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ORIGINAL ARTICLE

# Risk factors in IVIG-resistant Kawasaki disease and correlation with Japanese scoring systems — a study from Eastern India

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## Abstract

**Objectives** To assess the risk factors of intravenous immunoglobulin (IVIG)-resistant Kawasaki disease (KD) and to evaluate the performance of the three Japanese risk-scoring systems, namely the Kobayashi, Egami, and Sano scores in predicting IVIG resistance among the Indian patients.

**Methods** Prospective observational study on children admitted with KD at Institute of Child Health, Kolkata, over a period of 16 months, from January 2019 to April 2020. The study included 70 KD patients all of whom were treated with IVIG. Clinical parameters, laboratory variables, and risk scores were compared between the IVIG-responsive and the IVIG-resistant groups.

**Results** A total of 31.4% were IVIG non-responders. Skin rash was found to be significantly associated with IVIG-resistant KD. The IVIG-resistant group had higher total bilirubin, lower albumin, higher CRP levels, and higher ALT and AST levels. High Kobayashi score, high Egami score, and high Sano score were significantly associated with IVIG resistance, individually. Sano score had the highest sensitivity (81.8%) and Kobayashi score had the highest specificity (77.1%) in our cohort.

**Conclusion** The presence of skin rash, high total bilirubin, high CRP, high AST, high ALT, and low albumin were important predictors of IVIG resistance in our population. Among the three scores, Sano score is the most reliable in identifying potential non-responders to IVIG. But Sano score lacked good specificity. Therefore, Indian KD patients may need an exclusive scoring system to predict non-responsiveness to IVIG so that a more aggressive therapy can be instituted at the earliest.

**Key points**
- *Early prediction of IVIG-resistant KD is necessary to limit cardiac injuries.*
- *Sano score has high sensitivity to predict IVIG resistance in Indian population.*

**Keywords** IVIG resistance · Japanese risk scores · Kawasaki disease

## Introduction

Kawasaki disease (KD), an acute-onset systemic vasculitis, is steadily becoming the most common form of medium-sized primary vasculitis. KD particularly affects the coronary arteries, causing coronary artery aneurysms (CAA) in 15–25% of untreated patients while 2–3% of untreated cases die as a result of coronary vasculitis [1]. In view of the frequency and severity of coronary artery complications, there has been increasing interest in treatments to reduce the risk of CAA [2]. Administration of intravenous immunoglobulin (IVIG) lowers the prevalence of CAA to less than 5% [2]. However, 10–15% of KD patients show persistent fever despite treatment with high-dose IVIG (2 g/kg), a condition known as IVIG-resistant KD [3]. As the incidence of KD has increased, cases of IVIG-resistant KD have also increased [4]. It has been seen that children with IVIG resistance are more prone to develop cardiac injury [5, 6]. Therefore, early identification and appropriate treatment of resistant KD are of utmost importance to prevent cardiac damage. Recent research has focused on identification of predictors of IVIG resistance and several risk scoring algorithms have been developed [5,

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7]. In Japan, the Sano, Kobayashi, and Egami risk scores [7, 8] are commonly used. However, the performance of these scores was not satisfactory when applied to children with KD outside Japan. Different countries and ethnic groups will therefore need different models to predict IVIG-resistant KD.

The purpose of this study is to determine the variables associated with IVIG resistance and also to assess the performance of the three Japanese risk-scoring systems, developed to predict IVIG resistance, when applied to the Indian population.

## Methods

### Study design

This single-centre prospective observational study analyzed a series of patients who fulfilled the criteria for KD admitted at the pediatric ward of Institute of Child Health, Kolkata, India, from January 2019 to April 2020. The criteria for the diagnosis of complete KD followed the Japanese criteria (5th revision of the diagnostic guideline for KD). Patients having significant structural cardiac defect not related to KD or having insufficient laboratory data to perform the Kobayashi, Egami, and Sano scores were excluded.

All patients were treated with 2 g/kg of IVIG along with aspirin (30 mg/kg/day) at the acute phase of KD. Patients were classified into two groups:

(1) IVIG-resistant group (defined as those patients who had persistence or recurrence of fever 36 h after the end of initial IVIG infusion)
(2) IVIG-responsive group (defined as those patients who became afebrile after receiving a single dose of IVIG treatment).

Written informed consent was taken from the parents of the study subjects.

Demographic data of age, sex, and duration of fever before IVIG administration as well as clinical features like conjunctival injection, skin rash, mucosal changes, extremity changes, lymphadenopathy, perianal excoriation, and BCG scar reactivation were noted.

