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CLINICAL RESEARCH ARTICLE

# Comparison of IVIG resistance predictive models in Kawasaki disease

Ummusen Kaya Akca[1], Elif Arslanoglu Aydin[2], Hayrettin Hakan Aykan[3], Oguzhan Serin[2], Erdal Sag[1], Selcan Demir[1], Erdal Atalay[1], Muserref Kasap[1], Ezgi Deniz Batu[1], Tevfik Karagoz[3], Yelda Bilginer[1] and Seza Ozen[1]

**BACKGROUND:** We aimed to compare the ten different scores (by Kobayashi, Egami, Harada, Formosa, Sano, Piram et al., Wu et al., Yang et al., Tan et al., and Kanai et al.) to assess their performance in predicting IVIG resistance in Turkish children.
**METHODS:** Complete and incomplete KD patients diagnosed with KD at Hacettepe University between June 2007 and September 2019 were evaluated retrospectively.
**RESULTS:** A total of 129 patients, 79 boys (61.2%), with a median age 36 (IQR 19.5–57.0) months were evaluated. Sixteen patients (12.4%) had IVIG resistance. Sensitivity was low for all the ten scores. Tan, Sano, and Egami predictive models had the highest specificity (97.3, 89.4, 86.7%, respectively). Almost all scoring systems distinguished the group of patients with low risk for IVIG resistance but could not differentiate IVIG-resistant patients. Multivariate analysis for the laboratory features showed that platelet count $<300 \times 10^9$/L and GGT serum levels were independent risk factors for IVIG resistance (OR: 3.896; 95% CI: 1.054–14.404; $p = 0.042$ and OR: 1.008; 95% CI: 1.001–1.015; $p = 0.050$).
**CONCLUSIONS:** The current scoring systems had a low sensitivity for predicting the risk for IVIG resistance in Turkish children. On the other hand, increased serum GGT levels and low platelet count were risk factors for predicting IVIG resistance.

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**IMPACT:**

- Intravenous immunoglobulin (IVIG) resistance may be observed in 10–20% of patients diagnosed with Kawasaki disease.
- Coronary artery involvement is more frequent in IVIG-resistant patients.
- It is important to predict the patients who might develop IVIG resistance to improve prognosis.
- The performance of the IVIG resistance predictive models in Kawasaki disease in our population is limited due to the low sensitivity.

## INTRODUCTION

Kawasaki disease (KD) is an acute systemic vasculitis predominantly affecting medium-sized vessels, mainly the coronary arteries.[1] The incidence of disease varies between countries but is more common in East Asian countries, such as Japan, Korea, and Taiwan.[2] There are no epidemiologic studies on the incidence of KD in Turkey. We only know that it constitutes about 9% of the childhood vasculitis.[3] Coronary artery lesions are the most important complication of the disease. Intravenous immunoglobulin (IVIG) treatment within the first 10 days of disease significantly reduces the prevalence of coronary artery involvement.[4,5] While 25% of the untreated patients develop coronary artery abnormalities, this rate decreases to 3–5% in patients who had early treatment.[6] However, 10–20% of the KD patients are resistant to IVIG treatment.[7] The definition of IVIG resistance is persistent or recurring fever at least 36 h after the end of the IVIG infusion.[4,8] These patients require second-line therapy with a repeated dose of IVIG and/or corticosteroids, infliximab, or other biologics.[9] Coronary artery involvement is higher in IVIG-resistant patients compared to IVIG-responsive patients.[10] It is important to predict the patients who might develop IVIG resistance to improve prognosis.

In order to detect the risk factors of IVIG resistance, a number of predictive models including clinical and laboratory parameters of patients have been identified, such as Kobayashi, Egami, Sano scoring systems from Japan and Formosa scoring system from Taiwan. Sensitivity and specificity of scores may differ between populations. Do et al. reported that positive Kobayashi score could be used to identify high-risk population for IVIG resistance in Korean patients with KD.[11] Davies et al. reported that Kobayashi score had a low sensitivity for predicting IVIG resistance in British population.[12] A predicted model may not be sensitive or specific enough when performed in other ethnic groups. In our study, we aimed to evaluate and compare ten different risk scores to predict IVIG resistance in Turkish children. We also identified the predictors of IVIG resistance in our population.

