings: initial coronary dilatation, aneurysms, pericarditis, myocarditis, or ventricular dysfunction. As recommended,[1] coronary brightness and/or coronary irregularity were not included in the definition of abnormal echocardiography in the main analysis, but have been explored in a secondary analysis to see if it improved the score performances. Pericarditis was defined by the presence of pericardial effusion on echocardiography. Myocarditis was defined as acute left ventricular systolic dysfunction at echocardiography, associated with elevation of biomarkers of myocardial injury (Troponine I or T, CK-MB). Both definitions were based on the AHA and ESC criteria (AHA 2017 and ESC guidelines 2015 pericardial diseases). Complete KD was defined according to the AHA criteria, as KD Patients who meet the case definition based on the presence of prolonged unexplained fever and at least 4 of the 5 principal clinical findings.[1] Incomplete KD was defined according to the AHA criteria[1] as KD with prolonged unexplained fever, fewer than 4 of the principal clinical findings, and compatible laboratory or echocardiographic findings.[1] The first day of illness onset was defined as the first day that the patient presented with signs related to KD.

Outcome and outcome measures

The primary outcome was the proportion of therapeutic failure among children with KD, defined as the need for a second-line treatment before hospital discharge (a second infusion of IVIG or other treatments after the first IVIG dose, including corticosteroids, or anti-tumor necrosis factor agent, or anakinra, or cyclosporine). This outcome, rather than persisting fever on day 2, was chosen to reflect current practices, and because it was the main outcome used to build the Kawanet score.[17] As a sensitivity analysis, we considered therapeutic failure as persisting or relapsing fever on day 2 following the start of initial IVIG therapy. We also conducted the following additional analyses:

- An analysis restricted to children in whom the first echocardiography was performed before the first-line treatment,
- An analysis considering a maximal Z-score ≥ 2.5 to define initial coronary artery dilatation or aneurysm,
- An analysis including a delay between disease onset and first-line treatment > 10 days or not to build the score.

Secondary outcomes included the proportion of therapeutic failure in different subgroups, based on center (French and Italian), ethnicity, age at KD onset (<4 or ≥4 years), sex and complete versus incomplete KD.

For all outcomes, the Kawanet score performances, i.e. sensitivity, specificity, and area under the curve (AUC) of the receiver operator characteristic (ROC) curve were assessed, and compared to the performances of initial echocardiography findings alone, and a combination of the Kawanet score with initial echocardiography findings.

The Kawanet score included ALT level > 30 IU/L, hepatomegaly, lymphocyte count < 2400/mm^3 and time to treatment < 5 days, with 1 point per variable and cut-off ≥ 2 points.[17] Ethnicity was defined by origin of

parents and classified into different subgroups: European, African/Afro-Caribbean, Asian (Far East), or mixed ethnicity (children with parents from different areas) and other ethnicities.

Statistical analysis

We described patient characteristics as numbers and percentages for categorical variables, and median with interquartile range for quantitative ones. First, we assessed the association between Kawanet score (with a threshold of ≥2), initial echocardiography findings, and their combination with treatment failure using a univariate logistic regression model, and a multivariate logistic regression model adjusted for potential confounders (age, sex, ethnicity, complete Kawasaki disease, year of diagnosis, and delay between disease onset and first-line treatment). Then, we assessed the performances of the Kawanet score (AUC of the ROC curve, sensitivity and specificity with a cut-off ≥ 2), and compared it to the performances of initial echocardiography findings, and the combination of the Kawanet score and initial echocardiography findings. The cut-off of the modified Kawanet score was selected based on sensitivity and specificity for the different thresholds. A two-sided p-value <0.05 was considered statistically significant. All statistical analyses were performed using R v3.6.1 (http://www.R-project.org).

Role of the funding source

As there was no specific funding for this study, no funding source had any role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

We included 363 children with KD, 221 (61%) males and 141 (39%) females, with a median age at presentation of 2 years (IQR 1.2 – 3.5) (see Flow chart in supplementary Figure 1). Baseline characteristics of patients from France (n=186), Italy (n=177), and the entire study population are presented in Table 1. Overall, 227 (63%) patients had complete KD, 81 (22%) had persistent fever 48h after completion of the initial infusion of immunoglobulins and 57 (16%) required second-line treatment. Both the need for second-line treatment and persisting or relapsing fever on day 2 were significantly associated with occurrence of CAA at week 6 (OR 3.6, 95% CI [1.5; 8.3], p=0.003 and OR 2.6, 95% CI [1.1; 5.8], p=0.020, respectively, supplementary Table 1).

