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Baseline and Dynamic IL-10/IL-2R as Predictors of IVIG Resistance in Kawasaki Disease: A Comparative Study

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Abstract

Objectives

Intravenous immunoglobulin (IVIG) resistance in Kawasaki disease (KD) increases coronary artery lesion risk and necessitates early identification. This study compared the predictive efficacy of baseline serum interleukin-10 (IL-10) combined with interleukin-2 receptor (IL-2R), their dynamic post-treatment changes, and the traditional Kobayashi score for predicting IVIG resistance.

Methods

This retrospective cohort study enrolled 457 KD patients (November 2019–December 2025). Patients were categorized into IVIG-responsive and IVIG-resistant groups. Pre-treatment IL-10 and IL-2R levels and their 24-hour post-IVIG dynamic changes were measured. Multivariate logistic regression identified independent predictors. ROC curves and Bootstrap resampling (500 times) evaluated predictive performance of three models: pre-treatment IL-10 + IL-2R, dynamic changes, and Kobayashi score.

Results

Among 457 patients, 73 (15.97%) were IVIG-resistant. Resistant patients had significantly higher pre-treatment IL-10 (37.80 vs. 11.70 pg/mL) and IL-2R (298.20 vs. 159.65 ×10 U/mL), and greater post-treatment declines (both $P < 0.001$). Multivariate analysis confirmed pre-treatment IL-10 (OR 1.012) and IL-2R (OR 1.007), and their dynamic changes, as independent predictors. The pre-treatment IL-10 + IL-2R model showed excellent discrimination (AUC 0.842), significantly outperforming the Kobayashi score (AUC 0.635, $P < 0.001$). The dynamic change model performed comparably (AUC 0.832). Bootstrap validation confirmed robustness.

Conclusion

Both baseline IL-10 + IL-2R and their dynamic changes demonstrate superior predictive value for IVIG resistance compared to the Kobayashi score, supporting integration of cytokine profiling into clinical practice for early risk stratification and personalized treatment in KD.

Introduction

Kawasaki disease (KD) is an acute, self-limiting systemic vasculitis that predominantly affects children under five years of age and is the leading cause of acquired heart disease in this population in developed countries[1]. The most severe complications are coronary artery lesions (CALs), including dilation, aneurysm, and stenosis, which are strongly associated with long-term cardiovascular morbidity and life-threatening sequelae such as myocardial infarction[2]. Standard first-line therapy consists of high-dose

intravenous immunoglobulin (IVIG) administered alongside aspirin (acetylsalicylic acid), which significantly reduces the risk of CALs—from approximately 15–25% in untreated cases to less than 5% with timely intervention[3]. Nevertheless, approximately 10–20% of children with KD develop IVIG resistance; these non-responders require additional rescue therapies, including repeated IVIG, methylprednisolone, or biologics[4].

Therefore, early and accurate identification of patients at risk for IVIG resistance is critical for optimizing treatment and preventing adverse cardiac outcomes. Conventional prediction approaches have largely depended on clinical parameters embedded in established risk scores, such as the Kobayashi, Egami, Sano, Formosa, and Harada scores. However, external validation studies have consistently shown that these models have limited discriminative performance across diverse ethnic populations, characterized by low positive predictive values (PPV: 0.14–0.39) despite high negative predictive values (NPV: 0.85–0.92)[5].

Emerging evidence points to cytokines as key mediators of the inflammatory cascade in KD, with particular interest in IL-10 and IL-2R[6]. IL-10 is a potent anti-inflammatory cytokine that regulates immune responses by suppressing the synthesis of pro-inflammatory cytokines. Elevated IL-10 levels may contribute to immunoparalysis by inhibiting antigen-presenting cells, potentially diminishing the efficacy of IVIG[7]. Conversely, IL-2R—a marker of T-cell activation—reflects the degree of systemic immune hyperactivation[8]. In KD, sustained T-cell activation and IL-2R upregulation disrupt the Th1/Th2 balance and impair CD8 + T lymphocytes, promoting vascular endothelial injury and increasing the risk of CALs[9–11].

Previous studies have shown that both IL-10 and IL-2R are elevated in IVIG-resistant KD patients and serve as independent predictors[6]. However, most investigations have relied on single pre-treatment measurements, leaving the temporal dynamics of these cytokines during IVIG therapy unexplored. The trajectory of cytokine changes may offer additional insights into the underlying immune mechanisms and enhance predictive accuracy.

In this study, we evaluated the predictive value of pre-treatment IL-10 and IL-2R levels, as well as their dynamic changes, for IVIG resistance in a contemporary KD cohort. We further compared the performance of these cytokine-based models against the conventional Kobayashi risk score to establish their clinical utility.

Materials and Methods

Study Design and Population

This single-center retrospective cohort study enrolled children diagnosed with KD and admitted to the Pediatric Cardiac Center of Xinhua Hospital (affiliated with Shanghai Jiao Tong University School of Medicine) between November 2019 and December 2025. KD diagnosis strictly followed the 2017 American Heart Association (AHA) scientific statement criteria[12]. Figure 1. illustrates the patient

screening and selection process. The study protocol was reviewed and approved by the Institutional Ethics Committee of Xinhua Hospital (Approval No. XHEC-C-2025-243-1).