[1]Division of Pediatric Rheumatology, Department of Pediatrics, Faculty of Medicine, Hacettepe University, Ankara, Turkey; [2]Department of Pediatrics, Faculty of Medicine, Hacettepe University, Ankara, Turkey and [3]Division of Pediatric Cardiology, Department of Pediatrics, Faculty of Medicine, Hacettepe University, Ankara, Turkey
Correspondence: Seza Ozen (sezaozen@gmail.com)

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## METHOD

This study included retrospective analysis of 129 patients diagnosed with KD at the Hacettepe University Children's Hospital between June 2007 and September 2019. Diagnosis of KD was based on the criteria of the American Heart Association (AHA)[4]: the presence of fever for at least 5 days accompanied by the presence of at least 4 of the following 5 findings: bilateral non-exudative conjunctival injection, unilateral cervical lymphadenopathy (LAP), changes in the lips and oral cavity, skin rash, and changes in extremities, including indurative angioedema and desquamation. Incomplete KD was diagnosed in the presence of unexplained prolonged fever, two or three diagnostic criteria, and supporting compatible laboratory or echocardiogram findings.[4] Patients who had complete or incomplete KD were included in the study. Classification of the coronary abnormalities was performed according to the AHA guideline.[4] Demographic and clinical features of patients, including sex, age, presence of symptoms, duration of fever, time until diagnosis, response to IVIG therapy, additional treatment in case of IVIG resistance, and coronary artery status, were recorded. Laboratory parameters, including hemoglobin, hematocrit, white blood cell count, number and percentage of neutrophils and lymphocytes, platelet count, mean platelet volume, alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin (TB), direct bilirubin (DB), γ-glutamyl transferase (GGT), electrolytes, brain natriuretic peptide (BNP), lactic dehydrogenase (LDH), albumin, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), and urine analyses, were noted prior to IVIG treatment.

The following IVIG resistance risk scores were evaluated: Kobayashi, Egami, Harada, Sano, and Kanai scoring systems from Japan[10,13–16]; Formosa scoring system from Taiwan[17]; three different scores from China[18–20]; and a scoring system for non-Asian populations[21] (Table 1). Their sensitivity and specificity to predict IVIG resistance in our population were investigated. Also, the effectiveness of mean platelet volume-to-lymphocyte ratio in predicting coronary artery involvement reported by Bozlu et al. was assessed.[22] A lower mean platelet volume-to-lymphocyte ratio (≤2.5) was associated with coronary artery involvement in their study. This study has been approved by Hacettepe University Ethics Commission (Approval number: GO 20/568).

### Statistical analysis

Descriptive statistics were presented as frequency, percentage, mean, standard deviation (SD), median, and interquartile range (IQR). Shapiro–Wilk test, histograms, and Q-Q graphics were used for evaluation of normality of distribution. Fisher's Exact Test was used in the analysis of relationships between categorical variables. For the comparison of continuous variables, Student's *t* test was used with variables that showed normal distribution, while Mann–Whitney *U* test was used in those with non-normal distribution. Sensitivity and specificity of scores were calculated by generating 2 × 2 tables. receiver operating characteristic (ROC) curves and the area under the curves (AUCs) were computed to evaluate the performance of the predictive models in predicting IVIG resistance.

Univariate and multivariate logistic regression analyses were applied to identify risk factors for IVIG resistance in KD and to determine the independent risk factors. Odds ratios (ORs) were calculated with 95% confidence intervals (CIs). Statistical analyses were performed by using the SPSS version 20.0 package program. *p* Values of <0.05 were accepted to show statistical significance.

