

# Failure to Predict High-risk Kawasaki Disease Patients in a Population-based Study Cohort in Germany

André Jakob, MD,\* Rudiger von Kries, MD,† Judith Horstmann,‡ Markus Hufnagel, MD,§ Brigitte Stiller, MD,‡ Reinhard Berner, MD,¶ Eva Schachinger,‡ Karoline Meyer,‡ and Viola Obermeier, PhD†

**Background:** Diverse scores on high-risk Kawasaki disease (KD) patients have proven a good prognostic validity in the Japanese population. However, data on non-Japanese have been inconclusive. Do the Kobayashi, Egami and Sano scores or application of up-to-date statistical methods (Random Forest) predict response to standard intravenous immunoglobulin (IVIG) therapy and the risk of persistent coronary artery aneurysm (CAA) in patients with KD in a mainly Caucasian population in Germany?

**Methods:** Data on 442 children (German population-based survey, 2013 and 2014) were used to assess the prognostic validity of the Kobayashi, Egami and Sano scores for being refractory to IVIG treatment and for predicting the risk of persistent CAA. Additionally, an up-to-date statistical approach (Random Forest) was applied to identify a potentially more valid score.

**Results:** A total of 301 children were eligible for assessment of their response to IVIG treatment. Among those, 177 children were followed-up for 1 year to identify persistent CAA. Although all scores were significantly associated with being refractory to IVIG (relative risk range between 2.32 and 3.73), the prognostic properties were low (likelihood ratio positive: 1.83–4.57; sensitivity in the range of 0.28–0.53). None of the scores was a significant predictor of CAA 1 year after acute illness. Application of sta-

tistical analysis such as Random Forest did not yield a more valid score.

**Conclusions:** None of the available scores appears to be appropriate for identifying high-risk Caucasian children with KD who might need intensified therapy.

**Key Words:** Kawasaki disease, risk scores, Caucasian

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Kawasaki disease (KD) is an acute febrile vasculitis of unknown etiology. The process of vascular inflammation is especially evident at the coronary artery level. This accounts for persistent coronary artery aneurysms (CAAs) with a high impact on long-term morbidity and mortality. Most, but not all affected children respond to a first intravenous immunoglobulin (IVIG) treatment. Response to IVIG treatment has been found to be a negative predictor for incident and persistent CAA.<sup>1</sup> Currently, prediction of failure to respond to IVIG treatment is considered crucial for the purpose of identifying children who may need early supplementary immunosuppressive therapy. Although additional use of corticosteroids may have a positive impact on the course of fever and inflammation,<sup>2,3</sup> a beneficial effect on the aneurysm rate was only observed in high-risk Japanese children<sup>4–6</sup> identified by the Kobayashi score.

The Kobayashi score and other scores (Egami,<sup>7</sup> Sano<sup>8</sup>) have been evaluated for prediction of being refractory to initial IVIG treatment in Japanese children. Data on the ability of these scores to validly predict response to standard IVIG therapy outside Japan has been limited. Additionally, the association between response to therapy and risk of developing CAA has been ambiguous.<sup>9,10</sup> The latest scientific statement from the American Heart Association (AHA) from the year 2017 only recommended the adjunctive use of corticosteroids when high-risk patients can be clearly identified.<sup>11</sup>

From 2013 to 2014, a German study collected active surveillance data on 442 children with KD. The study addressed the following questions:

In a primarily Caucasian population in Germany, how well do the Kobayashi and other scores predict first response to standard IVIG therapy and the risk of persistent CAA in patients with KD? Does the application of up-to-date statistical methods such as Random Forest allow for the determination of a highly predictive score in this population?