Children were divided into two groups: IVIG-resistant KD, defined as persistent or recurrent fever (≥ 38.0°C) occurring at least 36 hours after the initial IVIG infusion[4], and IVIG-responsive KD, defined as sustained defervescence without recurrence after the initial IVIG infusion.

Exclusion Criteria: (1) children diagnosed with an infection at enrollment; (2) severe extra-cardiac organ complications; (3) primary congenital immunodeficiency disorders; (4) readmission for recurrent KD; (5) lack of inflammatory factors before and after treatment; (6) non-standard IVIG dosage or modified treatment regimens prior to baseline blood sampling.

Data Collection

Demographic and clinical data were collected from all enrolled patients, including age (months), gender, weight, body mass index (BMI), days from fever onset to IVIG initiation, clinical KD manifestations (fever, Cervical lymphadenitis, conjunctival injection, oral mucosal changes, skin rash, extremity changes), presence of CALs, IVIG response and calculated Kobayashi score for each patient.

Laboratory parameters measured before IVIG administration included: C-reactive protein (CRP), white blood cell count (WBC), neutrophil percentage, lymphocyte percentage, absolute lymphocyte count (ALC), hemoglobin (Hb), platelet count (PLT), alanine aminotransferase (ALT), aspartate aminotransferase (AST), total protein (TP), albumin (ALB) and sodium (Na).

Serum cytokine concentrations—including IL-6, IL-8, IL-10, IL-1β, TNF-α, and IL-2R—were measured using an electrochemiluminescence (ECL) immunoassay on a Cobas e 601 analyzer (Roche Diagnostics, Basel, Switzerland). Venous blood samples were collected at two time points: (1) pre-treatment: at hospital admission, before any medication (including IVIG and aspirin), during febrile episodes (≥ 38.0°C); and (2) post-treatment: 24 hours after completion of the initial IVIG infusion. The dynamic change (difference) for each cytokine was calculated as the pre-treatment value minus the post-treatment value.

Kobayashi Score

The Kobayashi score was calculated for each patient based on the following parameters: serum sodium (≤ 133 mmol/L), AST (≥ 100 IU/L), neutrophil percentage (≥ 80%), CRP (≥ 100 mg/L), PLT (≤ 300 ×10³/L), age (≤ 12 months), and duration of fever before treatment (≤ 4 days). Scores ≥ 4 were considered high risk for IVIG resistance[13].

Statistical Analysis

All statistical analyses were performed using SPSS 27.0 (IBM, USA), R (version 4.1.3) and EmpowerStats software (https://www.empowerstats.net/cn/, X&Y solutions, Inc., Boston, MA). Categorical variables were expressed as n (%) and compared via χ^2 test; non-normal continuous variables were reported as median (interquartile range, IQR) and compared using the Mann–Whitney U test. Two-sided $P < 0.05$ was defined as statistically significant.

All variables with $P < 0.05$ in univariate analysis were incorporated into multivariate logistic regression models with adjustment for age, sex, and BMI. Two separate regression models were constructed: Model 1 incorporated pre-treatment IL-10 and IL-2R levels; Model 2 incorporated post-IVIG dynamic changes of IL-10 and IL-2R. Variance inflation factor (VIF) was calculated to exclude multicollinearity (VIF < 5 indicated no significant collinearity). Odds ratios (OR) and corresponding 95% confidence intervals (CI) were extracted to identify independent predictors of IVIG resistance.

ROC curves were plotted for three prediction strategies: pre-treatment IL-10 + IL-2R combined model, dynamic change IL-10 + IL-2R combined model, and Kobayashi score. Area under the curve (AUC), optimal cutoff value, sensitivity, specificity, Youden index, positive predictive value (PPV), and negative predictive value (NPV) were calculated. Five-hundred-times Bootstrap resampling was conducted for internal validation to evaluate model stability and generalizability.

Results

Baseline Characteristics and Clinical Features

Of the 457 patients enrolled, 73 (16.0%) were resistant to initial IVIG therapy. The two groups were comparable in terms of sex, age, and weight (Table 1). Body mass index was slightly higher in the IVIG-resistant group (median 15.89 vs. 15.71 kg/m², $P = 0.028$). Clinical KD manifestations—including cervical lymphadenitis, conjunctival injection, skin rash, oral mucosal changes, and extremity changes—showed no significant intergroup differences. However, CALs were significantly more frequent in resistant patients (35.62% vs. 11.98%, $P < 0.001$). Although the median Kobayashi score was 2.00 in both groups, the interquartile range was wider in resistant patients (1.00–4.00 vs. 1.00–3.00, $P < 0.001$), indicating a higher-risk score distribution.