## RESULTS

A total of 129 patients, 79 boys (61.2%), with a median age 36 (IQR 19.5–57.0) months were included in the study. All people in Turkey

**Table 1.** Score models predicting the risk of IVIG resistance in Kawasaki disease patients.

| Year/nation | Score models | Point(s) |
|---|---|---|
| 2006 Japan | *Kobayashi prediction model (≥4 high risk)* | |
| | Sodium ≤133 mmol/L | 2 |
| | Days of illness at initial treatment ≤4 days | 2 |
| | Aspartate aminotransferase ≥100 IU/L | 2 |
| | Percentage of neutrophils ≥80% | 2 |
| | C-reactive protein ≥10 mg/dL | 1 |
| | Age ≤12 months | 1 |
| | Platelet count ≤300 × $10^9$/L | 1 |
| 2006 Japan | *Egami prediction model (≥3 high risk)* | |
| | Age <6 months | 1 |
| | Days of illness <4 days | 1 |
| | Alanine aminotransferase ≥80 IU/L | 2 |
| | C-reactive protein ≥8 mg/dL | 1 |
| | Platelets <300 × $10^9$/L | 1 |
| 1991 Japan | *Harada prediction model (≥4 high risk)* | |
| | Male gender | 1 |
| | Age ≤12 months | 1 |
| | Hematocrit <35% | 1 |
| | WBC count >12,000/$mm^3$ | 1 |
| | Platelet count <350,000/$mm^3$ | 1 |
| | C-reactive protein >3 mg/dL | 1 |
| | Albumin <3.5 g/dL | 1 |
| 2007 Japan | *Sano prediction model (≥2 high risk)* | |
| | C-reactive protein ≥7.0 mg/dL | 1 |
| | Total bilirubin ≥0.9 mg/dL | 1 |
| | AST ≥ 200 IU/L | 1 |
| 2015 Taiwan | *Formosa prediction model (≥3 high risk)* | |
| | Positive lymphadenopathy | 1 |
| | Percentage of neutrophils ≥60% | 2 |
| | Albumin <3.5 g/dL | 1 |
| 2020 China | *Wu prediction model (≥6.5 high risk)* | |
| | Age ≤24 months | 3 |
| | Neutrophil counts ≥10 × $10^9$/L | 3 |
| | Lymphocyte counts ≤3 × $10^9$/L | 3.5 |
| | Mean platelet volume ≥10.5 fL | 3.5 |
| | Albumin ≤37 g/L | 2.5 |
| 2018 China | *Yang prediction model (≥6 high risk)* | |
| | C-reactive protein ≥90 mg/L | 3 |
| | Percentage of neutrophils ≥70% | 2.5 |
| | Sodium <135 mmol/L | 3 |
| | Albumin <35 g/L | 2.5 |
| | Total bilirubin >20 μmol/L | 5 |
| 2020 Non-Asian population | *Piram prediction model (≥2 high risk)* | |
| | ALT level >30 IU/L | 1 |
| | Hepatomegaly | 1 |
| | Lymphocyte count <2400/$mm^3$ | 1 |
| | Time to treatment <5 days | 1 |
| 2020 China | *Tan score* | |
| | Log-odds of having IVIG resistance = 5.772 + 0.173 × RDW + (−0.001) × Platelet count + (−2.966) × Percentage of lymphocyte + 0.006 × Total bile acid + (−0.055) × Sodium + (−0.061) × Albumin +0.787 × D-CALs1 + 1.035 × D-CALs2 + 1.740 × D-CALs3 + (−0.738) × Age | |
| 2020 Japan | *Kanai prediction model* | |
| | Neutrophil-to-lymphocyte ratio ≥4.11 and platelet-to-lymphocyte ≥119 | |

*RDW* red blood cell distribution width, *D-CALs* degree of coronary artery lesions (D-CALs1, localized dilatation with internal diameter ≤4 mm; D-CALs2, dilatation with the internal diameter between 4 and 8 mm, *D-CALs3* dilatation with the internal diameter ≥8 mm.

