Predictive value for intravenous immunoglobulin resistance of Kobayashi and Kawanet scores in 722 children with Kawasaki disease across diverse ethnic backgrounds (KIWI study): an international cohort study

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Summary

Background **Intravenous immunoglobulin (IVIg) resistance affects 15–25% of children with Kawasaki disease (KD) and increases the risk of coronary artery abnormalities (CAA). The Kobayashi score has shown good predictive value in Japanese cohorts but limited accuracy in non-Asian populations. The Kawanet model was proposed as an alternative with improved applicability in non-Asian settings.**

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Methods A retrospective–prospective, observational, multicentre cohort study including children fulfilling the American Heart Association criteria for KD was conducted. The availability of all clinical and laboratory variables required to calculate both the Kobayashi and Kawanet IVIg-resistance scores was mandatory for inclusion (sodium, neutrophil percentage, AST, platelet count, CRP, age, illness days at first IVIg administration, ALT, hepatomegaly, lymphocyte count, time to treatment). All included patients were aged <18 years at the time of KD diagnosis. Prospectively enrolled patients (April 2022–January 2024) were combined with retrospective cases after Jan 1, 2015, from 19 paediatric rheumatology units in Europe (Italy, United Kingdom, Türkiye, Spain Croatia), South America (Brazil), and Asia (India, Thailand, Israel). The primary outcome was to assess the performance of Kobayashi and Kawanet scores and to identify predictors of IVIg resistance during the acute phase of KD in this multiethnic population. IVIg resistance was defined as persistent or recrudescent fever ≥48 h after infusion. This work is registered with ClinicalTrials.gov, NCT06305611.

Findings Among 722 patients (median age 2.4 years; 38.1% female), ethnicity was 59.4% Caucasian, 20.5% Indian, 14.3% other Asian, and 5.8% mixed. IVIg resistance occurred in 19.7% (n = 142), highest in mixed-ethnicity patients (33.3%), followed by Caucasian (21.2%), Indian (18.9%), and other Asian (9.7%). Independent predictors of IVIg resistance were prolonged fever (per day increase) (OR 1.09, 95% CI 1.06–1.13), cardiac involvement (OR 2.25, 95% CI 1.51–3.34), musculoskeletal involvement (OR 1.89, 95% CI 1.10–3.25), and macrophage activation syndrome (OR 4.14, 95% CI 1.13–15.13) while a complete KD phenotype resulted as a protective factor (OR 0.43, 95% CI 0.27–0.67). The Kobayashi score showed 71% sensitivity and 39% specificity (balanced accuracy 55%), whereas the Kawanet score showed 16% sensitivity and 90% specificity (balanced accuracy 53%), with no major ethnic differences.

Interpretation IVIg resistance was linked to ethnicity and phenotype. Both scores performed poorly, highlighting the need for inclusive, biomarker-based, adaptive models to guide early treatment intensification. Future research in larger, more ethnically balanced cohorts, with dedicated assessment of structural and sociodemographic determinants are required.

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Keywords: Kawasaki disease; IVIg-resistance; Kobayashi score; Kawanet score

Introduction

Kawasaki disease (KD) is an acute, self-limiting vasculitis, predominantly affecting medium-sized arteries and primarily occurring in children under five years of age.[1] Diagnosis is clinical and relies on the presence of prolonged fever (≥5 days) accompanied by at least four of the following features: bilateral non-exudative conjunctival injection, polymorphous rash, changes in the lips and oral mucosa (e.g., erythema, fissures, strawberry tongue), peripheral extremity changes (erythema and oedema of the hands and feet), and cervical lymphadenopathy ≥1.5 cm.[1] Coronary artery abnormalities (CAAs), including aneurysms and ectasia, are the most serious complications and result as the main determinants of long-term morbidity and mortality. Currently, due to its potential to cause myocardial ischaemia and sudden cardiac death, KD represents the leading cause of acquired heart disease in children in high-income countries.[2]

The incidence of KD varies significantly by geography and season, with the highest rates observed in children of Japanese descent.[3] Nationwide epidemiological survey from Japan have documented a rising trend, with incidence increasing from 218.6 per 100,000 in 2008 to over 330 per 100,000 by 2015.[4] Despite more than five decades of investigation, KD aetiology remains unknown. Current evidence supports a multifactorial pathogenesis involving a genetically determined immune response to an unidentified infectious or environmental trigger.[5]

Timely diagnosis can be challenging due to clinical overlap with other common febrile childhood illnesses and the lack of disease-specific laboratory findings and/or tests. The identification of reliable biomarkers to support early diagnosis and risk stratification remains a major unmet need, especially to prevent cardiovascular sequelae. First-line treatment consists of a single infusion of intravenous immunoglobulin (IVIg) at 2 g/kg, administered with acetylsalicylic acid (Aspirin, ASA). This approach reduces the incidence of CAAs from 25 to 30% to approximately 5%.[1] Although the precise mechanisms underlying the therapeutic effect of IVIg are not fully elucidated, it is supposed to exert broad immunomodulatory effects, including inflammatory

Research in context

Evidence before this study

Intravenous immunoglobulin (IVIg) resistance occurs in approximately 15–25% of patients with Kawasaki disease (KD) and is associated with an increased risk of coronary artery abnormalities, making early identification of high-risk patients clinically important. Several clinical risk scores have been developed to predict IVIg resistance, including the Kobayashi score, which performs well in Japanese cohorts but consistently shows lower accuracy in non-Asian settings, and the Kawanet (-echo) score, developed in Europe with the aim of improving applicability in ethnically heterogeneous populations. However, the extent to which these tools generalise to mixed, multiethnic real-world cohorts remains uncertain, as many validation studies have been conducted in single-ethnicity or predominantly Asian populations and/or in relatively small samples. To assess the available evidence specifically in heterogeneous settings before starting this study, we searched PubMed/MEDLINE and Embase from database inception to Sept 15, 2025, using the terms ("Kawasaki disease" AND ("IVIG" OR "intravenous immunoglobulin") AND ("resistance" OR "refractory") AND ("Kobayashi" OR "Kawanet") combined with terms related to multiethnic or mixed populations; we limited inclusion to English-language studies and restricted eligibility to studies reporting multiethnic or ethnically mixed cohorts. Only six studies met these criteria, and only one study evaluated both prediction scores simultaneously within the same multiethnic population, highlighting the limited availability of robust, large-scale comparative validation data in diverse populations. We aimed to address this knowledge gap.