Table 1
Baseline demographic and clinical characteristics

Variables	IVIG responsive (n = 384)	IVIG resistant (n = 73)	*P*
Demographic characteristics			
Male, n(%)	239 (62.24%)	46 (63.01%)	0.900
Age in months, median (IQR)	34.98 (18.88, 56.50)	33.13 (20.10, 49.73)	0.694
Weight(kg), median(IQR)	14.00 (11.00, 18.00)	14.00 (11.50, 17.90)	0.656
BMI	15.71 (14.51, 17.05)	15.89 (15.13, 17.59)	0.028*
Clinical characteristics			
Days from fever onset to IVIG initiation, median (IQR)	5.00 (5.00, 6.00)	5.00 (5.00, 6.00)	0.264
Fever, n(%)	384 (100)	73 (100)	1.000
Cervical lymphadenitis, n(%)	335 (87.24%)	64 (87.67%)	0.919
Conjunctival injection, n(%)	365 (95.05%)	69 (94.52%)	0.849
Oral mucosal changes, n(%)	277 (72.14%)	45 (61.64%)	0.072
Skin rash, n(%)	275 (71.61%)	59 (80.82%)	0.104
Extremity changes, n(%)	162 (42.19%)	31 (42.47%)	0.965
kobayashi score, median(IQR)	2.00 (1.00–3.00)	2.00 (1.00–4.00)	< 0.001*
CALs, n(%)	46 (11.98%)	26 (35.62%)	< 0.001*

*$p < 0.05$.

Abbreviations: BMI, body mass index; IQR, interquartile range; IVIG, intravenous Immunoglobulin; CALs, coronary artery lesions.

Routine Laboratory and Cytokine Level Comparisons

Table 2 summarizes routine laboratory parameters, pre-IVIG cytokine concentrations, and post-IVIG dynamic cytokine differences between the two groups. IVIG-resistant patients had significantly higher C-reactive protein, neutrophil percentage, and alanine aminotransferase, together with lower lymphocyte percentage, absolute lymphocyte count, albumin, total protein, and serum sodium ($P < 0.05$ for all).

Platelet count was markedly reduced in resistant patients ($P < 0.001$). Aspartate aminotransferase showed a non-significant upward trend ($P = 0.051$); white blood cell count and hemoglobin were similar.

Table 2
Laboratory and cytokine profiles

Variables	**IVIG responsive (n = 384)**	**IVIG resistant (n = 73)**	***P***
CRP(mg/L), median (IQR)	60.00 (34.75, 92.25)	74.00 (42.00, 109.00)	0.044*
WBC(·10^9/L), median (IQR)	13.03 (9.94, 15.89)	12.54 (8.50, 15.59)	0.445
Neutrophil%, median (IQR)	66.20 (55.30, 76.23)	72.40 (63.00, 83.30)	< 0.001*
Lymphocyte%, median (IQR)	23.95 (16.28, 34.32)	19.10 (11.20, 29.20)	0.001*
ALC(×109/L), median (IQR)	2.86 (2.02, 4.23)	2.24 (1.19, 3.52)	< 0.001*
Hb(g/L), median (IQR)	111.00 (105.00,117.00)	110.00 (103.00,115.00)	0.262
PLT(×109/L), median(IQR)	345.50 (279.75, 427.50)	299.00 (198.00, 367.00)	< 0.001*
ALT(U/L), median (IQR)	23.00 (14.00, 53.00)	32.00 (17.00, 79.00)	0.036*
AST(U/L),median (IQR)	31.00 (25.00, 42.62)	35.00 (27.00, 66.00)	0.051
TP(g/L),median (IQR)	64.40 (60.38, 69.30)	62.40 (58.30, 67.90)	0.027*
ALB(g/L),median (IQR)	37.80 (35.30, 40.42)	36.80 (33.60, 39.00)	0.015*
Na(mmol/L), median(IQR)	136.80 (135.20, 138.50)	135.40 (133.40, 137.10)	< 0.001*
Pre-Treatment			
IL-8(pg/mL), median(IQR)	21.35 (11.95, 58.23)	29.90 (21.10, 75.20)	0.002*
IL-1B(pg/mL), median(IQR)	14.50 (7.43, 24.32)	16.20 (8.75, 33.80)	0.167

*$p < 0.05$.

Abbreviations: ALB, albumin; ALC, absolute lymphocyte count; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CRP, C-reactive protein; Hb, hemoglobin; IL, interleukin; IL-2R, soluble interleukin-2 receptor; IQR, interquartile range; IVIG, intravenous immunoglobulin; TP, total protein; TNF-α, tumor necrosis factor-alpha; WBC, white blood cell count.