## PATIENTS AND METHODS

Nationwide active surveillance through the hospital-based German Pediatric Surveillance Unit (ESPED) was used to recruit eligible KD patients. For the years 2011 and 2012, the incidence of KD in Germany (children <5 years) recently has been determined to be 7.2 in 100,000.<sup>12</sup> Between January 1, 2013, and December 31, 2014, 442, presumed cases of KD were reported in Germany. Pseudonymous identifiers were employed in these ESPED reports. Reporting physicians were sent a standardized questionnaire explicitly requesting all parameters required for analysis. For numeric parameters, such as laboratory values, the reporting physicians were asked to document the measured values along with their respective units. For categorical parameters,

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From the \*Department of Pediatric Cardiology and †Department of Epidemiology, Institute of Social Pediatrics and Adolescent Medicine, Ludwig-Maximilians-University of Munich, Munich, Germany; ‡Department of Congenital Heart Disease and Pediatric Cardiology, University Heart Center Freiburg, Freiburg, Germany; §Division of Pediatric Infectious Diseases and Rheumatology, Department of Pediatrics and Adolescent Medicine, University Medical Center, Medical Faculty, University of Freiburg, Freiburg, Germany; and ¶Department for Pediatrics, Universitätsklinikum Carl Gustav Carus, Technische Universität Dresden, Dresden, Germany.

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Address for correspondence André Jakob, MD, Department of Pediatric Cardiology, Ludwig-Maximilian-University of Munich, Marchioninstr 15, D-81377 Munich, Germany. E-mail: andre.jakob@med.uni-muenchen.de

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correspondents were provided the option of checking either “yes” or “no.” Additionally, through a written informed consent request sent by the treating physician, parents were asked whether they would agree to the disclosure of their children’s identities for the study. In the cases where consent was provided, we validated the questionnaire data via discharge letters, recorded laboratory values and echocardiographic findings. Due to data protection regulations, follow-up only was possible in cases where parents had provided written consent. The ESPED reports were used to assess the diagnostic validity of Kobayashi and other scores in their ability to predict response to initial IVIG treatment. Due to the need for informed consent, long-term risk for persistent CAA was evaluated only in children with known identities. Exclusion criteria were: failure to comply with the clinical case definition; IVIG-untreated patients; steroid administration concurrent with the first IVIG therapy ( $\pm 2$  days); and, in cases where neither “yes” nor “no” was ticked on the questionnaire, uncertain steroid exposure. (In the context of the study, steroid administration was considered a confounder regarding clinical outcome.) Approval for the study was provided by the Ethics Committee of the University of Freiburg, in accordance with the ethical standards to the Declaration of Helsinki.

**DEFINITIONS**

**Kawasaki Disease**

AHA guidelines<sup>1</sup> were used to classify complete and incomplete KD cases. Complete cases were defined as those with persistent fever for  $\geq 5$  days or fever that resolved in  $< 5$  days in response to IVIG treatment. Additionally, display of at least 4 principal clinical features was required: (1) changes in extremities; (2) polymorphous exanthema; (3) bilateral conjunctival inflammation without exudate; (4) changes in the lips and oral cavity and (5) cervical lymphadenopathy. Incomplete cases included those with fever and those showing fewer than 4 clinical features but with detection of CAAs. As in other population-based surveillance studies,<sup>13</sup> diagnosis of CAA was determined based on the clinical judgment of the reporting physician. In Germany, 2 criteria for aneurysms are applied. The first criteria follow those of the Japanese Ministry of Health, which defines aneurysms as either a lumen  $> 3$  mm in children younger than 5 years, as a diameter 1.5 times the size of the surrounding segment, or as a clearly irregular lumen. The second criteria are defined as a Z score of  $> 2.5$  for one of the coronary arteries.<sup>14</sup> In accordance with AHA guidelines, cases with fever persisting for longer than 36 hours and therefore given a second dose of IVIG were defined as “refractory to IVIG.”

**Kobayashi Score**

The Kobayashi score assigns 2 points for each of the following: (1) sodium  $\leq 133$  mmol/L; (2) days of illness before initial

treatment  $\leq 4$ ; (3) aspartate aminotransferase (AST)  $\geq 100$  IU/L and (4) neutrophil count  $\geq 80$  %. Additionally, the score assigns one point for fulfilling the following criteria: (5) C-reactive protein (CRP)  $\geq 10$  mg/dL; (6) age  $\leq 12$  months and (7) platelet count  $\leq 30.0 \times 10^4$ /mm<sup>3</sup>. In the literature, different cutoff values have been applied for labeling high-risk patients (ie,  $> 3$  and  $> 4$ ).