Added value of this study

In this large, multiethnic cohort of 722 patients with KD from 19 international centres, both the Kobayashi and Kawanet scores showed suboptimal predictive performance across all major ethnic subgroups. Independent predictors of IVIg resistance included prolonged fever before treatment, cardiac and musculoskeletal involvement, and macrophage activation syndrome (MAS), whereas a complete KD phenotype was associated with a lower risk of resistance. Moreover, significant ethnic differences in clinical presentation and IVIg resistance rates were observed, with higher resistance among patients of mixed ethnicity and distinct symptom patterns across different groups.

Implications of all the available evidence

Taken together, the available evidence indicates that currently used risk scores are insufficient for reliably predicting IVIg resistance in multiethnic settings, highlighting the need for new, inclusive, and biomarker-enriched predictive models. Ethnicity and disease phenotype should be systematically incorporated into risk stratification strategies to support timely and tailored treatment decisions. These findings further support the need for future research in larger, more ethnically balance, cohorts; with dedicated assessment of structural and sociodemographic determinants in order to develop adaptive predictive tools that improve early identification and management of patients with KD at high risk of IVIg resistance.

cytokine inhibition, toxin neutralization, enhancement of regulatory T-cell activity, and provision of anti-idiotypic antibodies.[6]

Nonetheless, 15–25% of patients with KD are resistant to the IVIg therapy and are at significantly increased risk for coronary complications.[7] Several clinical predictive models, such as Fukunishi, Kobayashi, Sano, and Egami scores, have been developed to identify IVIg-resistant patients, based on clinical and biochemical parameters including C-reactive protein (CRP), liver enzymes, haemoglobin, platelet count, and serum sodium. While these scores demonstrate good specificity, their sensitivity is limited in non-Asian populations.[8–14] More recently, the French Kawanet group proposed a new scoring system that showed promising accuracy in European cohorts; however, further validation in larger and multiethnic population is required.[15]

The primary aim of this study was to evaluate the performance of the Kobayashi and Kawanet scores in predicting IVIg resistance among KD children of European and Asian descent. Additionally, the study sought to identify demographic, clinical and echocardiographic factors associated with IVIg resistance, and to assess potential differences in clinical presentation and treatment response among different ethnic groups.

Methods

Study design

The KIWI study (Comparison and performance of Kobayashi and Kawanet IVIg resistance scores in a multi-centric European and North Indian cohort of KaWasaki dIsease) is a retrospective-prospective, observational, international multicenter study, supported by the 2020 Pediatric Rheumatology European Society/Paediatric Rheumatology International Trials Organisation (PReS/PRINTO, www.pres.eu and www.printo.it) grant. This work is registered with ClinicalTrials.gov, NCT06305611.

Ethics

This study was conducted in accordance with the Guidelines for Good Clinical Practice, as well as the principles of the Declaration of Helsinki and with

applicable national and international regulations governing observational research. The study protocol was reviewed and approved by the Ethics Committee/Institutional Review Board (IRB) of the coordinating site Meyer Children's Hospital IRCCS, Florence, Italy, as the reference ethics committee (ID 18/2022), and by the local Ethics Committees of all participating centres, where required. The specific names of the authorities that granted ethical approval for the study are available in the Supplementary Materials (Supplementary Table S6), along with the reference numbers.

Written informed consent was obtained from all participants prior to inclusion, in accordance with all applicable European Union and international and local regulatory frameworks and ethical standards. All data were collected, stored, and analysed in compliance with data protection and privacy regulations, including the General Data Protection Regulation (GDPR, EU Regulation 2016/679), or equivalent local legislation.

The investigators confirm that the study posed no additional risks or burdens to participants beyond standard clinical care and that all procedures adhered to recognized ethical standards for research involving humans.

Participants

Patients were enrolled from paediatric rheumatology units at 19 participating centres in Europe (Italy, United Kingdom, Türkiye, Spain Croatia), South America (Brazil), and Asia (India, Thailand, Israel).

Children fulfilling the American Heart Association (AHA) diagnostic criteria for KD were prospectively enrolled between April 2022 and January 2024, once follow-up information beyond the subacute phase (at least 12 weeks) was available.[1] In addition, retrospective data were collected for patients diagnosed on or after Jan 1, 2015.

The availability of all clinical and laboratory variables required to calculate both the Kobayashi and Kawanet IVIg-resistance scores was mandatory for inclusion (sodium, neutrophil percentage, AST, platelet count, CRP, age, illness days at first IVIg administration, ALT, hepatomegaly, lymphocyte count, time to treatment).[15,16] All included patients were under 18 years at the time of KD diagnosis.

Data collection and outcomes

Medical records were reviewed to extract data on age, sex at birth, ethnicity and relevant comorbid conditions. Clinical features present at disease onset were documented alongside laboratory parameters, echocardiographic findings, treatment modalities, and clinical outcomes.