**Table 2.** Comparison of demographic, clinical, and laboratory features in IVIG-resistant and IVIG-responsive groups.

| Variables | IVIG-resistant group (*n*: 16) | IVIG-responsive group (*n*: 113) | *p* |
|---|---|---|---|
| Age, months | 44.6 (10–151) | 42.75 (2–161) | 0.87 |
| Sex (male/female) | 10/6 | 69/44 | 0.91 |
| Duration of fever (day) | 9.75 (5–30) | 8.4 (3–32) | 0.15 |
| Time to treatment (day) | 9.56 (2–30) | 9.12 (3–45) | 0.88 |
| Cervical LAP, *n* (%) | 12 (75%) | 79 (69.9%) | 0.67 |
| Changes in extremities, *n* (%) | 15 (93.8%) | 91 (80.5%) | 0.19 |
| Skin rash, *n* (%) | 11 (68.8%) | 89 (78.8%) | 0.36 |
| Conjunctival injection, *n* (%) | 10 (62.5%) | 94 (83.2%) | 0.08 |
| Oral mucosal changes, *n* (%) | 15 (93.8%) | 93 (82.3%) | 0.46 |
| Complete KD, *n* (%) | 10 (62.5%) | 77 (68.1%) | 0.65 |
| Coronary involvement, *n* (%) | 4 (25%) | 40 (35.4%) | 0.41 |
| Hemoglobin (g/dL), median (IQR) | 10.8 (9.2,11.7) | 10.9 (10.05, 11.7) | 0.46 |
| Hematocrit (%), median (IQR) | 32.0 (26.6, 34.9) | 32.3 (29.8, 34.8) | 0.52 |
| Red blood cell distribution width (%), median (IQR) | 15.6 (13.0, 17.2) | 14.3 (13.6, 15.3) | 0.15 |
| White blood cell ($10^9$/L), median (IQR) | 14.1 (8.2, 20.0) | 14.8 (11.2, 17.4) | 0.91 |
| Neutrophil count ($10^9$/L), median (IQR) | 6.6 (5.1, 14.5) | 8.7 (6.5, 12.0) | 0.47 |
| Percentage of neutrophil, median (IQR) | 66.2 (44.9, 76.3) | 67.8 (51.5, 77.5) | 0.64 |
| Lymphocyte count ($10^9$/L), median (IQR) | 2.8 (0.7, 5.2) | 2.9 (2.0, 4.6) | 0.32 |
| Percentage of lymphocytes, median (IQR) | 18.5 (8.9, 34.4) | 22.4 (13.8, 32.9) | 0.33 |
| Platelet count ($10^9$/L), median (IQR) | 334.0 (210.7, 540.7) | 414.0 (314.5, 602.0) | 0.12 |
| Mean platelet volume (fL), median (IQR) | 7.7 (6.5, 8.6) | 7.1 (6.6, 7.5) | 0.08 |
| Neutrophil-to-lymphocyte ratio (NLR), median (IQR) | 3.0 (1.2, 5.9) | 2.9 (1.5, 5.3) | 0.93 |
| Platelet-to-lymphocyte ratio (PLR), median (IQR) | 153.8 (88.0, 274.8) | 132.1 (93.5, 224.6) | 0.56 |
| C-reactive protein (mg/dL), median (IQR) | 14.8 (6.1, 21.6) | 9.5 (4.0, 16.4) | 0.17 |
| Erythrocyte sedimentation rate (mm/h), median (IQR) | 68.5 (44.7, 80.7) | 60.0 (39.0, 76.2) | 0.42 |
| Serum sodium (mEq/L), median (IQR) | 135.5 (132.5, 137.0) | 136.0 (134.0, 138.0) | 0.84 |
| Creatinine (mg/dL), median (IQR) | 0.31 (0.26, 0.41) | 0.27 (0.22, 0.36) | 0.28 |
| Albumin (g/dL), median (IQR) | 3.4 (3.0, 3.8) | 3.6 (3.2, 3.9) | 0.36 |
| Alanine aminotransaminase (U/L), median (IQR) | 41.0 (18.7, 112.7) | 26.0 (14.0, 58.2) | 0.07 |
| Aspartate aminotransferase (U/L), median (IQR) | 43.5 (32.5, 91.7) | 32.0 (24.0, 45.2) | **0.01** |
| Glutamyl transpeptidase (U/L), median (IQR) | 79.6 (37.0, 186.0) | 27.5 (14.0, 88.5) | **0.007** |
| Total bilirubin (mg/dL), median (IQR) | 0.67 (0.26, 2.4) | 0.30 (0.22, 0.60) | **0.05** |
| Direct bilirubin (mg/dL), median (IQR) | 0.17 (0.06, 1.66) | 0.08 (0.04, 0.14) | **0.03** |
| Serum calcium (mg/dL), median (IQR) | 8.7 (8.4, 9.1) | 9.1 (8.8, 9.6) | **0.01** |
| Pro-BNP, median (IQR) | 52.5 (10, —) | 43.5 (10.0, 83.4) | 0.9 |
| Lactic dehydrogenase, median (IQR) | 725.0 (572.0, 1007.5) | 398.0 (263.0, 552.0) | **0.008** |
| Sterile pyuria | 5 (31.3%) | 19 (16.8%) | **0.04** |