**Sano Score**

The Sano score labels patients as high risk when at least 1 of the 2 following criteria apply: (1) CRP  $\geq 7.0$  mg/dL; (2) bilirubin  $\geq 0.9$  mg/dL or (3) AST  $\geq 200$  IU/L.

**Egami Score**

The Egami score assigns patients to the high-risk group when at least 3 of 6 possible points apply: (1) age  $\leq 6$  months (1 point); (2) days of illness at initial treatment  $\leq 4$  (1 point); (3) platelet count  $\leq 30.0 \times 10^4$ /mm<sup>3</sup> (1 point); (4) CRP  $\geq 8$  mg/dL (1 point) and (5) alanine aminotransferase  $\geq 80$  IU/L (2 points).

In our main analysis, missing values in one of the required laboratory parameters were rated as “absence of the risk factor.” A sensitivity analysis used only cases with complete information on all risk factors.

**STATISTICAL ANALYSIS**

Descriptive statistics were performed using the statistical software R (R 3.1.0). For all outcomes “refractory to IVIG,” “aneurysm after 4 weeks” and “aneurysm after 1 year,” we assessed the risk increase related to high-risk classification in 3 scores (Kobayashi, Egami und Sano). We additionally assessed indicators of the prognostic value—that is, sensitivity, specificity, positive and negative prognostic value and positive likelihood ratio (LR+). On this basis, we calculated 95% confidence interval (CI) for relative risk and likelihood risk. In a sensitivity analysis, the respective risk ratios and LR+ also were determined for cases that had obtained complete information regarding the defining score parameters (Table, Supplemental Digital Content 1, <http://links.lww.com/INF/C969>). Additional sensitivity analyses were conducted including all eligible KD cases (Tables, Supplemental Digital Content 3–5, <http://links.lww.com/INF/C971>; <http://links.lww.com/INF/C972>; <http://links.lww.com/INF/C973>).

The relative risk for being refractory to IVIG, along with that for coronary aneurysms after 4 weeks and after 1 year, was assessed in relation to the 3 risk scores (Tables 1 and 2).

To develop a potentially more discriminating score for defining high-risk groups in non-Japanese children, our study attempted—via univariate analysis—to identify clinical, echocardiographic and laboratory parameters significantly associated with being refractory to initial IVIG treatment (Table 3). For

**TABLE 1.** CAA After 4 wk (n = 22/175): Numbers at High Risk for CAA After 4 wk According to Different Scores and Indicators of Prognostic Validity for the Respective Scores

High-risk According to Score	Aneurysm High-risk Children n (%)	Relative Risk: High- vs. Low-risk Cases (95% CI)	Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value	Positive Likelihood Ratio (95% CI)
Kobayashi $> 4$ n = 37	7 (19)	1.74 (0.77–3.95)	0.32	0.80	0.19	0.89	1.60 (0.81–3.24)
Kobayashi $> 3$ n = 60	11 (18)	1.92 (0.88–4.16)	0.50	0.68	0.18	0.90	1.56 (0.97–2.52)
Sano n = 18	5 (28)	2.57 (1.08–6.12)	0.23	0.92	0.28	0.89	2.88 (1.06–6.78)
Egami n = 49	9 (18)	1.78 (0.81–3.90)	0.41	0.74	0.18	0.90	1.58 (0.89–2.76)

**TABLE 2.** CAA After 1 yr (n = 10/177): Numbers at High Risk for CAA After 1 yr According to Different Scores and Indicators of Prognostic Validity for the Respective Scores

High-risk According to Score	Aneurysm High-risk Children n (%)	Relative Risk: High- vs. Low-risk Cases (95% CI)	Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value	Positive Likelihood Ratio (95% CI)
Kobayashi >4 n = 37	3 (8)	1.62 (0.44–5.97)	0.30	0.80	0.08	0.95	1.50 (0.55–3.98)
Kobayashi >3 n = 60	5 (8)	1.95 (0.59–6.47)	0.50	0.67	0.08	0.96	1.52 (0.79–2.93)
Sano n = 18	2 (11)	2.21 (0.51–9.61)	0.20	0.90	0.11	0.95	2.00 (0.56–7.85)
Egami n = 50	4 (8)	1.69 (0.50–5.75)	0.40	0.72	0.08	0.95	1.43 (0.65–3.23)