Data collection included timing and dosage of IVIg administration (expressed as days from symptom onset) and treatment response. Treatment response was defined as resolution of fever within 48 h of IVIg administration. IVIg resistance was defined as persistent or recrudescent fever beyond 48 h after IVIg infusion.[1]

Statistical analysis

Statistical analyses were conducted to explore associations between IVIg resistance and patient characteristics. Continuous variables were described using either means with standard deviations or medians and interquartile ranges, depending on data distribution. Categorical variables were reported as absolute frequencies and percentages. Group comparisons (IVIg resistant vs responders, Caucasian vs Indian vs Other Asian vs Mixed ethnicity) were performed using chi-square tests with Fisher's exact test correction for categorical variables, t-tests or Mann–Whitney U tests, for continuous variables, as appropriate. In order to identify independent predictors of IVIg resistance, univariate analyses of the entire cohort and stratified for the different ethnic subgroups were first conducted including relevant demographic, clinical and laboratory variables. Variables showing a statistically significant association with IVIg resistance were considered eligible for inclusion in the multivariable logistic regression model. Multicollinearity among predictors was evaluated prior to model fitting using Variance Inflation Factors (VIF), tolerance statistics and condition indices. All variables entered in the model showed VIF values <1.05 and tolerance >0.95, with a maximum condition index of 6.99, indicating the absence of relevant multicollinearity. A backward stepwise elimination strategy was subsequently applied, with all candidate predictors initially included and non-significant variables progressively removed to optimise model performance and minimise overfitting. Results were expressed as odds ratios (OR) with 95% confidence intervals (CI), and a p-value <0.05 was considered statistically significant. Addittionally, a post-hoc receiver operating characteristic (ROC) curve analysis based on the predicted probabilities derived from the multivariable logistic regression model was performed to assess its ability to discriminate between IVIg-resistant and IVIg-responsive patients and allowed for the assessment of area under the curve (AUC). All these analyses were performed using SPSS software, version 29.0.

In order to evaluate whether the Kobayashi and Kawanet scores reproduced the diagnostic performance reported in their original validation studies, fixed reference performance values were applied. Based on the published derivation cohorts, reference targets were defined as 70% sensitivity and 80% specificity for the Kobayashi score, and 77% sensitivity and 60% specificity for the Kawanet score. These thresholds reflect the accuracy metrics initially proposed by the score developers and were therefore used as predefined comparators for reproducibility assessment. Cut-off values were applied according to the original validation criteria

(≥4 for Kobayashi, ≥2 for Kawanet), enabling direct comparison between our multiethnic cohort and the original study populations. The extent to which our results approached the reference sensitivity/specificity values was interpreted as an indicator of potential clinical applicability of both scoring systems beyond their initial derivation setting.[15,16]

The predictive performance of the Kobayashi and Kawanet scores was assessed by comparing their outcomes with the corresponding observed IVIg resistance. For each score standard classification metrics were computed, including balanced accuracy, sensitivity and specificity. Positive and negative predictive value were additionally computed as post-hoc analysis. These metrics provide a comprehensive evaluation of the scores' performance, accounting for both class imbalance and discriminative ability. Confusion matrices were generated to visually represent the distribution of true positive, false positive, true negative, and false negative classifications. In addition, post-hoc receiver operating characteristic (ROC) curve analyses were performed to further evaluate the discriminative ability of the scores. ROC curves were generated for the overall study population as well as for subgroups stratified by ethnicity. The analyses were based on predicted probabilities and allowed for the assessment of area under the curve (AUC) values as a global measure of discrimination. These ROC analyses were not prespecified in the original study protocol and are therefore explicitly reported as post-hoc analyses. The statistical analyses regarding IVIg resistance scores were performed using custom scripts written in Python (version 3.12.9). The following libraries were used: NumPy (version 2.2.5) and pandas (version 2.2.3) for data handling and preprocessing; scikit-learn (version 1.6.1) for performance evaluation; and matplotlib (version 3.10.1) and seaborn (version 0.13.2) for data visualisation.

Role of the funding source

2020 PReS/PRINTO grant provided support in data collection, data quality control and verification, and data extraction for the purposes of the analyses. Current Research Annual Funding of the Italian Ministry of Health. Was not involved in study design, data collection, data analyses, data interpretation, or the writing of the report.

Results

Between April 1, 2022, and January 31, 2024, 722 patients with KD were included across 19 paediatric rheumatology units: 38.1% (n = 275) were females, with a median age of 2.4 years (interquartile range [IQR] 1.19–4.30). Fig. 1 represents STARD diagram reporting flow of participants through the study. Ethnic distribution included 59.4% Caucasian (n = 429), 20.5% Indian (n = 148), 14.3% other Asian (n = 102), and 5.8% of mixed ethnicity (Hispanic and African, n = 42). Complete KD was diagnosed in 54.8% of patients (n = 396), incomplete KD in 41.0% (n = 296), and atypical features were noted in 2.5% (n = 18) (vomiting 8/18, diarrhoea 6/18, sterile pyuria 3/18, arthritis 3/18, hepatomegaly 1/18, myositis 1/18, seizures 1/18). KD shock syndrome (KDSS) was observed in 1.7% of patients (n = 12). Cardiac involvement occurred in 39.6% of patients (n = 286), with coronary vessel ectasia reported in 12% of cases (n = 87), and aneurysms in 25.1% (n = 181) (Table 1). IVIg resistance rate was 19.7% (n = 142). Demographic and clinical data are detailed in Table 1. Laboratory parameters at KD onset and type of received treatment are reported in Supplementary Tables S1 and S2, respectively.

Significant variation in clinical features, were observed across the different ethnic groups. Conjunctivitis ($p < 0.001$) and cheilitis ($p = 0.002$) were more frequent in the other Asian group, while extremity desquamation was more common in Indian patients (44.1%, n = 64) ($p < 0.001$). Musculoskeletal involvement was significantly lower in Indian patients (4.7%, n = 7) compared to Caucasian (14.9%, n = 64) and mixed ethnicities group (16.7%, n = 7) ($p = 0.002$). Gastrointestinal symptoms ($p < 0.001$), lymphadenopathy ($p < 0.001$), and cardiac involvement ($p = 0.003$) were more frequently reported among Indian and other Asian patients. Neurological manifestations were strikingly more prevalent in the Indian subgroup (26.4%, n = 39) and entirely absent in the other Asian group (0.0%, n = 0) ($p < 0.001$). Genitourinary involvement was also significantly higher in the other Asian cohort (27.2%, n = 28) compared to all other groups ($p < 0.001$). Regarding disease phenotype, complete KD was most frequently observed in the other Asian group (59.2%, n = 252) and least in the mixed-ethnicity cohort (38.1%, n = 16), whereas incomplete KD was most prevalent among Indian patients (51.4%, n = 76). Both distributions differed significantly across ethnicities ($p < 0.001$) (Supplementary Table S4).