Laboratory parameters like total white cell count, neutrophil percentage, lymphocyte percentage, hemoglobin level, platelet count, sodium level, ALT, AST, total bilirubin, albumin, C-reactive protein (CRP), and erythrocyte sedimentation rate (ESR) were noted. Echocardiography was done at diagnosis. The Kobayashi, Egami, and Sano scores were individually calculated for all the study subjects.

### Ethics

The study was approved by the Institutional Ethics Committee of Institute of Child Health, Kolkata (IEC/172/2018).

### Statistical analysis

For statistical analysis, data were entered into a Microsoft Excel spreadsheet and then analyzed by SPSS (version 27.0; SPSS Inc., Chicago, IL, USA) and GraphPad Prism version 5. Data had been summarized as mean and standard deviation for numerical variables and count and percentages for categorical variables. Two-sample *t*-tests for a difference in mean involved independent samples or unpaired samples. Unpaired proportions were compared by chi-square test or Fisher's exact test, as appropriate. $p$-value $\leq 0.05$ was considered statistically significant.

## Results

A total of 71 children were admitted with KD during the 16-month study period, but 1 was excluded due to the presence of moderate VSD. In the final group with 70 patients, 48 (i.e., 68.6%) responded to IVIG (IVIG-responsive group) and 22 (i.e., 31.4%) did not respond to IVIG (IVIG-resistant group). In majority of the responsive cases, defervescence was achieved within 12–24 h except one whose fever subsided after 30 h of IVIG infusion. All resistant cases were given infliximab (IFX) at 5 mg/kg. Of the 22 IVIG-resistant patients, 20 became afebrile within 24 h of IFX administration and remaining 2 within 48 h. However, these findings were not analyzed any further.

In IVIG-resistant group, 13 (59.1%) patients had complete KD and 9 (40.9%) patients had incomplete KD. In both the groups, majority of patients belonged to the age group of 13–60 months (68.2% and 68.8% respectively). There was no significant correlation between IVIG resistance and age, gender, or duration of fever before IVIG treatment.

No significant differences were found between IVIG-responsive and IVIG-resistant groups based on clinical features like conjunctival injection, mucosal changes, extremity changes, lymphadenopathy, perianal excoriation, and BCG scar reactivation ($p$ values non-significant). Interestingly though, skin rash was found to be significantly associated with IVIG-resistant KD (86.4% vs 62.5%; $p$ value = 0.04) (Table 1).

Among the laboratory parameters, the two groups were statistically similar with respect to total counts, neutrophil percentage, lymphocyte percentage, hemoglobin level, platelet count, sodium level, and ESR. However, there was a significant correlation between liver enzymes and IVIG

**Table 1** Comparison of clinical features between IVIG-resistant and IVIG-responsive groups

| Clinical features | IVIG-resistant group | IVIG-responsive group | *p* value | Comment |
|---|---|---|---|---|
| Mean duration of fever before IVIG administration(days) | 6.04 | 7.21 | 0.07 | Non-significant |
| Conjunctivitis | 17 (77.3%) | 36 (75.0%) | 0.84 | Non-significant |
| Mucosal changes | 19 (86.4%) | 42(87.5%) | 0.89 | Non-significant |
| Skin rash | 19 (86.4%) | 30 (62.5%) | **0.04*** | **Significant** |
| Extremity changes | 12 (54.5%) | 29 (60.4%) | 0.64 | Non-significant |
| Lymphadenopathy | 12 (52.2%) | 29 (61.7%) | 0.32 | Non-significant |
| Perianal excoriation | 5 (22.7%) | 20 (41.7%) | 0.12 | Non-significantNon-significant |
| BCG scar reactivation | 4 (18.2%) | 6 (12.5%) | 0.53 | Non-significant |

The symbol * signifies the *p* values which are statistically significant

resistance. The mean ALT (mean ± s.d.) of patients in IVIG-resistant group was 97 ± 87.9 and in IVIG-responsive group, the value came as 62 ± 47.9. The mean AST (mean ± s.d.) of patients was 105 ± 140.07 and 41 ± 22.74 in IVIG-resistant group and IVIG-responsive group respectively. Thus, ALT and AST levels were significantly higher ($p = 0.04$, $p = 0.003$ respectively) in patients with resistant KD. It was also found that compared with IVIG-responsive group, the resistant group had higher total bilirubin (1.34 ± 1.01 vs 1 ± 0.41; *p* value = 0.04), lower albumin (2.9 ± 0.04 vs 3.2 ± 0.32; *p* value = 0.002), and higher CRP levels (136 ± 105.94 vs 121 ± 85.06; *p* value = 0.002).