**TABLE 3.** Laboratory Values for Refractory and Nonrefractory Patients (n = 301)

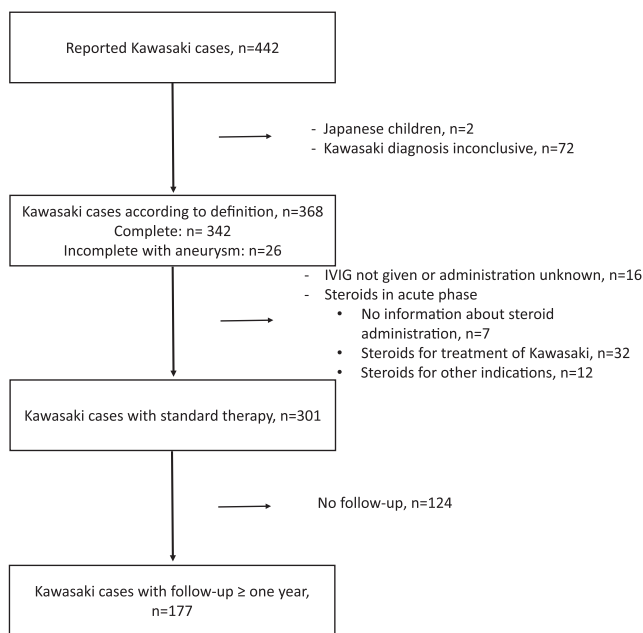
Laboratory	Refractory: Yes (n = 47) Mean	Refractory: No (n = 245) Mean	P value t test
Albumin (g/dL)	2.65	3.04	0.008
AST (U/L)	162.81	94.86	0.049
Total protein (g/dL)	8.18	7.58	0.825
ALT (U/L)	150.10	93.54	0.024
Gamma-GT (U/L)	119.24	82.40	0.156
Bilirubin (mg/L)	8.42	6.10	0.415
CRP (mg/L)	160.88	104.28	<0.0001
Sodium (mmol/L)	132.26	134.18	0.006
Potassium (mmol/L)	3.91	4.23	0.130
ESR (mm/h)	112.22	90.68	0.003
Thrombocytes (count/ $\mu$ L)	734.57	547.58	<0.0001
Hemoglobin (g/dL)	8.81	10.33	<0.0001
WBC count (count/ $\mu$ L)	23.13	16.77	0.002
Neutrophils (%)	77.53	68.66	0.059
Gallbladder hydrups (n) ( $\chi^2$ test)	11	21	0.006

ALT indicates alanine aminotransferase; ESR, erythrocyte sedimentation rate; WBC, white blood cell count.

these, we calculated Random Forests,<sup>15</sup> a statistical method that expands on well-known classification and regression trees.<sup>16</sup> Classification and regression trees (CART) uses a given set of covariates and identifies optimal cutoff values to best divide a data set into 2 groups relating to a response variable (eg, refractory “yes” or “no”). Based on different cutoffs, Random Forests averages a large number of classification and regression tree decisions to provide an efficient and computationally stable method for detecting the most predictive variables for explaining the respective response variable without also providing cutoff values.

**RESULTS**

Out of 442 presumed KD cases reported, 342 were classified as complete and 26 as incomplete according to the AHA guidelines (Fig. 1). From the total, 72 children did not meet the required clinical definition criteria. Additionally, 2 Japanese children were excluded. All 301 patients included in our analysis had had at least 1 IVIG dose and were labeled as “Kawasaki cases with standard therapy.” Follow-up for 1 year was available for 177 of the children. Cases with and without follow-up did not differ with respect to sociodemographics or to clinical symptoms during the acute phase (Table, Supplemental Digital Content 2, <http://links.lww.com/INF/C970>). Among the follow-up cases, there was 1 case treated with



**FIGURE 1.** Flow chart of the study cohort.

infliximab, methotrexate and anakinra. This child already had had giant CAA early in the course of the disease, and this CAA persisted at the 1-year follow-up. In fact, according to all scores when treated with IVIG, this child would have been assigned as high risk.