*KD* Kawasaki disease, *LAP* lymphadenopathy.
Statistically significant $p < 0.05$ values are in bold.

are white Caucasian but have different ethnicities. The majority are Turkish but we have Kurds, Albanians, Laz people, etc. We are not able to comment on the ethnicity of the children in our study population. Sixty-nine patients (53.5%) were diagnosed in spring and winter. Complete KD was diagnosed in 87 patients (67.4%). All patients had fever and the median duration of fever was 7.0 (IQR 5–10) days. The frequency of other disease criteria were as follows: changes in the lips and oral cavity in 108 (83.7%), changes in extremities in 106 (82.2%), conjunctival injection in 104 (80.6%), skin rash in 100 (77.5%), and cervical LAP in 91 (70.5%) patients. The median time to the diagnosis following the onset of symptoms was 7 (IQR 5–10.5) days, which was significantly longer in patients with incomplete KD ($p = 0.01$).

The number of patients with IVIG resistance was 16 (12.4%). While cervical LAP, changes in extremities, and oral mucosal changes were more common in the patients with IVIG resistance, skin rash and conjunctival injection were more frequent in IVIG-responsive group. However, these differences did not reach statistical significance ($p > 0.05$; Table 2). Second-line therapy for IVIG-resistant group were as follows: second dose IVIG in 3 (18.7%), corticosteroids in 7 (43.7%), both corticosteroid and second dose IVIG in 6 patients (37.5%), and additional infliximab therapy in 1 patient (6.2%).

Ten different risk scores for IVIG resistance were calculated and their sensitivity and specificity were evaluated (Table 3). Yang score had the highest sensitivity (50%) among all scores while the sensitivity of others were all <50%. The Tan predictive model had the highest specificity, and the specificity of the other scores ranged from 51.3 to 89.4%. Yang score had the highest AUC (0.600), but the differences between scores were not statistically significant ($p = 0.17$; Table 3).

**Table 3.** Evaluation of specificity and sensitivity of IVIG resistance scoring systems.

| | Sensitivity (%) | Specificity (%) | Area under the ROC curve | *p* value | 95% CI |
|---|---|---|---|---|---|
| Kobayashi score | 25 | 80.5 | 0.52 | 0.72 | 0.65–0.84 |
| Egami score | 25 | 86.7 | 0.55 | 0.44 | 0.40–0.71 |
| Harada score | 31.2 | 54.9 | 0.56 | 0.37 | 0.42–0.71 |
| Sano score | 25 | 89.4 | 0.57 | 0.35 | 0.41–0.73 |
| Formosa score | 43.8 | 51.3 | 0.47 | 0.75 | 0.32–0.62 |
| Wu score | 12.5 | 70.8 | 0.41 | 0.28 | 0.27–0.55 |
| Yang score | 50 | 70.8 | 0.60 | 0.17 | 0.45–0.75 |
| Piram score | 31.2 | 78.8 | 0.55 | 0.51 | 0.39–0.70 |
| Tan score | 12.5 | 97.3 | 0.54 | 0.52 | 0.38–0.70 |
| Kanai score | 25.0 | 73.3 | 0.50 | 0.92 | 0.33–0.68 |

*ROC* receiver operating characteristic, *CI* confidence interval.