Variables	IVIG responsive (n = 384)	IVIG resistant (n = 73)	*P*
IL-6(pg/mL), median(IQR)	38.65 (17.25, 88.03)	61.40 (27.70, 151.00)	0.003*
IL-10(pg/mL), median(IQR)	11.70 (5.85, 22.72)	37.80 (13.10, 83.10)	< 0.001*
TNF-a(pg/mL), median(IQR)	21.20 (15.38, 28.55)	29.30 (22.20, 36.90)	< 0.001*
IL-2R(x10 U/mL), median(IQR)	159.65 (116.70, 228.48)	298.20 (242.60, 449.70)	< 0.001*
Difference			
IL-8(pg/mL), median(IQR)	4.90 (-2.30, 41.85)	13.90 (1.90, 50.90)	0.066
IL-1B(pg/mL), median(IQR)	5.90 (0.00, 16.30)	3.75 (0.00, 15.30)	0.151
IL-6(pg/mL), median(IQR)	34.31 (13.17, 84.67)	53.50 (16.49, 142.58)	0.050
IL-10(pg/mL), median(IQR)	5.13 (0.15, 16.52)	28.30 (7.00, 76.88)	< 0.001*
TNF-a(pg/mL), median(IQR)	0.35 (-4.43, 7.50)	3.00 (-6.60, 12.80)	0.568
IL-2R(x10 U/mL), median(IQR)	39.65 (14.53, 77.70)	136.90 (74.10, 278.90)	< 0.001*
*$p < 0.05$.			
Abbreviations: ALB, albumin; ALC, absolute lymphocyte count; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CRP, C-reactive protein; Hb, hemoglobin; IL, interleukin; IL-2R, soluble interleukin-2 receptor; IQR, interquartile range; IVIG, intravenous immunoglobulin; TP, total protein; TNF-α, tumor necrosis factor-alpha; WBC, white blood cell count.			

Pre-treatment concentrations of IL-8, IL-6, IL-10, TNF-α, and IL-2R were all significantly elevated in the resistant group (all P < 0.01), whereas IL-1β showed no significant difference. After therapy, the dynamic

change (difference) for each cytokine was substantially larger in resistant patients for IL-10 (28.30 vs. 5.13 pg/mL, $P < 0.001$) and IL-2R (136.90 vs. 39.65 × 10 U/mL, $P < 0.001$); whereas IL-8, IL-1β, IL-6, and TNF-α dynamic differences lacked statistical significance ($P > 0.05$).

Multivariate Logistic Regression Analysis of Independent Predictors

Two multivariate logistic regression models were constructed to identify independent predictors of IVIG resistance, with adjustment for age, sex, and BMI. Model 1 incorporated pre-treatment IL-10 and IL-2R concentrations (Table 3), while Model 2 incorporated post-IVIG dynamic changes of IL-10 and IL-2R (Table 4).

Table 3
Multivariable logistic regression analysis of independent predictors of IVIG resistance using pre-treatment cytokine levels

Variables	B	SE	OR(95%CI)	*p*
Sex	0.48	0.34	1.610 (0.820, 3.160)	0.166
Age in months	0.00	0.01	0.999(0.983, 1.015)	0.928
BMI	0.12	0.09	1.131 (0.954, 1.342)	0.157
CALs	1.34	0.38	3.827 (1.831, 7.999)	< 0.001*
CRP(mg/L)	-0.01	0.00	0.994 (0.986, 1.001)	0.106
Neutrophil%	0.01	0.02	1.010 (0.978, 1.043)	0.547
ALC(×109/L)	-0.10	0.14	0.905 (0.690, 1.186)	0.468
PLT(×109/L)	0.00	0.00	0.999 (0.996, 1.002)	0.510
ALT(U/L)	0.00	0.00	0.999 (0.996, 1.003)	0.756
TP(g/L)	0.01	0.03	1.008 (0.948, 1.072)	0.791
ALB(g/L)	-0.01	0.05	0.988 (0.890, 1.098)	0.824
Na(mmol/L)	-0.01	0.07	0.995 (0.872, 1.136)	0.944
IL-8(pg/mL)	0.00	0.00	1.000 (0.999, 1.003)	0.244
IL-6(pg/mL)	0.00	0.00	1.001 (0.999, 1.003)	0.388
IL-10(pg/mL)	0.01	0.01	1.012 (1.001, 1.023)	0.031*
TNF-a(pg/mL)	0.00	0.01	1.002 (0.998, 1.017)	0.738
IL-2R(x10U/mL)	0.01	0.00	1.007 (1.004, 1.010)	< 0.001*

*$p < 0.05$.

Abbreviations: ALC, absolute lymphocyte count; ALB, albumin; ALT, alanine aminotransferase; BMI, body mass index; CALs, coronary artery lesions; CI, confidence interval; CRP, C-reactive protein; IL, interleukin; Na, sodium; OR, odds ratio; SE, standard error; PLT, platelet count; IL-2R, interleukin-2 receptor; TNF-α, tumor necrosis factor-α; TP, total protein.