Among the cases, the proportion of boys was 65%. Ethnic background was available in 90% of cases and showed a breakdown of 95% Caucasian, 3% Asian and 2% black African.

Over half the patients (189 or 63%) were 1 to 4 years old, 47 (16 %) were refractory to IVIG, 67 (22%) had CAA in the acute phase, 22 (13% had CAA after 4 weeks) and 10 (6%) had CAA after 1 year. High-risk status was assigned to 21% of the cases according to the Kobayashi score >4 (33% Kobayashi score >3), 9% according to the Sano score and 28% according to the Egami score (Table 4).

All scores indicated an increased risk for being refractory (all 95% CI’s excluded 1: no effect, Table 5). The LR+ of the Sano score was 4.67 (95% CI: 2.39–9.19). This indicates a 46% probability of being refractory, given that the Sano score is high (post-test probability) as compared with the 16% probability of being refractory in the entire cohort without the application of any score (pretest probability). The respectively predicted post-test probabilities for the Kobayashi score >4 were 31% (>3, 25%) and 27% for the Egami score.

**TABLE 4.** General Patient and Score Defining Characteristics of the Included Standard Kawasaki Cases (n = 301)

General Characteristics	n (%)
Gender: boys	196 (65)
Age (yr)	
<1	52 (17)
1–4	189 (63)
≥5	60 (20)
Refractory to IVIG: yes	47 (16)
CAA	
In acute phase	67 (22)
After 4 wk*	22 (13)
After 1 yr†	10 (6)
Kobayashi score >4/>3	64 (21)/99 (33)
Days of illness at initial treatment ≤4	82 (27)
Age ≤1 yr	52 (17)
Sodium ≤133 mmol/L	103 (34)
AST ≥100 IU/L	62 (21)
Neutrophils ≥80%	65 (22)
CRP ≥10 mg/dL	141 (47)
Thrombocytes ≤300 × 10 <sup>9</sup> /L	35 (12)
Sano score >1	28 (9)
CRP ≥7 mg/dL	185 (62)
Bilirubin ≥0.9 mg/dL	20 (7)
AST ≥200 IU/L	27 (9)
Egami score >2	85 (28)
Age ≤6 mo	24 (8)
Days of illness at initial treatment ≤4	82 (27)
CRP ≥8 mg/dL	166 (55)
Thrombocytes ≤300 × 10 <sup>9</sup> /L	35 (12)
ALT ≥80 IU/L	102 (34)

\*Follow-up 4 weeks after onset of disease: N = 175.

†Follow-up 1 year after onset of disease: N = 177.

ALT indicates alanine aminotransferase.

After 4 weeks, only the Sano score indicated an increased risk for aneurysm. After 1 year, none of the scores predicted an increased risk. Accordingly, the LRs+ for CAA after 4 weeks were only significantly increased for the Sano score (Tables 1 and 2). Being refractory to IVIG was associated with an increased risk for CAA after 4 weeks (Relative Risk = 2.46, 95% CI: 1.17–5.08); however, there was no association with an increased risk of having an aneurysm after 1 year (RR = 1.33, 95% CI: 0.37–4.68).

As shown in Table 3, several laboratory values and hydrops of the gallbladder were significantly associated with being refractory. Laboratory values measured on a continuous scale were fed into the analysis without prior dichotomization. Therefore, no cutoffs for these parameters are provided. The model underlying the Random Forest method using hydrops of the gallbladder, albumin, AST,

alanine aminotransferase, CRP, sodium, erythrocyte sedimentation rate, thrombocytes, hemoglobin and white blood cell count is based on repetitive CART trees and provides a summary estimate. The Random Forest method identified 14 patients as high-risk patients. The most discriminating variable was hemoglobin, followed by AST and thrombocytes. The respective specificity for the high-risk group was 98%, accounting for a high LR+ of 15 (CI: 5.10–31.15). Unfortunately, sensitivity achieved was only 30%—that is, however not higher than that for the established scores (Table 6).