**Table 4.** Evaluation of risk factors for IVIG resistance and coronary artery involvement in children with Kawasaki disease by univariate logistic regression analysis.

| | *B* | S.E. | Wald | *p* | OR | 95% CI |
|---|---|---|---|---|---|---|
| *IVIG resistance risk factors* | | | | | | |
| Age ≤12 months | −0.83 | 1.069 | 0.604 | 0.437 | 0.436 | 0.054–3.542 |
| Total bilirubin (mg/dL) | 0.529 | 0.235 | 5.042 | 0.025 | 1.697 | 1.070–2.692 |
| Alanine aminotransaminase (U/L) | 0.004 | 0.002 | 4.925 | 0.026 | 1.004 | 1.001–1.008 |
| Aspartate aminotransferase (U/L) | 0.006 | 0.003 | 4.148 | 0.042 | 1.006 | 1.000–1.012 |
| Glutamyl transpeptidase (U/L) | 0.008 | 0.003 | 5.713 | 0.017 | 1.008 | 1.001–1.015 |
| Platelet count <300,000/mm$^3$ | 1.311 | 0.550 | 5.671 | 0.017 | 3.708 | 1.261–10.906 |
| C-reactive protein (mg/dL) | 0.031 | 0.027 | 1.370 | 0.242 | 1.032 | 0.979–1.087 |
| *Coronary artery involvement risk factors* | | | | | | |
| Male sex | −0.934 | 0.411 | 5.169 | 0.023 | 0.393 | 0.176–0.879 |
| Age under 1 year | 1.354 | 0.556 | 5.937 | 0.015 | 3.873 | 1.303–11.507 |
| Changes in extremities | 0.925 | 0.468 | 3.910 | 0.048 | 2.523 | 1.008–6.313 |
| Lymphocyte count | 0.214 | 0.086 | 6.141 | 0.013 | 1.239 | 1.046–1.467 |
| Mean platelet volume to lymphocyte ratio (≤2.5) | 1.022 | 0.417 | 6.020 | 0.014 | 2.779 | 1.228–6.289 |
| IVIG resistance | 0.497 | 0.610 | 0.664 | 0.415 | 1.644 | 0.497–5.433 |
| Incomplete KD | 0.413 | 0.391 | 1.117 | 0.290 | 1.511 | 0.703–3.249 |

*OR* odds ratio, *CI* confidence interval.

Compared with the IVIG-responsive group, the IVIG-resistant group had higher serum AST, GGT, TB, DB, and LDH levels; lower serum calcium levels; and a higher frequency of sterile pyuria (Table 2). The risk factors for IVIG resistance were evaluated by univariate analysis. High serum levels of TB, ALT, AST, GGT, and platelet count $<300 \times 10^9$/L were associated with developing IVIG resistance (OR: 1.697; 95% CI: 1.070–2.692; $p = 0.025$, OR: 1,004; 95% CI: 1.001–1.008; $p = 0.026$, OR: 1.006; 95% CI: 1.000–1.012; $p = 0.042$, OR: 1.008; 95% CI: 1.001–1.015; $p = 0.017$, and OR: 3.708; 95% CI: 1.261–10.906; $p = 0.017$, respectively). On the other hand; younger age and high CRP levels were not risk factors (Table 4).

Five risk factors that were significant in the univariate analysis were re-evaluated with multivariate analysis; platelet count $<300 \times 10^9$/L and GGT serum levels were independent risk factors for IVIG resistance (OR: 3.896; 95% CI: 1.054–14.404; $p = 0.042$ and OR: 1.008; 95% CI: 1.001–1.015; $p = 0.050$; Table 5).

Coronary artery involvement was detected in 44 of the 129 patients (34.1%). There were coronary artery dilatations (*Z* score 2–<2.5) in 14 patients (10.8%), small aneurysm (*Z* score ≥2.5–<5) in 18 patients (13.9%), medium aneurysm (*Z* score ≥5–<10 and absolute dimension <8 mm) in 7 patients (5.4%), and giant aneurysm (*Z* score ≥10 or absolute dimension ≥8 mm) in 5 patients (3.8%). Patients with extremity changes had more common coronary artery involvement ($p = 0.04$). We observed a significant association with young age, male sex, high levels of white blood cell count, high lymphocyte count, high lymphocyte percentage, low mean platelet volume-to-lymphocyte ratio ($p = 0.01$, $p = 0.02$, $p = 0.04$, $p = 0.002$, $p = 0.009$, $p = 0.002$, respectively), and coronary abnormalities. In univariate analysis, male sex, age under 1 year, changes in extremities, high lymphocyte counts, and low mean platelet volume-to-lymphocyte ratio (≤2.5) were associated with coronary involvement (OR: 0.393; 95% CI: 0.176–0.879; $p = 0.023$, OR: 3.873; 95% CI: 1.303–11.507; $p = 0.015$, OR: 2.523; 95% CI: 1.008–6.313; $p = 0.048$, OR: 1.239; 95% CI: 1.046–1.467; $p = 0.013$, and OR: 2.779; 95% CI: 1.228–6.289; $p = 0.014$, respectively) while duration of fever, IVIG resistance, incomplete form of disease, white blood cell count, ESR, and CRP did not reach significance (Table 4). The multivariate analysis identified young age (<1 year of age) and male sex as independent risk factors for coronary involvement (OR: 4.534; 95% CI: 1.227–16.758; $p = 0.023$ and OR: 0.372; 95% CI: 0.144–0.959; $p = 0.041$, respectively; Table 5).