First, we assessed the association between need of second-line treatment and i) Kawanet score ≥ 2, ii) Initial maximal Z-score ≥ 2 iii) abnormal initial echocardiography (presence of either initial maximal Z-score ≥ 2, pericarditis, myocarditis, or ventricular dysfunction). All

	Italian cohort, N=177	French cohort, N=186	Total, N=363
Age at disease onset, years	2.1 [1.1; 3.4]	2.0 [1.2; 3.7]	2.0 [1.2; 3.5]
Female	64 (36%)	77 (41%)	141 (39%)
Ethnicity, NA=19			
European	142 (80%)	41 (25%)	183 (53%)
African/Afro-Caribbean	10 (6%)	100 (60%)	110 (32%)
Asian	11 (6%)	26 (16%)	37 (11%)
Complete KD	105 (59%)	122 (66%)	227 (63%)
Modifications of extremities	106 (60%)	103 (55%)	209 (58%)
Diffuse exanthema	139 (79%)	158 (85%)	297 (82%)
Conjunctival injection	147 (83%)	148 (80%)	295 (81%)
Cervical adenitis >1.5 cm	74 (42%)	99 (53%)	173 (48%)
Modifications of oral mucosa	154 (87%)	162 (87%)	316 (87%)
Delay between disease onset and first-line treatment (days)	7 [5; 9]	6 [5; 8]	7 [5; 8]
Initial cardiac complications	58 (33%)	53 (28%)	111 (31%)
Coronary artery maximal Z- score ≥2.0	54 (31%)	35 (19%)	89 (25%)
Coronary artery maximal Z-score ≥2.5	44 (25%)	31 (17%)	75 (21%)
Myocarditis	1 (1%)	3 (2%)	4 (1%)
Pericarditis	2 (1%)	27 (15%)	29 (8%
Need for second-line therapy	26 (15%)	31 (17%)	57 (16%)
Persisting fever 48h after the start of the initial IVIG therapy	27 (15%)	54 (29%)	81 (22%)

***Table 1*: Baseline characteristics of the population, N=363.**
Categorical variables are expressed as numbers (percentage), and quantitative variables are expressed as median [interquartile range].

variables were significantly associated with need of second-line treatment and fever 48h after first line immunoglobulins, both in univariate and multivariate analysis (Table 2).

Second, we studied the performance of the Kawanet score, baseline coronary artery maximal Z-score ≥ 2.0 and initial abnormal echocardiography, in predicting IVIG resistance and persistence or relapse of fever 48h after IVIG treatment (Table 3). The Kawanet score, baseline maximal Z-score ≥ 2.0 and abnormal initial echocardiography had respectively a sensitivity (Se) of 43%, 55% and 65% and a specificity of 73%, 78%, 73% for predicting the need for second-line treatment. Because of the poor sensitivity of the Kawanet score, we designed new scores based on the combination of the Kawanet score with baseline coronary artery maximal Z-score ≥2.0 or abnormal initial echocardiography, called modified Kawanet scores. Modified-Kawanet score 1 is based on a combination of Kawanet score (1 point per variable) and presence of coronary dilatation and/or aneurysm (2 points if any is present). Modified-Kawanet score 2 (box 1), is based on a combination of Kawanet score (1 point per variable) and presence of abnormal initial echocardiography findings (coronary dilatation, aneurysm, pericarditis, myocarditis, ventricular dysfunction; 2 points if at least one is present), Both modified scores 1 and 2 have a cut-off of ≥ 2. The Kawanet score was substantially improved by the addition of maximal Z-score ≥ 2.0 (score 1; Se 69%, Sp 56%, AUC 0.69, Table 3). Combining the Kawanet score with abnormal initial echocardiographic findings (which also include presence of peri- or myocarditis or ventricular dysfunction) further increased the performance (score 2; Se 76%, Sp 54%, AUC 0.71; Table 3). A further addition of the presence of coronary brightness or irregularity to the abnormal initial echocardiographic findings did not improve the modified Kawanet score (supplementary Tables 2,3). Similar results were obtained when analyzing the performances of these scores in predicting persistence of fever 48h after first-line treatment (Table 3). ROC curves of the Kawanet and modified Kawanet scores 1 and 2, as well as the sensitivity and specificity for different cut-off are shown in supplementary Figure 2 and supplementary Table 4. The modified Kawanet score 2 had the best performance in predicting the need for second-line therapy as well as persistent fever at H48 (supplementary Table 5). Similar results were obtained when restricting the analysis to children in whom the first echocardiography was performed before the first-line treatment, or when considering a maximal Z-score ≥ 2.5 to define initial coronary artery dilatation or aneurysm (supplementary Tables 6 and 7). Including the delay between disease onset and the first-line treatment did not improve the performances of the score (supplementary Table 8).