### DISCUSSION

By applying different scores for KD in a primarily Caucasian population, we were able to assess and compare their predictive value regarding being refractory in relation to standard IVIG and regarding risk of mid- or long-term (1 year) CAA. Although high-risk cases as assigned by all scores were associated with an increased risk for being refractory, the prognostic value of these scores was low as indicated by poor sensitivity and by a small LR+. This was irrespective of the cutoff values applied by the Kobayashi score. In terms of predicting CAA, only the Sano Score showed a significantly elevated risk and LR+ for CAA after 4 weeks but with poor sensitivity and positive predictive value. Although several laboratory values and hydrops of the gallbladder were significantly associated with being refractory in our mainly Caucasian patient cohort, the Random Forest approach unfortunately, did not yield a more valid prognostic score.

We have focused the discussion on the outcome of being refractory, because the 3 Japanese scores were originally designed to detect resistance to IVIG. For a number of studies, reported in the literature, we have listed the published study characteristics and prognostic indicators in Table 7, Supplemental Digital Content, <http://links.lww.com/INF/C975>. Although all studies gave sensitivity and specificity, few showed the positive and negative predictive values and none the LR+. While the assessed scores appeared to be fairly predictive in Japanese children,<sup>5–8,17,18</sup> they seemed to be of less clinical relevance in non-Japanese Asian KD children.<sup>19,20</sup> A study evaluating all 3 scores in Korean KD children even yielded somewhat lower sensitivities for IVIG nonresponsiveness than our study did (range of 28%–34%). In a KD patient cohort from east China, both scores' sensitivity (Egami and Kobayashi) was 57.1% with regard to response to IVIG. In Caucasian children, these scores also failed to validly predict high risk in KD children (sensitivity through all scores was 26%–58%). A Medline search on the phrase “Kawasaki disease and scores and/or IVIG resistance” yielded 5 publications that focused primarily on Caucasian children. Three publications were from Europe<sup>10,21,22</sup> and 2 from the United States.<sup>9,23</sup> Regarding being refractive to IVIG, an English<sup>10</sup> and Polish<sup>22</sup> study evaluated the Kobayashi score in a monocentric, small sample size study; meanwhile, a Catalanian study group assessed the

**TABLE 5.** KD Cases Refractory to IVIG (n = 47/301): Numbers at High Risk for Being Refractory According to Different Scores and Indicators of Prognostic Validity for the Respective Scores

High-risk According to Score	Refractory High-risk Children n (%)	Relative Risk: High- vs. Low-risk Cases (95% CI)	Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value	Positive Likelihood Ratio (95% CI)
Kobayashi >4 n = 64	20 (31)	2.74 (1.65–4.56)	0.43	0.83	0.31	0.89	2.53 (1.60–3.77)
Kobayashi >3 n = 99	25 (25)	2.32 (1.38–3.90)	0.53	0.71	0.25	0.89	1.83 (1.31–2.54)
Sano n = 28	13 (46)	3.73 (2.25–6.19)	0.28	0.94	0.46	0.88	4.67 (2.39–9.19)
Egami n = 85	23 (27)	2.44 (1.46–4.07)	0.49	0.76	0.27	0.89	2.04 (1.39–2.88)



**TABLE 6.** Outcome Refractory (47/301): High-risk Classification by Random Forests, Numbers Exposed, Risk for Being Refractory Related to High Risk and Prognostic Validity of the Classification

High Risk According to	Refractory High-risk Children n (%)	Relative Risk: High- vs. Low-risk Cases (95% CI)	Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value	Positive Likelihood Ratio (95% CI)
Random Forests n = 20	14 (70)	5.96 (3.88–9.17)	0.30	0.98	0.70	0.88	15.00 (5.10–31.15)