**Table 5.** Evaluation of risk factors for IVIG resistance and coronary artery involvement in children with Kawasaki disease by multivariate logistic regression analysis.

| | *B* | S.E. | Wald | *p* | OR | 95% CI |
|---|---|---|---|---|---|---|
| *IVIG resistance risk factors* | | | | | | |
| Platelet count <300,000/mm$^3$ | 1.360 | 0.667 | 4.154 | 0.042 | 3.896 | 1.054–14.404 |
| Total bilirubin (mg/dL) | 0.265 | 0.314 | 0.713 | 0.398 | 1.303 | 0.705–2.410 |
| Alanine aminotransaminase (U/L) | −0.005 | 0.007 | 0.635 | 0.425 | 0.995 | 0.982–1.008 |
| Aspartate aminotransferase (U/L) | 0.005 | 0.006 | 0.688 | 0.407 | 1.005 | 0.993–1.017 |
| Glutamyl transpeptidase (U/L) | 0.007 | 0.004 | 3.825 | 0.050 | 1.008 | 1.001–1.015 |
| *Coronary artery involvement risk factors* | | | | | | |
| Age under 1 year | 1.512 | 0.667 | 5.137 | 0.023 | 4.534 | 1.227–16.758 |
| Male sex | −0.988 | 0.483 | 4.186 | 0.041 | 0.372 | 0.144–0.959 |

*OR* odds ratio, *CI* confidence interval.

## DISCUSSION

In our study, IVIG resistance was present in 12.4% of patients. This rate varies between 11 and 26% in different countries.[23–25] Genetic and immunological predisposition might have an impact on the development of IVIG resistance. Identifying high risk factors for IVIG resistance would play an important crucial role in KD treatment. In addition to scoring systems such as the Kobayashi, Harada, and Egami scores, new prediction models have been developed in recent years to assess the risk of IVIG resistance.[18–20]

We compared the performance of ten different score models predicting IVIG resistance. The sensitivity in all scoring systems were ≤50% while specificity values were acceptable. Tan, Sano, and Egami scores had the highest specificity (97.3%, 89.4%, and 86.7%, respectively) in our population. Tan et al. had excluded incomplete KD patients, but we found that the predictive model still had high specificity despite the inclusion of incomplete KD patients to our study.[20] Sleeper et al. performed the Japanese IVIG risk scores (Kobayashi, Egami, and Sano risk scores) in the North American cohort and found low sensitivity and good specificity, as in our study.[26] Tremoulet et al. evaluated the performance of Egami score in 362 children with KD in San Diego county and found low sensitivity (38.3%) and good specificity (83.8%) as well.[7] Existing scoring systems distinguished the group of patients with low risk for IVIG resistance but could not differentiate patients who might need second-line treatment and require closer observation. Therefore, for predicting IVIG resistance, centers could use one or more of these scoring systems. However, they should be aware of the low sensitivity for all these scoring systems in Turkish patients. We suggest that platelet counts and GGT levels could help predicting IVIG resistance in KD patients.

The difference in the incidence of IVIG resistance among populations may also be related to genetic and immunological factors.[7,27] Although we expected the non-Asian 2020 score suggested by Piram et al. to perform better in our eastern Mediterranean population, this was not the case.