Out of the 22 IVIG-resistant patients, 14 (63.6%) patients had high Kobayashi score (≥ 4), 15 (68.2%) had high (3–5) Egami score, and 18 (81.8%) had high Sano scores (> 2). So, there was a significant association between IVIG resistance and high Kobayashi, Egami, and Sano scores individually (*p* value = 0.0009; *p* value = 0.01; *p* value = 0.026 respectively). The sensitivity and specificity of Kobayashi score for predicting IVIG resistance were 63.6% and 77.1% respectively (Fig. 1). Positive predictive value was 56.0, negative predictive value was 82.2, and accuracy was 72.8. The sensitivity and specificity of Egami score was 68.2% and 64.6% respectively. Positive predictive value was 46.9, negative predictive value was 81.6, and accuracy was 65.7. The sensitivity and specificity of Sano score came as 81.8% and 45.8% respectively. Positive predictive value was 40.9, negative predictive value was 84.6, and accuracy was 57.0.

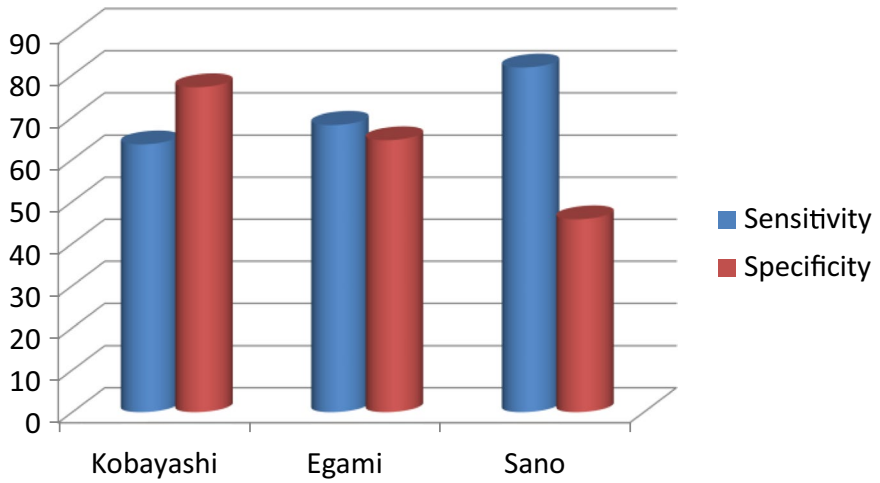


**Fig. 1** Comparison of items evaluated in the three risk scores

| Score | Sensitivity | Specificity |
|---|---|---|
| Kobayashi | 63.6% | 77.1% |
| Egami | 68.2% | 64.6% |
| Sano | 81.8% | 45.8% |

## Discussion

Early identification of IVIG resistance is critical to initiate more effective therapies aimed to limit serious cardiac complications, especially coronary dilatations and aneurysms. This study has focused on recognizing early predictors of IVIG resistance by comparing demographic, clinical, and laboratory parameters between IVIG-responsive and -resistant groups.

Among demographic parameters, we had compared age, gender, and fever duration, none of which was found to be significantly associated with IVIG resistance. This was in stark contrast to previous studies that had established male sex as an independent risk factor [9–11] and also contradicted the findings of Do YS et al. [12] who had demonstrated the febrile period to be significantly longer in the resistant group. According to previous studies, IVIG-resistant cases tend to be younger with peak incidence occurring below 6 months of age [13]. However, there was no significant correlation between IVIG resistance and age in this study. The reason for such differences could be due to the small size of our study group which was not sufficient to demonstrate any difference in demographic pattern. Among clinical features, polymorphous rash has been identified as a risk factor for IVIG resistance, a finding similar to previous studies by [14, 15].

Raised inflammatory markers, hepatic dysfunction, and their association with IVIG resistance have been described before [6, 9, 10, 14, 16–18]. In this study too, high CRP and liver enzymes were found to be strongly associated with IVIG resistance (Table 2). Also, the resistant group was found to have higher bilirubin and lower albumin levels. Raised liver enzymes and high bilirubin may suggest more severe systemic inflammation and vasculitis in liver in resistant cases. Inflammatory cell infiltration in hepatic sinusoids and portal areas and Kupffer cell proliferation have been described in previous literature [19, 20]. Lower albumin levels have been associated with resistant KD and may reflect higher degrees of inflammation and vascular leakage [21–24].