IVIg resistance was significantly associated with ethnicity ($p = 0.008$), with the highest frequency observed in mixed ethnicity patients (33.3%, n = 14), followed by Caucasians (21.2%, n = 91), Indians (18.9%, n = 28), and other Asians (9.7%, n = 10). No significant differences were observed in age and sex distribution between the resistant and responsive groups. Extremity desquamation ($p = 0.017$), musculoskeletal signs ($p = 0.006$), cardiac involvement ($p < 0.001$), macrophage activation syndrome (MAS) ($p = 0.008$), prolonged fever ($p < 0.001$) and long-term sequelae ($p < 0.001$) were significantly more common in the IVIg-resistant group. Notably, patients presenting with complete KD were significantly less likely to be resistant to IVIg ($p = 0.008$), with higher proportions of resistance observed in incomplete and atypical forms.

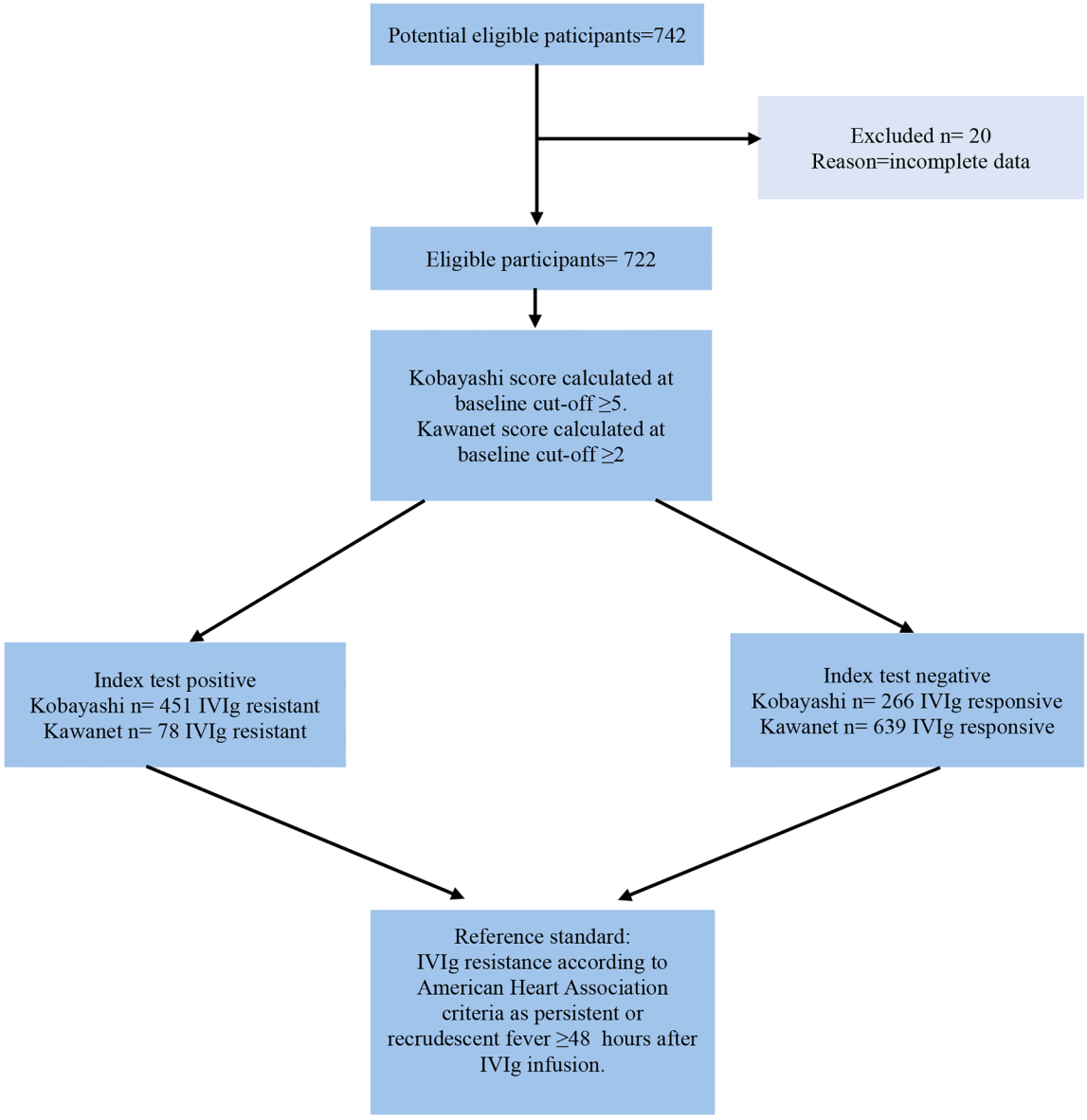

Fig. 1: STARD diagram reports flow of participants through the study.

Statistically significant higher erythrocyte sedimentation rate (ESR) (61 vs 53 mm/h p = 0.002), absolute neutrophil count (8.80 vs 9.75, 10^9/L, p = 0.021), alanine aminotransferase (ALT) (38 vs 26 IU/L, p = 0.001), and aspartate aminotransferase (AST) (38 vs 31 IU/L, p < 0.001) values were reported in IVIg-resistant patients (Supplementary Table S3).