Table 4
Multivariable logistic regression analysis of independent predictors of IVIG resistance using cytokine difference

Variables	B	SE	OR(95%CI)	*p*
Sex	0.27	0.34	1.311 (0.670, 2.567)	0.429
Age in months	0.00	0.01	0.996 (0.980, 1.011)	0.578
CALs	1.36	0.37	3.875 (1.874, 8.016)	< 0.001*
BMI	0.12	0.09	1.132 (0.957, 1.340)	0.147
CRP(mg/L)	-0.01	0.00	0.995 (0.998, 1.002)	0.148
Neutrophil%	0.01	0.02	1.012 (0.979, 1.046)	0.476
ALC(×109/L)	-0.10	0.14	0.906 (0.682, 1.202)	0.492
PLT(×109/L)	0.00	0.00	0.999 (0.996, 1.002)	0.452
ALT(U/L)	0.00	0.00	1.000 (0.996, 1.003)	0.820
TP(g/L)	-0.01	0.03	0.995 (0.937, 1.056)	0.866
ALB(g/L)	-0.02	0.05	0.982 (0.891, 1.082)	0.715
Na(mmol/L)	-0.05	0.07	0.952 (0.836, 1.084)	0.458
IL-10(pg/mL)	0.01	0.00	1.014 (1.006, 1.021)	< 0.001*
IL-2R(x10U/mL)	0.01	0.00	1.010 (1.006, 1.013)	< 0.001*

*$p < 0.05$.

Abbreviations: ALC, absolute lymphocyte count; ALB, albumin; ALT, alanine aminotransferase; BMI, body mass index; CALs, coronary artery lesions; CI, confidence interval; CRP, C-reactive protein; Na, sodium; OR, odds ratio; SE, standard error; PLT, platelet count; IL-2R, interleukin-2 receptor; TP, total protein.

In Model 1, CALs (OR 3.827, 95% CI 1.831–7.999, P < 0.001), pre-IVIG IL-10 (OR 1.012, 95% CI 1.001–1.023, P = 0.031), and pre-IVIG IL-2R (OR 1.007, 95% CI 1.004–1.010, P < 0.001) were confirmed as independent risk factors for IVIG resistance. All other routine laboratory and cytokine indices lost statistical significance after multivariate adjustment.

In Model 2, CALs (OR 3.875, 95%CI 1.874–8.016, P < 0.001), the change for IL-10 (OR 1.014, 95%CI 1.006–1.021, P < 0.001), and the change for IL-2R (OR 1.010, 95%CI 1.006–1.013, P < 0.001) remained independent predictors of IVIG resistance, consistent with Model 1 results. No multicollinearity was detected across all variables (VIF < 5, see supplement S1 and S2).

Predictive Performance of Combined Biomarkers

Supplementary S3 summarizes the ROC curve metrics of the three prediction models, and Fig. 2. visualizes comparative ROC curves. The pre-treatment IL-10 + IL-2R combined model achieved the highest AUC value (0.842, 95%CI:0.79–0.89), with optimal cutoff value 0.12, sensitivity 73.44%, specificity 84.39%. The dynamic cytokine change combined model exhibited slightly lower AUC (0.832, 95%CI:0.77–0.89) but higher sensitivity (80.73%) at the cost of reduced specificity (76.71%). The Kobayashi score showed markedly inferior discriminative power (AUC 0.635, 95%CI 0.56–0.71), with extremely low specificity of only 38.36%.

Comparative Diagnostic Performance of IL-2R + IL-10 Combinations and the Kobayashi Score

ROC analyses were performed to evaluate the predictive capacity of IL-2R combined with IL-10. As shown in A, the diagnostic efficacy of the pre-treatment IL-2R + IL-10 combination was comparable to that of the dynamic difference (P = 0.26), indicating the baseline measurement alone is sufficient for prediction. Notably, both the dynamic difference model (B) and the pre-treatment combination (C) significantly outperformed the Kobayashi score (both P < 0.01;see in Supplementary S4). Collectively, these findings demonstrate that the IL-2R + IL-10 combination provides superior predictive value over the conventional Kobayashi score, regardless of whether baseline or dynamic changes are assessed.

Discussion

This study systematically compared the predictive efficacy of a baseline IL-10 + IL-2R combination, post-IVIG dynamic cytokine changes, and the Kobayashi score for IVIG resistance in Chinese children with KD. The combined biomarker panel, whether based on pre-treatment levels or dynamic changes, outperformed the conventional Kobayashi risk score, with AUC values of 0.842 and 0.832, respectively. These findings advance our understanding of immune dysregulation in IVIG-resistant KD and provide a clinically applicable tool for early risk stratification.

Mechanistic Basis for IL-2R and IL-10 as Predictive Biomarkers

Among the biomarkers, IL-2R exhibited the strongest discriminative power (AUC 0.825), with high specificity (85.23%) that minimizes false-positive identifications. The IL-2R, which consists of α, β, and γ chains, is an essential component of the high-affinity IL-2R complex that is indispensable for T-lymphocyte activation and proliferation[14]. Elevated IL-2R levels serve as a biomarker of enhanced immune cell activation and have been linked to a range of immune-mediated diseases[6, 15]. In KD, systemic hyperactivation of T cells—including both CD4 + helper and CD8 + cytotoxic subsets—is a well-documented immunological hallmark[16, 17].