Egami score in a population-based study.<sup>21</sup> The English study assessing the Kobayashi score for prediction of CAA in Caucasian children was based on small numbers (n = 20) and confined for CAA in the acute phase only. Loomba et al<sup>23</sup> evaluated the Egami score vis-à-vis predicting IVIG resistance in KD among different ethnicities in a Midwest US population. Although they did not find a clinically meaningful difference among the different ethnic groups, their cohort included just 9 children of Asian origin. Among the studies discovered, only the US study by Sleeper et al<sup>19</sup> may be seen as comparable with ours with respect to assessment of all 3 scores in their prediction of IVIG resistance and CAA (5 weeks after the acute phase of illness). Here, only the Kobayashi score seemed to significantly predict a high coronary artery Z score ( $P < 0.05$ ). The association, however, was weak, showing a Spearman correlation coefficient of just 0.29.

### STRENGTH AND LIMITATIONS

Our study is the first European study to evaluate all 3 established Japanese risk scores in relation to a cohort of primarily Caucasian children. It is also the first to provide data on the utility of these scores in predicting persistence of aneurysm after standard therapy up to 1 year after acute KD. Originally, the 3 Japanese scores were designed to detect resistance to IVIG. However, the most important impact of KD on long-term morbidity is the persistence of CAA. To our knowledge, to date, the association between high-risk cases as identified by the Japanese scores and persistent aneurysm up to 1 year after the acute illness has not been evaluated. In our population, the rates of CAA were 13% after 4 weeks and 6% after 1 year. This is in accordance with CAA rates reported after IVIG introduction in other studies.<sup>24,25</sup> Because reporting physicians did not report coronary artery diameters for all patients, we had to rely on the validity of their diagnosis. For a subsample of 15 of 22 cases with CAA at 4 weeks, we were able to validate the physicians' diagnosis of CAA since specific coronary artery dimensions were reported. We used the Z score equation proposed by Dallaire et al.<sup>14</sup> In all 15 cases, the Z score was  $>2.5$ .

Because of lack of statistical power, our study did not allow for a meaningful assessment of the prognostic validity of these scores in relation to aneurysm after 4 weeks and 12 months. This most likely explains our failure to identify an association between being refractory and CAA after 12 months. Because our study originally was designed to assess the incidence of KD in Germany, statistical power calculations regarding the predictive value of different scores in identifying CAA had not been performed.

We conducted a number of sensitivity analyses: Among the 301 cases in the main analysis, we reran the score test statistics only for those with complete data on all parameters. This yielded results similar to those in the main analysis (Table, Supplemental Digital Content 1, <http://links.lww.com/INF/C969>). To assess external validity with respect to the excluded children, we ran the score analyses for all children combined (Tables, Supplemental Digital Content 3–5, <http://links.lww.com/INF/C971>; <http://links.lww.com/INF/C972>; <http://links.lww.com/INF/C973>).

This showed nearly identical results. We additionally compared clinical characteristics in excluded children vis-à-vis those included in the main analysis. These data show that exclusion of cases given steroids or cases for whom there was lacking information on steroid administration, did not account for lack of external validity by confining the main analysis to KD cases at a lower risk (Table, Supplemental Digital Content 6, <http://links.lww.com/INF/C974>).

### CLINICAL IMPLICATIONS OF THIS STUDY

A recent meta-analysis confirmed the effectiveness of corticosteroids in treating high-risk children.<sup>26,27</sup> The challenge, however, is to identify children at high risk for KD in non-Japanese children. This is again outlined in the recent AHA's scientific statement from the year 2017.<sup>11</sup> Adjunctive administration of corticosteroid was only recommended if high-risk patients can be identified.<sup>11</sup> Our in-depth assessment of the 3 major Japanese scores, plus an additional data-driven score, did not indicate a reliable tool for predicting failure to respond to IVIG in primarily Caucasian (ie, non-Japanese) children. Because valid scores to identify high-risk KD children in Caucasian children are unavailable, supplementing IVIG with steroids for all children can be supported—as suggested by a recent Cochrane review<sup>28</sup>—at least until those who do not need this therapy escalation can be identified.

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