In order to identify independent predictors of IVIg resistance, a univariate logistic regression stratified by ethnicity (Supplementary Table S5), and a multivariable logistic regression analysis on the entire KIWI cohort (Table 2). Prolonged fever duration before treatment (per day increase) was significantly associated with IVIg resistance (OR = 1.09, 95% CI 1.06–1.13, p < 0.001). Compared with patients without cardiac involvement, those with cardiac involvement had higher odds ratio of resistance (OR = 2.25, 95% CI 1.51–3.34 p < 0.001), as did patients with musculoskeletal manifestations compared with those without (OR = 1.89, 95% CI 1.10–3.25, p = 0.022). Conversely, complete KD, when compared with incomplete/atypical forms, was associated with lower odds of IVIg resistance (OR = 0.43, 95% CI 0.27–0.67, p < 0.001). The presence of MAS was also associated with an increased likelihood of resistance relative to patients without MAS, although the confidence interval remained wide despite the elevated odds

Number of patients	722/722 (100)
Sex (female)	275/722 (381)
Median age (years)	2.4/722 (1.19–4.30)
Ethnicity	
Caucasian	429/722 (59.4)
Indian	148/722 (20.5)
Other Asian	103/722 (14.3)
Mixed (African, Hispanic)	42/722 (5.8)
Median fever duration (days)	8 (7–12)
Hospitalization duration	7 (5–10)
Mucocutaneous manifestations	710/722 (98.3)
Cheilitis	505/722 (69.9)
Conjunctivitis	558/722 (77.3)
Extremities-edema	306/722 (42.2)
Extremities desquamation	216/722 (29.9)
Musculoskeletal manifestations[a]	84/722 (11.6)
Gastrointestinal manifestations[b]	303/722 (42.0)
Lymphoid involvement[c]	425/722 (58.9)
Neurological manifestations[d]	75/722 (10.4)
Genitourinary signs[e]	76/722 (10.5)
Cardiac involvement	286/722 (39.6)
Pericardial effusion	38/722 (5.3)
Myocarditis	56/722 (7.8)
Coronary ectasia	87/722 (12.0)
Coronary aneurisms	18//722 (25.1)
KD category	
Complete	396/722 (54.8)
Incomplete	296/722 (41.0)
Atypical	18/722 (2.5)
KDSS	12/722 (1.7)
MAS	12/722 (1.7)
IVIg resistance	142/722 (19.7)
Cardiac sequalae	67/722 (9.3)

KD = Kawasaki disease; KDSS = Kawasaki disease shock syndrome; MAS = macrophage activation syndrome; IVIg = intravenous immunoglobulins. [a]Musculoskeletal manifestations: arthralgia, arthritis, myositis, myalgia, bone pain. [b]Gastrointestinal manifestations: abdominal pain, vomiting, diarrhoea, GI bleeding, intestinal vasculitis, hepatitis. [c]Lymphoid involvement: cervical lymphadenopathy ≥1.5 cm, generalized lymph nodes enlargement, hepatomegaly, splenomegaly. [d]Neurological manifestations: irritability, aseptic meningitis, seizures, cranial nerve palsy, vertigo, ataxia. [e]Genitourinary signs: sterile pyuria), urethritis, dysuria, scrotal swelling/epididymitis.

Table 1: **Demographic profile, initial clinical presentation, and long-term cardiovascular outcomes in the KIWI study cohort.**

ratio (OR = 4.14, 95% CI 1.13–15.13, p = 0.032). The ROC analysis based on predicted probabilities from the multivariable logistic regression model yielded an AUC of 0.739 (SE 0.023, 95% CI 0.694–0.784; p < 0.001) in distinguishing IVIg-resistant from IVIg-responsive patients (Supplementary Figure S1).

Other clinical and demographic variables, including conjunctivitis, cheilitis, extremities oedema, gastrointestinal and lymphoid involvement, neurological involvement, age at diagnosis and ethnicity, did not reach statistical significance. The inclusion of laboratory parameters in the multivariable logistic regression model did not improve the model's predictive performance.

	OR	95% CI (Lower-Upper)	p
MAS	4.137	1.131–15.130	0.032
Cardiac involvement	2.248	1.514–3.337	<0.001
Musculoskeletal involvement	1.889	1.097–3.254	0.022
Fever duration at diagnosis (days)	1.093	1.059–1.128	<0.001
Complete KD	0.427	0.274–0.665	<0.001

KD = Kawasaki disease; MAS = macrophage activation syndrome; OR = odds ratio, CI = confidence interval. Reference categories: no MAS, no cardiac involvement, no musculoskeletal involvement, and non-complete KD (Incomplete/Atypical/KDSS). Fever duration analysed as a continuous predictor.

Table 2: **Multivariate Logistic regression model including IVIg-resistance clinical predictors.**

Regarding the performance of IVIg resistance prediction scores within the KIWI cohort, the Kobayashi score yielded a balanced accuracy of 55% with sensitivity and specificity of 71% and 39%, respectively (Fig. 2 and Table 3). The Kawanet demonstrated a comparable overall performance, with a balanced accuracy of 53% reporting a sensitivity and specificity of 16% and 90%, respectively (Fig. 2 and Table 3). When stratified by the three main ethnic subgroups—Caucasian, Indian, and other Asian—the performance of both scores remained consistent with the trends observed in the overall population (Fig. 3 and Table 3).

Discussion

This international, multicentre cohort study, encompassing 722 Kawasaki Disease (KD) patients from 19 paediatric rheumatology units across 9 countries, provides valuable insight into the clinical expression and treatment response of KD in ethnically diverse populations. The size of the cohort, its geographic spread, and the inclusion of non-Caucasian ethnicities offer a unique opportunity to assess demographic and clinical features, identify novel ethnic-specific trends in KD phenotype and evaluate the performance of predictive scores beyond Asian-centric settings.