Our results demonstrate that higher pre-treatment IL-2R levels are significantly associated with IVIG resistance, consistent with earlier reports linking abnormal T-cell activation to poor treatment

response[18]. Furthermore, the greater dynamic change in IL-2R in resistant patients (136.90 vs. 39.65 ×10 U/mL) suggests that these patients mount a more vigorous, yet ultimately insufficient, immune response to IVIG. This paradoxical observation—higher baseline activation followed by a greater decline—may reflect the inability of IVIG to adequately suppress an excessively hyperactivated T-cell compartment, which necessitates additional immunomodulatory therapy.

IL-10 demonstrated independent predictive value with moderate discriminative ability (AUC 0.767) and higher sensitivity (78.23%) compared to IL-2R. Interleukin-10 (IL-10), a pivotal anti-inflammatory cytokine, modulates immune responses by downregulating the production of pro-inflammatory cytokines and impairing the function of antigen-presenting cells[19]. In KD, dysregulation in the balance between pro-inflammatory and anti-inflammatory cytokines is thought to play a critical role in driving vasculitis pathogenesis[20].

Our findings of the greater post-treatment decline in IL-10 among resistant patients (28.30 vs. 5.13 pg/mL) mirrors the pattern observed for IL-2R. This suggests that IVIG-resistant patients experience a more profound but ultimately inadequate cytokine response, consistent with the hypothesis that these patients have a fundamentally different immunological trajectory.

Notably, other pro-inflammatory cytokines such as IL-6, IL-8, and TNF-α were increased in the univariate analysis between resistant and responsive cohorts, yet their independent predictive value diminished following multivariate adjustment. This suggests that while these mediators represent a broad inflammatory load, they do not possess the disease-specific immune regulatory significance of IL-10 and IL-2R in forecasting IVIG resistance, aligning with our previously published findings.

Superiority of Dynamic Changes as Predictors

An important novel contribution of this study is the evaluation of dynamic cytokine changes (from pre- to 24-hour post-IVIG) as predictors of resistance. The dynamic change model performed comparably to the pre-treatment model (AUC 0.832 vs. 0.842), offering higher sensitivity (80.73% vs. 73.44%) at the expense of slightly lower specificity (76.71% vs. 84.39%). This trade-off may be clinically advantageous in settings where identifying all potential non-responders is prioritized, even at the expense of some false positives.

Dynamic changes provide information not captured by single pre-treatment measurements. The magnitude of cytokine decline reflects the in vivo response to IVIG therapy, offering a functional readout of treatment efficacy. Patients exhibiting greater reductions in IL-10 and IL-2R—despite initially presenting with elevated baseline concentrations—appear to harbor a hyperactivated immune system that mounts a robust yet incomplete response to IVIG. This immunological profile aligns with the concept of immune exhaustion or pathway-level treatment resistance, wherein the immune system's regulatory capacity to suppress inflammation is overwhelmed.

Comparison with Existing Risk Scores

The Kobayashi score—one of the most widely used risk prediction tools—demonstrated poor discriminative ability in our cohort (AUC 0.635), consistent with previous reports of its limited applicability outside Japanese populations[21, 22]. Both the pre-treatment and dynamic cytokine models outperformed the Kobayashi score ($P < 0.001$), highlighting the need for biomarker-based approaches that transcend population-specific clinical parameters.

The superior performance of cytokine-based models is mechanistically grounded. While the Kobayashi score relies on indirect markers of inflammation (CRP, neutrophil percentage, sodium, AST) and demographic factors, IL-10 and IL-2R directly reflect the underlying immune dysregulation driving IVIG resistance. This mechanistic relevance likely accounts for their discriminative power and applicability across populations.

Clinical Implications and Proposed Implementation

The identification of IL-10 and IL-2R as predictors has important translational potential. The optimal cut-offs determined in this study (pre-treatment IL-10 ≥ 2.695 pg/mL, IL-2R ≥ 21.84 × 10 U/mL) provide clinically applicable thresholds that could guide early intervention. Patients exceeding these thresholds—particularly those with both biomarkers elevated—may benefit from prompt consideration of adjunctive therapies, such as corticosteroids or biologics, before developing severe coronary complications.

We propose a two-tiered approach to implementation: Pre-treatment risk stratification: Measure IL-10 and IL-2R at admission. Patients with both markers above threshold are high-risk and may warrant more intensive initial therapy. Dynamic monitoring (24h post-IVIG): Re-measure cytokines 24 hours after IVIG completion. In patients who meet the pre-treatment high-risk criteria, a paradoxical massive decline (large Δ values) in IL-10 and IL-2R—rather than an inadequate drop—should raise a red flag. As our data show, such exaggerated decreases are significantly associated with IVIG resistance ($P < 0.001$), reflecting an intense but futile counter-regulatory response. These patients, especially if fever persists, should be prioritized for early rescue therapy, as they are prone to post-IVIG immune rebound.