Third, we investigated the performance of the Kawanet score, initial abnormal echocardiography, and

Variable	Need for second-line treatment						Persistent fever at H48					
	Yes, N=57/363 (16%)	No, N=306/363 (84%)	Univariate analysis		Multivariate analysis[c]		Yes, N=81/363 (22%)	No, N=282/363 (78%)	Univariate analysis		Multivariate analysis[c]	
			OR [95% CI]	*P* value	OR [95% CI]	*P* value			OR [95% CI]	*P* value	OR [95% CI]	*P* value
Kawanet score[b] (NA=23)	23/53 (43%)	78/287 (27%)	2.1 [1.2; 3.7]	0.019	2.2 [1.1; 4.3]	0.021	32/77 (42%)	69/263 (26%)	2.0 [1.2; 3.4]	0.010	2.3 [1.3; 4.2]	0.007
Baseline coronary artery maximal Z-score ≥ 2.0	29/57 (51%)	60/306 (20%)	4.2 [2.4; 7.7]	<0.0001	5.6 [2.9; 11.1]	<0.0001	30/81 (37%)	59/282 21%)	2.2 [1.3; 3.8]	0.003	3.0 [1.7; 5.5]	0.0003
Abnormal initial echocardiography (NA=4)[a]	34/57 (60%)	77/302 (25%)	4.4 [2.5; 8.0]	<0.0001	5.7 [3.0; 11.2]	0.0001	38/81 (47%	73/278 (26%)	2.5 [1.5; 4.2]	0.0004	3.1 [1.8; 5.5]	0.0001

Table 2: **Association of Kawanet-score, initial echocardiography findings, and their combination with treatment failure, N=363.**

[a] Defined as initial maximal Z-score ≥ 2, pericarditis, myocarditis, or ventricular dysfunction.

[b] With a threshold ≥ 2.

[c] Adjusted on age, sex, ethnicity, complete Kawasaki disease, year of diagnosis, and delay between disease onset and first-line treatment.

Score	Need for second-line treatment			Persistent fever at H48		
	AUC	Sensitivity	Specificity	AUC	Sensitivity	Specificity
Kawanet score (1 point per variable)[b] (NA=23)	0.60	43%	72%	0.59	41%	73%
Baseline coronary artery maximal Z-score ≥2.0	0.67	55%	80%	0.58	39%	78%
Abnormal initial echocardiography[a] (NA=4)	0.69	65%	74%	0.61	49%	73%
Kawanet score (1 point per variable) + baseline maximal Z-score ≥2.0 (2 points) (NA=23)[b]	0.69	69%	56%	0.62	61%	56%
Kawanet score (1 point per variable) + abnormal initial echocardiography[a] (2 points) (NA=27)[b]	0.71	76%	54%	0.64	67%	54%

***Table 3*: Performances of the Kawanet and modified-Kawanet scores, N=363.**
[a] Defined as initial coronary maximal Z-score ≥ 2.0, pericarditis, myocarditis, or ventricular dysfunction.
[b] With a threshold ≥ 2.

modified Kawanet score 2 stratified on geographic and ethnic background (Table 4). In both the Italian and French cohorts, the modified Kawanet score 2 had the best performance (AUC 0.72 and AUC 0.70, respectively; Table 4). With respect to ethnicity, the modified Kawanet score 2 performed better than the Kawanet score and initial echocardiography alone in all studied ethnicities (Table 4). The performance of the modified Kawanet score 2 according to complete/incomplete KD and age (<2, <4 or≥ 4 years) are shown in Table 4 **and supplementary Table 9**.

Discussion

Our study developed a scoring system, based on a modification of the Kawanet score, that allows early identification of severe forms of KD in multi-ethnic populations. This scoring system, which we propose to call the Kawanet-echo score, can predict patients requiring second-line treatment after the first dose of IVIG with a sensitivity of 76% and specificity of 54%. Its performance was similar in an Italian and a French cohort, suggesting that it is robust for multi-ethnic populations in Europe. If validated in other populations of children with KD, it may help in the implementation of specific treatment strategies for patients at risk for severe KD.