The median age and male predominance in our cohort are consistent with other international cohorts.[8–15,17–20] A particularly notable feature of our results is the high proportion of incomplete (41%) and atypical (2.5%) KD presentations, accounting for over 43% of all cases. This is a markedly elevated rate compared to historical Japanese cohorts, where the incidence is highest and typical presentation are most common.[17,18] The predominance of incomplete forms in our population may reflect both the multiethnic composition and the diagnostic challenges in non-endemic regions. Similar trends have been observed in Mediterranean and Western contexts, where atypical or incomplete KD is more frequently reported and may

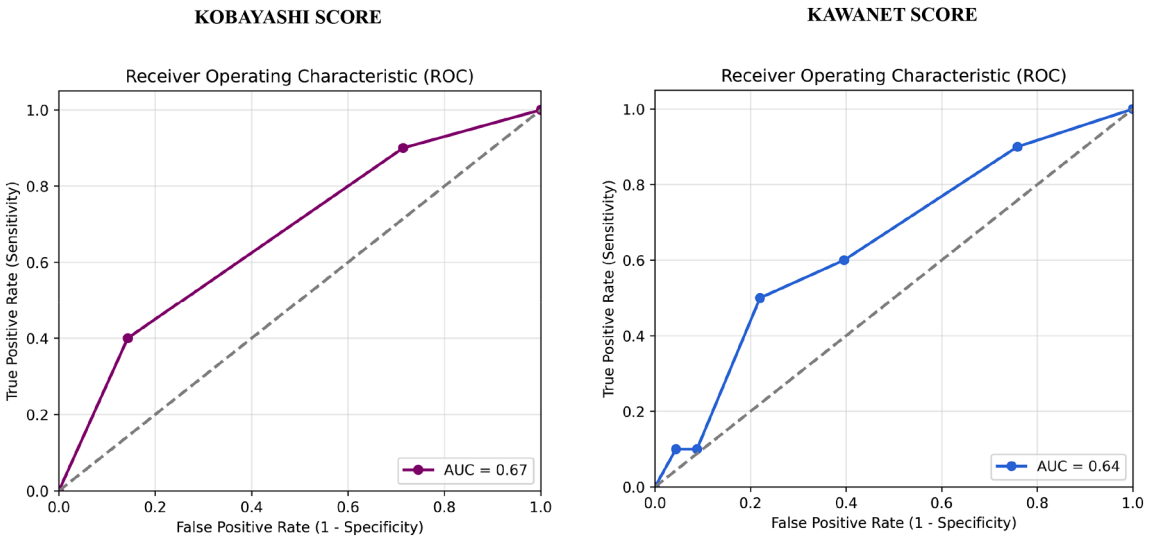

Fig. 2: ROC curves reporting Kobayashi and Kawanet score performance in the KIWI cohort.

contribute to diagnostic delays.[11,19,20] This finding highlights the need for broader awareness of non-classical presentations, especially in centres with high ethnic heterogeneity. Consistent with these findings, in our cohort, complete KD was most frequently observed in the other Asian group (59.2%), whereas incomplete KD predominated among Indian patients (51.4%). KDSS, a severe presentation characterized by hypotension and myocardial dysfunction, was rare overall (1.7%) but more frequent in the mixed ethnicity subgroup (11.9%). This is consistent with previous data showing overrepresentation of African American and Hispanic children among KDSS cases.[21–23]

Marked ethnic differences were observed in mucocutaneous and systemic features. Conjunctivitis and cheilitis were significantly more common in other Asian patients, suggesting stronger mucosal involvement, in line with previous Japanese and Korean reports.[24–26] Conversely, Indian patients presented a distinct pattern with a significantly higher frequency of neurological signs (26.4%), possibly suggesting ethnic-specific neuroinflammatory susceptibility. Genitourinary signs, often underreported, were disproportionately present in other Asian patients (27.2%, $p < 0.001$), raising the question as to whether these signs are overlooked in standard clinical assessments or genuinely more prevalent in this population.

Notably, 25.1% of patients in our cohort developed CAA, a proportion exceeding that reported in several Japanese cohorts and more closely aligning with data from Hispanic and European populations.[15,17–20,27] This relatively high CAA prevalence likely results from multiple factors, including delayed diagnosis, particularly in incomplete or atypical cases-both of which were overrepresented among IVIg-resistant patients. Furthermore, differences in early detection and treatment approaches could contribute to variability in cardiac outcomes. Genetic predisposition may also play a role, especially in mixed or diverse populations. The elevated CAA rate draws attention to the importance of early echocardiographic assessment in patients with risk factors such as prolonged fever, IVIg resistance, or systemic inflammation, and may justify the implementation of more aggressive follow-up strategies in selected subgroups. However, due to the multicenter design of the study, reliability and validity in measuring CAA among the 19 countries belonging to the KIWI study (detection bias) cannot be excluded.

The IVIg resistance rate was 19.7%, in line with previously reported rates in both Asian and non-Asian

Score	Ethnicity	Balanced accuracy	Sensitivity	Specificity	PPV	NPV
Kobayashi						
	Overall population	0.553	0.713	0.392	0.226	0.846
	Caucasian	0.563	0.736	0.390	0.248	0.844
	Indian	0.530	0.643	0.417	0.205	0.833
	Other Asian	0.593	0.900	0.286	0.122	0.963
	Mixed	0.583	0.611	0.556	0.355	0.781
Kawanet						
	Overall population	0.533	0.161	0.904	0.259	0.812
	Caucasian	0.543	0.184	0.903	0.340	0.802
	Indian	0.514	0.179	0.850	0.217	0.816
	Other Asian	0.528	0.100	0.956	0.200	0.906
	Mixed	0.506	0.056	0.956	0.333	0.717

PPV = positive predictive value, NPV = negative predictive value.