Limitations and Future Directions

Several limitations should be acknowledged. First, this was a single-center study, and the relatively small number of IVIG-resistant cases ($n = 73$) may limit generalizability. Second, cytokine levels were measured at only two time points (pre-treatment and 24 hours post-treatment), preventing assessment of longer-term trajectories or peak responses. Third, while we adjusted for key confounders, residual confounding from unmeasured variables cannot be excluded. Fourth, the Kobayashi score—while widely used—may not be the optimal comparator in Chinese populations; future studies should compare our biomarker panel against multiple risk scoring systems. Finally, external validation in multi-center, ethnically diverse cohorts is essential before clinical implementation.

Future research should focus on prospective, multi-center validation of IL-10 and IL-2R as predictive biomarkers in diverse populations. Serial cytokine measurements at additional time points (e.g., 48

hours, 72 hours post-treatment) may provide further insights into the temporal dynamics of immune recovery.

Conclusion

Pre-treatment IL-10 and IL-2R, as well as their dynamic changes following IVIG therapy, are robust independent predictors of IVIG resistance in Kawasaki disease. The combined biomarker panel substantially outperforms conventional risk scores, offering a clinically applicable tool for early risk stratification. The dynamic change model provides complementary predictive information with higher sensitivity, which may be advantageous in certain clinical settings.. These findings support the integration of cytokine profiling into routine KD management to enable personalized, risk-adapted treatment strategies.

Declarations

Competing Interests

The authors have no relevant financial or non-financial interests to disclose.

Ethics approval

This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Institutional Ethics Committee of Xinhua Hospital (Approval No. XHEC-C-2025-243-1). As this was a retrospective analysis of anonymized data, informed consent was waived.

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Author Contribution

All authors contributed to the study conception and design. Material preparation, data collection, prepared figures and analysis were performed by Qiuling Xie, Liya Zhang, Xianting Jiao, and Huiying Wang. The first draft of the manuscript was written by Huiying Wang and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Data availability

Data available on request from the corresponding author.