Variable	Points
ALT level >30 IU/L	1
Hepatomegaly	1
Lymphocyte count <2400/mm^3	1
Time to treatment < 5 days	1
Abnormal initial echocardiography	2
Presence at least 1 of the following:	
*Coronary maximal Z-score ≥ 2.0	
*Pericarditis	
*Myocarditis	
*Ventricular dysfunction	
Total	6
Cut-off	≥2

***Box 1*: Calculation of the modified Kawanet score 2.**

In the literature many predictive scores have been developed to identify patients with severe forms of KD. Most of them perform well in Asian populations[7–9] but perform poorly in European and North American populations.[10–15] The study reporting the initial Kawanet-score showed a good performance of this score to predict need for second-line treatments in French children with KD (sensitivity 77%; specificity 60%), which is in contrast with a poor performance of the Kawanet score in our study population (sensitivity 43%; specificity 72%), though we used the same primary readout. Different modalities of patient recruitment and their biases (voluntary register-based study versus consecutive patient cohorts) and demographic differences may have contributed to these divergent observations. Because of the poor sensitivity of this score in our population we developed a new scoring system that combines the Kawanet-score and data from the initial echocardiography findings.

Previous studies indicated that abnormal coronary and extra-coronary findings on initial echocardiography may be associated with resistance to IVIG[15,19] and subsequent CAA development.[20,24,22] Our study confirms, in two European KD cohorts, the association between a coronary artery maximal Z-score ≥ 2.0 at the initial echocardiography and severe KD, as measured by the need for second-line treatments and persistence of fever 48h after the end of initial IVIG treatment. Baseline z scores had moderate sensitivity and the highest specificity of all the models in this cohort. Furthermore, our results show that in addition to a maximal Z-score ≥ 2.0, other findings on the initial echocardiogram should also be included in the prediction of severe disease, namely pericarditis, myocarditis or ventricular dysfunction. In contrast, adding more subjective variables, such as the presence of coronary brightness or irregularity, does not further improve the performance of the initial echocardiogram in predicting severe disease.

Cohort	Score	Need for second-line treatment		
		AUC	Sensitivity	Specificity
Italian cohort, N=177	Kawanet score[a] (NA=23)	0.55	30%	76%
	Abnormal initial echocardiography[b] (NA=4)	0.68	65%	70%
	Kawanet score + abnormal initial echocardiography[a,b] (NA=27)	0.72	80%	53%
French cohort, N=186	Kawanet score[a]	0.62	52%	69%
	Abnormal initial echocardiography[b]	0.68	48%	87%
	Kawanet score + abnormal initial echocardiography[a,b]	0.70	74%	55%
European ethnicity, N=183	Kawanet score[a] (NA=17)	0.60	36%	78%
	Abnormal initial echocardiography[b] (NA=4)	0.69	64%	74%
	Kawanet score + abnormal initial echocardiography[a,b] (NA=21)	0.73	80%	56%
African/Afro-Caribbean ethnicity, N=110	Kawanet score[a] (NA=2)	0.60	53%	66%
	Abnormal initial echocardiography[b]	0.66	47%	86%
	Kawanet score + abnormal initial echocardiography[a,b] (NA=2)	0.65	65%	51%
Asian ethnicity, N=37	Kawanet score[a]	0.69	75%	67%
	Abnormal initial echocardiography[b]	0.70	50%	90%
	Kawanet score + abnormal initial echocardiography[a,b]	0.85	100%	61%
Complete KD, n=227	Kawanet score[a] (NA=13)	0.58	44%	67%
	Abnormal initial echocardiography[b] (NA=4)	0.66	47%	84%
	Kawanet score + abnormal initial echocardiography[a,b] (NA=17)	0.70	76%	49%
Incomplete KD, n=136	Kawanet score[a] (NA=10)	0.62	41%	80%
	Abnormal initial echocardiography[b]	0.72	71%	73%
	Kawanet score + abnormal initial echocardiography[a,b] (NA=10)	0.71	88%	47%
Male, n=222	Kawanet score[a] (NA=12)	0.54	42%	68%
	Abnormal initial echocardiography[b] (NA=2)	0.70	61%	79%
	Kawanet score + abnormal initial echocardiography[a,b] (NA=14)	0.67	78%	47%
Female, n=141	Kawanet score[a] (NA=11)	0.70	47%	77%
	Abnormal initial echocardiography[b] (NA=2)	0.60	40%	81%
	Kawanet score + abnormal initial echocardiography[a,b] (NA=13)	0.78	87%	51%
age <4 years, n=291	Kawanet score[a] (NA=17)	0.59	39%	77%
	Abnormal initial echocardiography[b] (NA=2)	0.71	63%	79%
	Kawanet score + abnormal initial echocardiography[a,b] (NA=19)	0.71	79%	52%
age ≥4 years, n=72	Kawanet score[a] (NA=6)	0.56	54%	50%
	Abnormal initial echocardiography[b] (NA=2)	0.57	31%	83%
	Kawanet score + abnormal initial echocardiography[a,b] (NA=8)	0.67	85%	33%