Table 3: **Classification performance metrics for the two clinical scores across the entire patient cohort and stratified by ethnic subpopulations (Caucasian, Indian, other Asian and Mixed).**

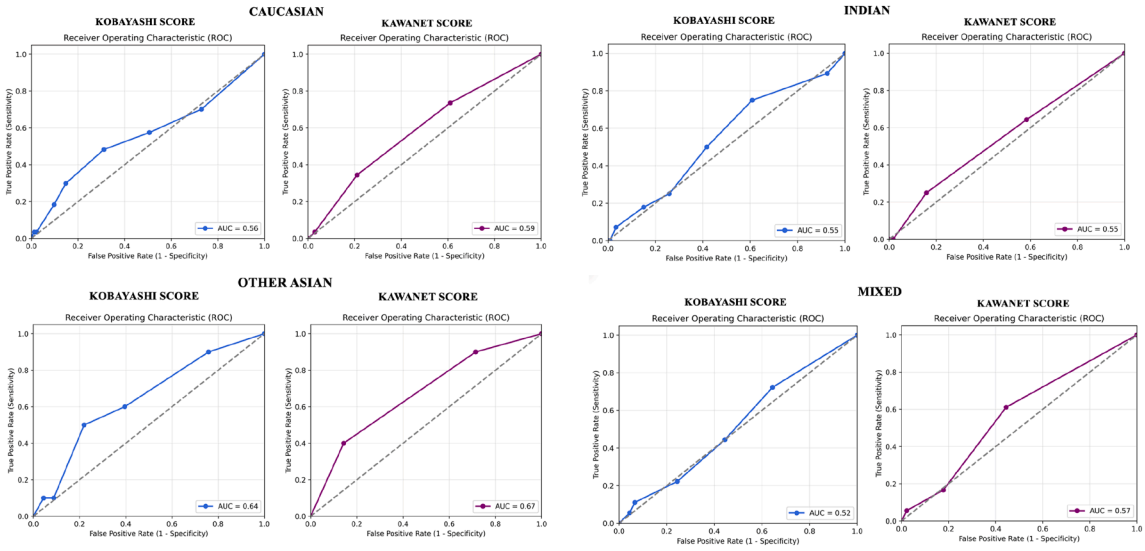

Fig. 3: ROC curves reporting Kobayashi and Kawanet score performance in the four ethnic subgroups of Kawasaki disease patients included in the KIWI cohort.

populations.[17–20,28] IVIg resistance was reported in 22% of patients in the Kawanet cohort,[15] closely mirroring the 21% rate observed in Kobayashi's original Japanese cohort.[9] Ethnicity was significantly associated with IVIg resistance in our study: mixed-ethnicity patients exhibited the highest rate (33.3%), followed by Caucasian (21.0%), Indian (18.9%), and other Asian (9.7%) subgroups. The mixed-ethnicity subgroup appears heterogeneous in both genetic and sociodemographic background, and its limited sample size does not support firm conclusions regarding the higher resistance rate observed. While potentially meaningful, this finding should be interpreted with caution and considered exploratory rather than definitive. However, these results are in line with the evidence reported by Loomba et al., who observed increased treatment failure rates among African, Hispanic and Caucasian children.[28]

Clinically, IVIg-resistant patients more frequently exhibited extremity desquamation, musculoskeletal involvement, MAS, cardiac complications, and long-term sequelae.

MAS showed a high odds ratio (OR = 4.37) but with a very large confidence interval, likely reflecting the limited case numbers. However, although rare, MAS was almost exclusively observed in the resistant subgroup, as mirror of hyperinflammation and poor therapeutic response setting. These findings, reflecting MAS as complication of a severe KD, underscore the milestone role of early recognition and timely management.[29,30]

IVIg-resistant patients had significantly elevated ESR, absolute neutrophil counts, ALT, and AST levels, suggesting a higher degree of systemic inflammation and hepatic involvement, features supported by the Kobayashi and Egami scoring systems.[8,9] However, in our multivariable logistic regression model, only prolonged fever before treatment, cardiac and musculoskeletal involvement remained independent predictors of resistance, while complete KD was protective (OR = 0.427, $p < 0.001$). Because IVIg was systematically administered at the time of diagnosis and at a uniform dose of 2 g/kg across centres, treatment timing largely overlapped with fever duration at presentation. Accordingly, longer fever duration prior to diagnosis, used as a proxy for time to treatment, emerged as an independent predictor of IVIg resistance. Additionally, the inverse association between complete KD and IVIg resistance underscores the prognostic value of disease phenotype. Indeed, when the presentation is complete, KD is more promptly recognized, allowing earlier initiation of therapy. Consistently, in our cohort, patients with overt clinical features exhibited a shorter median duration of fever before treatment (8 days in complete KD and 7.5 days in KDSS), whereas those with incomplete or atypical forms experienced significantly longer durations (9 and 10.5 days, respectively; $p = 0.035$). Interestingly, musculoskeletal symptoms were significantly associated to IVIg resistance in the regression model ($p = 0.022$). Despite being underreported in the literature, these symptoms may represent extra-vascular inflammation, and future studies might focus and include these findings. Interestingly, traditional mucocutaneous signs, such as conjunctivitis, cheilitis, oedema, or lymphadenopathy, along with ethnicity, neurologic signs, and age, were not independently predictive of resistance.

First-line therapy mainly consisted of a single 2 g/kg dose of IVIg. In resistant cases, a second-line treatment, most commonly a second IVIg dose or systemic glucocorticoids, was administered. According to the recent updated AHA recommendations, an intensification of first-line treatment should be considered in high-risk patients.[31] These strategies include the early addition of glucocorticoids or biologic agents during the initial treatment phase in selected subgroups of patients with KD.[31] However, in our cohort, biologics such as infliximab and anakinra were rarely employed. While the AHA statement proposes a shift toward individualized therapy based on risk stratification, including the early use of these agents in high-risk patients under 6 months of age, with CAA at baseline or with features suggestive of MAS,[31] at the moment this implementation remains limited in real world practice. This may be attributed to institutional variability, financial constraints, and lack of robust validation studies.

Prediction scores for IVIg resistance remain a key focus of KD research, especially in settings where timely identification may prompt an adjunctive/intensive treatment. We analysed the performance of two validated IVIg resistance prediction tools, Kobayashi and Kawanet, although their adoption differs across population. In our multiethnic cohort, both performed sub optimally. The Kobayashi score yielded a sensitivity of 71% and specificity of 39% (balanced accuracy 55%), while the Kawanet score had a sensitivity of 16% and specificity of 90% (balanced accuracy 53%).