The association between clinical parameters and IVIG resistance varies among KD patients in different ethnic groups and regions. A meta-analysis of 28 studies comprising 4442 IVIG-resistant and 21,818 IVIG-responsive KD patients showed that patients with cervical LAP, swelling of the extremities, polymorphous rash, oral mucosa alterations, and taking IVIG treatment within the first 4 days of symptoms were associated with IVIG resistance.[28] However, there was no significant association between clinical symptoms and IVIG resistance in our study.

The IVIG-resistant group had increased serum AST, GGT, TB, DB, and LDH levels; decreased serum calcium levels; and increased frequency of sterile pyuria compared to the IVIG-responsive patients (Table 2). Platelet count <300 × 10$^9$/L and increased GGT serum levels were detected as independent predictors for IVIG resistance (Table 5). Previous studies have confirmed the association between IVIG resistance and GGT.[7,29,30] It is hypothesized that changes in GGT levels can contribute to IVIG resistance by blocking IVIG-induced neutrophil apoptosis.[29]

Low platelet count was used as a parameter predicting IVIG resistance in Kobayashi, Egami, and Tan scoring systems. Chantasiriwan et al. reported low platelet count as an IVIG resistance risk factor, as well.[31] In a study evaluating 5151 KD patients in Korea, high serum N-terminal pro-BNP, CRP, AST, and ALT levels were associated with IVIG resistance.[32] In our previous study, we also reported increased GGT serum levels as an independent predictor for IVIG resistance.[30]

KD is the leading cause of acquired heart disease in children in developed countries.[4] The previous studies reported the rate of coronary artery involvement around 15–20%, whereas it was 34.1% in our study.[33,34] On the other hand, the incidence of coronary artery involvement has been reported as approximately 25–33%, and the rate of IVIG resistance was noted as 3–15% in studies from Turkey.[35,36] Increased incidence of coronary artery involvement despite low IVIG resistance may be due to the genetic or environmental factors in the eastern Mediterranean or may be due to being a tertiary reference hospital. The high variability in timing of IVIG administration (2–45 days) might explain the high frequency of coronary artery involvement, including the high rate of giant aneurysms. Li et al. reported that initial administration of IVIG ≤4 days after the onset of symptoms were more likely to be IVIG resistant.[28] Also, receiving IVIG treatment beyond 10 days of onset of symptoms was identified as a risk factor for coronary involvement.[37] Raising awareness about KD among physicians and starting treatment rapidly in the early period might decrease this rate. Previous studies had showed that the risk of coronary involvement increased in patients younger than 1 year and in those with male sex.[14,38–40]

This study has some limitations. First, it was a retrospective study. Second, since our hospital is a tertiary reference center, the rate of coronary artery involvement may not reflect the population. In addition, the high variability in the timing of IVIG administration might have affected the results of our study. Third, the study consists of single-center data, and multi-center studies are needed. Despite this limitations, the strengths of our study was to evaluate and compare the performances of IVIG resistance scores, many of which were recently published. Turkey is an Eastern Mediterranean country with a Caucasian population and many of the minorities whose exact number is unknown. We evaluated the effectiveness of IVIG prediction models developed in both Asian and non-Asian patients.

## CONCLUSION

Current risk-scoring systems had good specificity but low sensitivity for predicting IVIG resistance in the Turkish population. Increased serum GGT levels and low platelet count were risk factors for predicting IVIG resistance in our society. Further multi-center studies are necessary to develop risk score systems with an effective performance.

## AUTHOR CONTRIBUTIONS

U.K.A., E.A.A., O.S., E.S., S.D., E.A., and M.K. conceptualized and designed the study, drafted the initial manuscript, reviewed and revised the manuscript. H.H.A. conceptualized and designed the study, drafted the initial manuscript, and critically reviewed the manuscript for important intellectual content. E.D.B. and T.K. conceptualized and designed the study, coordinated and supervised data collection, and critically reviewed the manuscript for important intellectual content. Y.B. and S.O. conceptualized and designed the study, coordinated and supervised data collection, and critically reviewed and revised the manuscript. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

## ADDITIONAL INFORMATION

**Competing interests:** The authors declare no competing interests.

**Ethics approval:** This study has been approved by Hacettepe University Ethics Commission (Approval number: GO 20/568). Due to the retrospective nature of the study, informed consent was not required.

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