***Table 4*: Performances of the Kawanet, abnormal initial echocardiography and modified-Kawanet score among different cohorts, ethnicities and patient characteristics, N=363.**

[a] With a threshold ≥ 2.

[b] Defined as initial coronary dilatation, aneurysm, pericarditis, myocarditis, or ventricular dysfunction. Kawanet score: 1 point per variable. Modified Kawanet score 2: 1 point per variable for the Kawanet score, 2 points for the initial echocardiography.

In our study cohort, the difference between the number of patients requiring second-line treatment (n=57/363, 16%) and patients with persistent fever at 48h (n=81/363, 22%) appears to be quite high. Our data did not allow us to identify the exact factors that contributed to the decision not to treat some of the patients with persistent fever at 48 h after completion of IVIG. Because physicians, in case of patients in good clinical conditions, typically decide on treatment during regular daytime shifts it is conceivable that some treatment decisions were made a few hours after the 48-hour threshold that defined persistent fever. For patients with improving general clinical conditions who became apyretic after the 48-hour cutoff but before the clinical round, physicians may have decided not to administer any second-line treatment.

Our study has several limitations. It is based on patient cohorts from two tertiary centers in two different European countries, which allows for some degree of external validation. Because both participating centers are tertiary centers located in large cities, we cannot exclude selection bias. The Kawanet score is likely to be subject to some variability because it includes a rather subjective clinical variable, hepatomegaly, which however has the advantage of being widely available. Our data did not allow us to assess whether ultrasound assessment of hepatomegaly would improve the performance of this score. Because the sensitivity and

specificity of the proposed score are not perfect, there remains a risk of not detecting patients at risk. In addition, its use in low-resource countries (where high-dose IVIGs can be purchased out of pocket) may raise concerns given the low specificity. Furthermore, echocardiography measurements are operator-dependent, and it has to be considered that a pediatric cardiologist may not be present in all centers, making our score potentially more difficult to implement in settings where such expertise is not available. The proposed score seemed to perform better in Asian and European (respectively sensitivity 100% and 80%; specificity 61% and 56%) than in African/Afro-Caribbean patients (sensitivity 65%; specificity 51%). Because the prognosis of patients with KD of African descent has varied in the literature and because of the relatively small number of patients in our subgroup analysis, additional studies in larger cohorts are needed to conclude on the performance of the score according to ethnicity and specific clinical features.

Conclusion

Our study proposes a score that allows early identification of children with KD requiring second-line treatment in multi-ethnic populations. If validated in other larger multi-ethnic populations of children with KD, it could help in the implementation of specific treatment strategies for patients of different ethnicities at risk for severe KD.

Contributors

NO, RMD, ST, LM, RC and UM designed the study and verified data. NO and UM performed the statistical analysis. NO, RMD, ST, MC, LM, AL, GB, CB, CD, IM, RS, RC and UM interpreted the data and drafted the article. All authors revised and approved the manuscript. NO, RMD, ST, LM, RC and UM had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Data sharing statement

All data generated or analyzed during this study are included in this published article. Individual participant data that underlie the results reported in this article, after de-identification, will be made available to researchers who provide a methodologically sound proposal.

Declaration of interests

All authors: None to declare.

Acknowledgements

The authors thank Professor Albert Faye for his trust, support and constant advice. We would like to thank all the physicians who participated in the clinical management of the patients in Paris and Milan. Professor Rolando Cimaz passed away during the preparation of this manuscript. We will miss his energy, his enthusiasm, his kindness and his sense of humor. Ciao Rolando.

Funding

None.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.lanepe.2022.100481.

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