The modest performance of these scores aligns with previous external validations.[10–13,20,32–34] The Kobayashi score, originally developed in Japanese populations,[9,16] consistently shows poor sensitivity and/or specificity in non-Asian populations.[10,14,20,32,33] A recent meta-analysis confirmed that the Kobayashi, Egami, and Sano scores all have limited external applicability. The summary C–statistics were 0.65 (95% confidence interval [CI] 0.57–0.73), 0.63 (95% CI 0.55–0.71), 0.58 (95% CI 0.55–0.60) for the Kobayashi, Egami, and Sano models, respectively. All models showed low positive predictive values (0.14–0.39) and high negative predictive values (0.85–0.92).[33]

Notably, in our study, score performance did not significantly differ across the three largest ethnic subgroups. Similar findings were reported by Loomba et al., who demonstrated the limited sensitivity of the Egami score across all ethnic groups in a U.S. cohort.[28] This limitation is especially evident in our Indian subgroup, where both the Kobayashi and Kawanet scores failed to identify IVIg resistance adequately, signalling the methodological challenge of applying static thresholds to a dynamic, multifactorial condition such as KD.

The Kawanet score, specifically developed in a French cohort excluding Asian patients,[15] failed to demonstrate generalizable predictive accuracy in our large population, although due to its apparent ethnic and geographic specificity should have been better fit and more suitable. Later on, the Kawanet score, integrating cardiac ultrasound parameters, as hence named Kawanet-echo-score, improved its performance in a French Italian validation study. However, this score system remains of restricted applicability, limited to emergency setting, and un-reliable for a wider use.[35] While echocardiography is pivotal for cardiac risk stratification, its limited availability prior to IVIg administration in many centres weaken its utility for score-based triage and hampers its validity.

Of note, recent meta-analyses pointed out the limitations of single population scoring systems and suggested a shift toward risk models developed and validated in multinational cohorts.[33,34] Lam et al. have also proposed machine-learning-based algorithms to overcome the limitations of linear prediction. However, even these approaches have struggled to achieve satisfactory sensitivity and specificity when externally validated.[36] In our experience, the logistic regression model, although statistically significant, demonstrated similar limitations: very high sensitivity for responders (98.3%) but poor specificity for resistant cases (7.7%). This imbalance reinforces the need for inclusive, dynamic prediction models that account for clinical phenotype, timing of intervention, and potentially emerging biomarkers.

Our study presents several limitations. First, the retrospective component may have introduced information bias, particularly for subjective symptoms such as irritability or musculoskeletal involvement, which may be under-reported or inconsistently documented in clinical records. Moreover, recruitment from paediatric rheumatology units may represent a potential limitation; however, given the routine cardiological assessment and shared cardiology–rheumatology follow-up across centres, the risk of selection bias or underestimation of cardiac involvement is likely minimal. Second, IVIg resistance was not centrally adjudicated, potentially contributing to variability in classification across centres. Third, although completeness was high for core clinical and laboratory variables, some laboratory parameters were not consistently available and could not be included in all analyses. In addition, differences in healthcare organisation and socioeconomic context across participating centres may have influenced referral pathways, diagnostic thresholds, access to specialist care and timing of treatment initiation. Despite the adoption of shared AHA diagnostic criteria and standardised procedures, unmeasured inter-centre variability cannot be fully excluded and should be considered when interpreting differences in disease course or treatment response. These health-system and socioeconomic drivers, although not systematically measured, represent plausible modifiers of clinical presentation and management heterogeneity within the cohort. A further consideration concerns ethnicity-

related observations. Although differences were identified among ethnic groups, these results derive from an observational design and should therefore be interpreted as associative rather than causal. Ethnicity represents a multifaceted construct shaped by genetic ancestry, socioeconomic factors, healthcare access and environmental context—variables that were not comprehensively captured and may partly underlie the patterns observed. Moreover, the mixed-ethnicity subgroup was small and heterogeneous (e.g., Hispanic and African descent), limiting the strength of subgroup-specific conclusions and warranting cautious interpretation.

Nevertheless, the diversity of patient backgrounds and healthcare settings contributes positively to the external relevance of our findings and reflects real-world KD management across heterogeneous systems. These results should be regarded as hypothesis-generating and may serve as a foundation for future research in larger, more ethnically balanced cohorts, with dedicated assessment of structural and socio-demographic determinants.

Our findings have direct implications for clinical practice. First, ethnicity and clinical phenotype should be carefully considered in risk stratification strategies for IVIg resistance. Second, currently available tools—including the Kobayashi and Kawanet scores—are inadequate for reliably predicting resistance in multi-ethnic populations. While the inclusion of echocardiographic findings and/or coronary abnormalities may improve predictive accuracy,[35] these parameters are not always available before starting a timely treatment initiation and needs accuracy, standardization and trained skills for appropriate detections.

In summary, there is a pressing need for more inclusive, biomarker-enriched, dynamically adaptive predictive models. Integrating laboratory, clinical features, and imaging findings with proteomic and simple transcriptomic biomarkers represents a promising approach. The development of these models will require large-scale, prospective, multiethnic registries with harmonized data collection protocols.

Ultimately, improving the early identification of IVIg-resistant patients will require not only better predictive algorithms but also a deeper understanding of the disease immunopathology, particularly in under-represented ethnic groups, to ensure diagnostic and therapeutic precision for all KD children.

Contributors

MVM: Data curation, Formal analysis, Investigation, Writing—original draft. MVM AND GS: Conceptualization, Methodology, Funding acquisition, Project administration, Supervision, Writing—original draft. MVM, GC, EB, AB: Statistical analysis. VP, MC, AT, SV, JA, WS, BS, SO, SR, JSM, RH, PP, ARF, AK, NB, LV, DM, MCM, AT, RP, MM, JC, RS, KU, ZB, YB, MG, EP, NR: Investigation, Validation, Writing-review and editing. NR, MG, EP: Software. MVM and VP accessed and verified the underlying data. All the authors reviewed the manuscript.

Data sharing statement

Data derived from this study are available upon reasonable request to the corresponding author through the PReSTaR domain in accordance with applicable data protection regulations and ethical agreement (https://www.pres-tar.org/).

Declaration of interests

All the authors declare no competing interests.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.eclinm.2026.103813.

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