It has been well established that high neutrophil percentage and low sodium levels are predictors of IVIG resistance [14, 16]. The association between low platelet count and IVIG resistance has also been demonstrated before [6, 9, 14, 25]. In contrast, the two groups in our study were similar with respect to total counts, neutrophil percentage, lymphocyte percentage, hemoglobin level, platelet count, sodium level, and ESR. Therefore, it can be inferred that the risk factors for IVIG resistance seem to vary between different countries and ethnic groups. The reasons for such a difference could be due to genetic difference or some other environmental factors and need to be investigated further.

In the Japanese population, the sensitivity and specificity of all the three risk scores were moderate to high (Kobayashi: sensitivity 86%, specificity 67%; Egami: sensitivity 78%, specificity 76%; Sano: sensitivity 77%, specificity 86%) [22, 26, 27]. However, these scores were found to have limited predictive value for IVIG responsiveness in other countries as confirmed by previous studies in North America [11], UK [28], China [15, 29], Italy [30], and Iran [31]. Similar studies carried out in the Korean [17] and German [32] children with KD reported that the Japanese risk-scoring systems had low sensitivity for predicting IVIG resistance. Therefore, the formulation of separate and specific scoring systems for individual countries and ethnic groups is necessary.

In our study, among the three scores, Kobayashi score had the highest specificity (77.1%). However, our main aim being early identification of high-risk patients, high sensitivity of scoring system is essential. Kobayashi score and Egami score lacked good sensitivity (63.6% and 68.6% respectively) whereas Sano score had the highest sensitivity (81.8%) (Fig. 2). Therefore, it can be concluded that among the three scores, Sano score may be the most reliable scoring system when applied to Indian population.

**Table 2** Comparison of laboratory parameters between IVIG-resistant and IVIG-responsive groups

| Laboratory values | IVIG-resistant group | IVIG-responsive group | *p* value | Comment |
|---|---|---|---|---|
| Mean total counts (mm3) | 16,644 | 18,189 | 0.38 | Non-significant |
| Mean neutrophil (%) | 72 | 69 | 0.34 | Non-significant |
| Mean lymphocyte (%) | 24 | 26 | 0.39 | Non-significant |
| Mean Hb (gm/dL) | 9.8 | 10 | 0.57 | Non-significant |
| Mean platelet (lakh/$mm^3$) | 5.6 | 4.9 | 0.57 | Non-significant |
| Mean sodium (mmol/L) | 131 | 132 | 0.28 | Non-significant |
| Mean ALT (IU/L) | 97 | 63 | **0.04*** | Significant |
| Mean AST (IU/L) | 105 | 41 | **0.003*** | Significant |
| Mean total bilirubin (mg/dL) | 1.34 | 1 | **0.04*** | Significant |
| Mean albumin (g/dL) | 2.9 | 3.2 | **0.002*** | Significant |
| Mean CRP( mg/dL) | 136 | 121 | **0.002*** | Significant |
| Mean ESR (mm/h) | 79 | 75 | 0.57 | Non -Significant |

The symbol * signifies the *p* values which are statistically significant

**Fig. 2** Comparison of sensitivity and specificity of Kobayashi, Egami and Sano scores

| Items | Egami score | Kobayashi score | Sano score |
|---|---|---|---|
| CRP | • | • | • |
| Age | • | • | |
| Days of illness | • | • | |
| ALT | • | | |
| Total bilirubin | | | • |
| AST | | • | • |
| Sodium | | • | |
| Neutrophil(%) | | • | |
| Platelet count | • | • | |

The only drawback is that the specificity of Sano score was low (45.8%). The accurate prediction of potentially IVIG-resistant patients still remains a challenge.

This study had several limitations: (1) The sample size was small. (2) The study was conducted in a single center. (3) The study was carried out in a tertiary medical center, so hospital bias cannot be ruled out.

In conclusion, the results of our analyses have shown a correlation between IVIG resistance and presence of skin rash, high total bilirubin, high CRP, high AST, high ALT, and low albumin. Therefore, these parameters can serve as predictors of IVIG resistance and alert clinicians to implement necessary therapeutic approach. Our study has also revealed a significant association between IVIG resistance and high Kobayashi, Egami, and Sano scores. Among the three scores, Sano score had the highest sensitivity and negative predictive value and thus may be considered a useful score in identifying potential IVIG-resistant KD patients. However, Sano score lacked good specificity. Therefore, formulation of an exclusive scoring system for the Indian population is the need of the hour and similar studies focusing on this matter should be encouraged.

**Data availability** The data underlying this article will be shared on reasonable request to the corresponding author.

## Declarations

**Disclosures** None.

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