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Figures

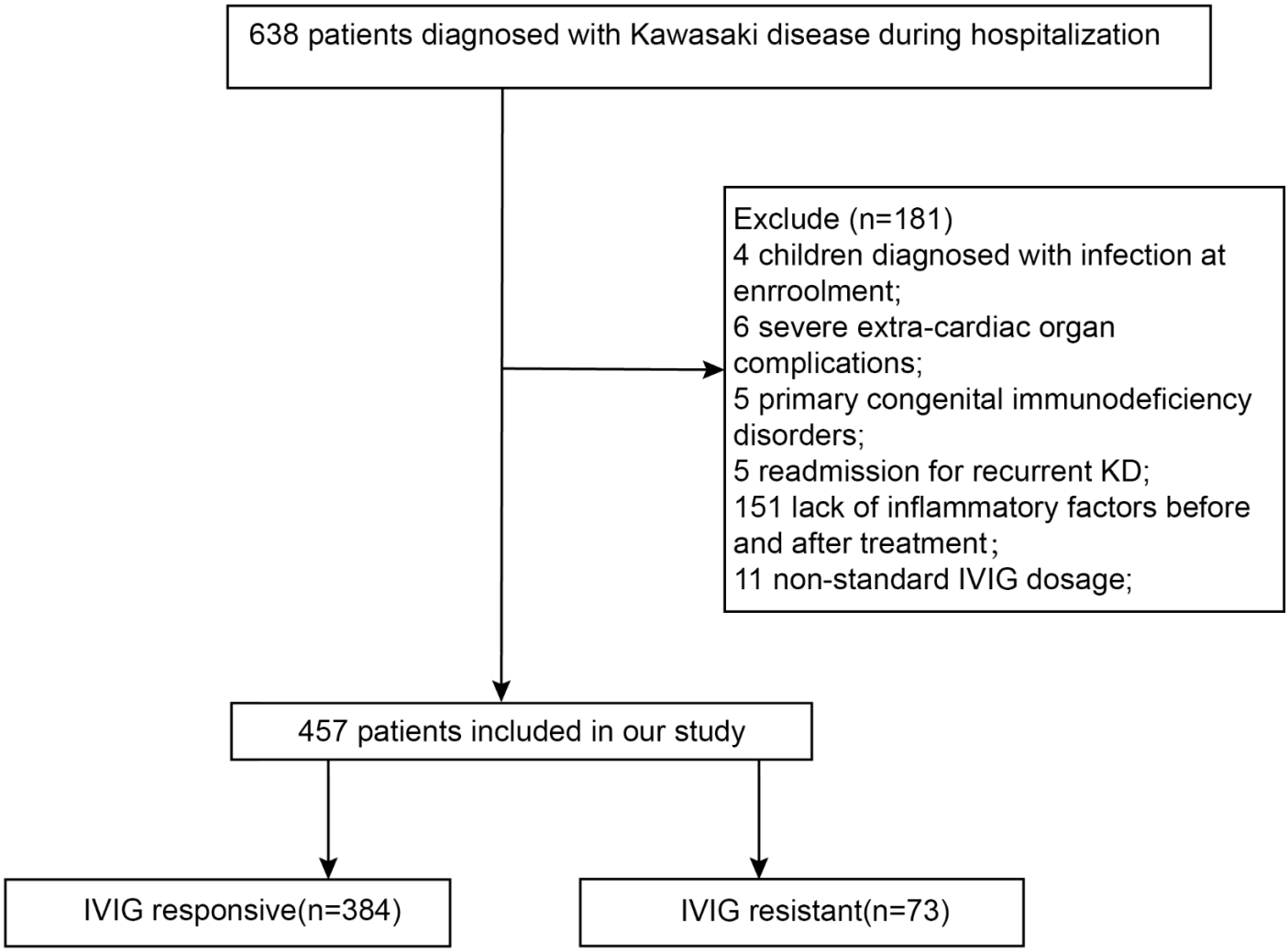

Figure 1

Flow diagram of patient screening and selection

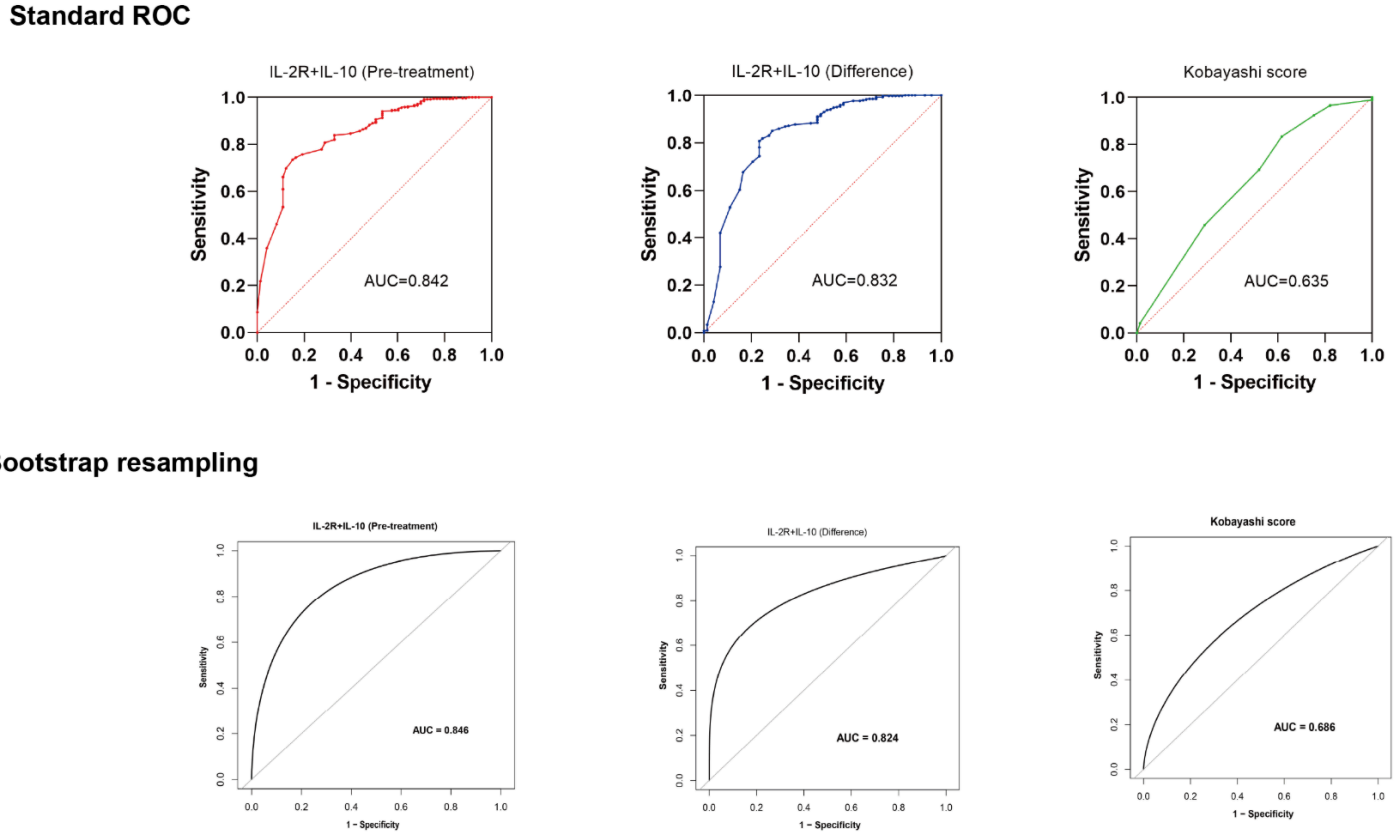

Figure 2

ROC curve analysis of serum IL-2R combined with IL-10 and the Kobayashi score for predicting IVIG resistance, with internal validation via bootstrap resampling

(a–c) Standard ROC curves. (a) Pre-treatment IL-2R + IL-10, AUC = 0.842. (b) Difference in IL-2R + IL-10, AUC = 0.832. (c) Kobayashi score, AUC = 0.635.

(d–f) Bias-corrected ROC curves from bootstrap resampling (500 iterations). Bias-corrected AUCs: (d) 0.846, (e) 0.824, (f) 0.686.

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