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A novel scoring system based on sIL-2R for predicting IVIG resistance in Chinese children with KD

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Abstract

Objective This study aimed to develop a novel scoring system utilizing circulating interleukin (IL) levels to predict resistance to intravenous immunoglobulin (IVIG) in Chinese patients with Kawasaki disease (KD). We further compared this scoring system against six previously established scoring methods to evaluate its predictive performance.

Methods A retrospective analysis was conducted on KD patients who were treated at the cardiovascular medical ward of our institution from January 2020 to December 2022. Six scoring systems (Egami, Formosa, Harada, Kobayashi, Lan and Yang) were analyzed, and a new scoring system was developed based on our data.

Results In our study, 521 KD patients were recruited, 42 of whom (8.06%) were identified as resistant to IVIG. Our study indicated that IVIG-resistant KD patients were at an increased risk for the development of coronary arterial lesions (CALs) ($P=0.001$). The evaluation of IVIG resistance using various scoring systems revealed differing levels of sensitivity and specificity, as follows: Egami (38.10% and 88.52%), Formosa (95.24% and 41.13%), Harada (78.57% and 43.22%), Kobayashi (66.67% and 74.95%), Lan (66.67% and 73.49%), and Yang (69.05% and 77.24%). Our novel scoring system utilizing sIL-2R demonstrated the highest sensitivity and specificity of 69.29% and 83.91%, respectively, and calibration curves indicated a favorable predictive accuracy of the model.

Conclusion Our newly developed scoring system utilizing sIL-2R demonstrated superior predictive performance in identifying IVIG resistance among Chinese patients with KD.

Keywords Kawasaki disease, Intravenous immunoglobulin resistance, Risk scoring systems, Soluble interleukin-2 receptor

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Introduction

Kawasaki disease (KD) is characterized by acute febrile systemic vasculitis that affects small- to medium-sized blood vessels throughout the body, particularly the coronary arteries [1]. It is recognized as the primary contributor to acquired heart disease in children in developed nations [2]. The proper treatment of KD with intravenous immunoglobulin (IVIG) has been shown to significantly decrease the likelihood of developing coronary artery lesions (CALs) from approximately 25–5% [3]. However, 15% ~ 25% of patients with KD remain febrile following the completion of initial IVIG therapy, which necessitates further treatment [4] and increases the risk for the development of CALs [5]. CAL, a serious complication of KD, can lead to coronary stenosis and subsequent ischemic heart disease [6]. Therefore, prompt and accurate identification of KD patients who are resistant to IVIG is crucial for the implementation of more aggressive initial treatment and to potentially prevent the occurrence of CALs. A prior investigation revealed a greater incidence of IVIG resistance in patients exhibiting specific pretreatment laboratory values, such as a C-reactive protein (CRP) level ≥ 100 mg/L [7]. Several scoring systems that incorporate diverse combinations of clinical and laboratory data have been developed in different countries to promptly predict IVIG resistance.

We selected six scoring systems: Egami [8], Formosa [9], Harada [10], Kobayashi [11], Lan [12] and Yang [13]. The Egami and Kobayashi scoring systems originated in Japan, whereas the approach by Harada et al. was developed in the United States. Methods established by Formosa et al., Lan et al., and Yang et al. were developed in China. These scoring systems were selected because of their prominence in the field, particularly within the Asian population. The Lan and Yang scoring systems, which are based on extensive data from Chinese KD patients, were selected to assess their efficacy, specifically in children with KD in China. However, the accuracy of these findings has not been rigorously validated in Chinese children.

Multiple studies have demonstrated that dysregulated expression of proinflammatory cytokines, particularly various interleukins (ILs), such as IL-1 [14], soluble interleukin-2 receptor (sIL-2R) [15], IL-6 [16, 17], IL-10 [15], IL-17 [18], and IL-18 [19], is significantly implicated in coronary artery damage in KD. These cytokines are elevated during the acute phase of KD and have the potential to serve as biomarkers to assess the severity and progression of the inflammatory response in children with KD, thereby aiding in the early prediction of therapeutic outcomes. Notably, increasing evidence has shown a relationship between the sIL-2R level and the development of CALs in KD patients [20, 21], as well as its potential as a marker for IVIG resistance in these patients [22, 23]. However, none of the existing scoring systems incorporates IL levels into their predictive models. Additionally, due to variations in ethnic groups, the selection of predictive factors and the lack of internal and external validation, the sensitivity and specificity of predictive models either do not meet clinical expectations or cannot be applied to different populations [24–26]. Therefore, we aimed to develop a novel scoring system utilizing the level of ILs, particularly sIL-2R, and tested this system in a Chinese KD patient cohort to accurately predict IVIG resistance.

In summary, this study aimed to evaluate the effectiveness of the six risk scoring systems mentioned above and to develop a novel scoring system utilizing IL levels with the goal of individualizing the initial treatment to mitigate the likelihood of CALs in KD patients.

Methods

This study was approved by the Children's Hospital of Nanjing Medical University Research Ethics Committee (202302036-1). The need for informed consent was waived.

Patients

A retrospective analysis was conducted on 839 children who were diagnosed with KD and treated at the cardiovascular medical ward of our institution from January 2020 to December 2022 (Fig. 1). The diagnosis of KD was made according to the clinical criteria outlined in the 2017 American Heart Association (AHA) guidelines [3] and included classical and incomplete presentations. A diagnosis of classical KD required the presence of fever lasting at least 5 days (with the first day of fever considered illness day 1) and at least 4 of the 5 following principal clinical features: (1) oral changes (erythema and cracking of the lips, strawberry tongue, and/or erythema of the oral and pharyngeal mucosa); (2) bilateral bulbar conjunctival injection without exudate; (3) cervical lymphadenopathy, usually unilateral; (4) rash (maculopapular, diffuse erythroderma, or erythema multiforme-like); and (5) peripheral extremity changes (erythema and edema of the hands and feet in the acute phase and/or periungual desquamation in the subacute phase). Incomplete KD was diagnosed when all 3 of the following criteria were met: (1) patients experienced unexplained fever for at least 5 days and were associated with 2 or 3 clinical criteria; (2) CRP level ≥ 30 mg/L and/or a erythrocyte sedimentation rate (ESR) ≥ 40 mm/h; and (3) at least 3 supplemental laboratory criteria (anemia for age, platelet count (PLT) $\geq 450\times10^9$/L after the 7th day of fever, albumin (ALB) < 30 g/L, elevated alanine aminotransferase (ALT) level, white blood cell count (WBC) $\geq 15\times10^9$/L, WBC in urine ≥ 10 WBC/hpf) or positive echocardiogram. The children were divided into two groups: those

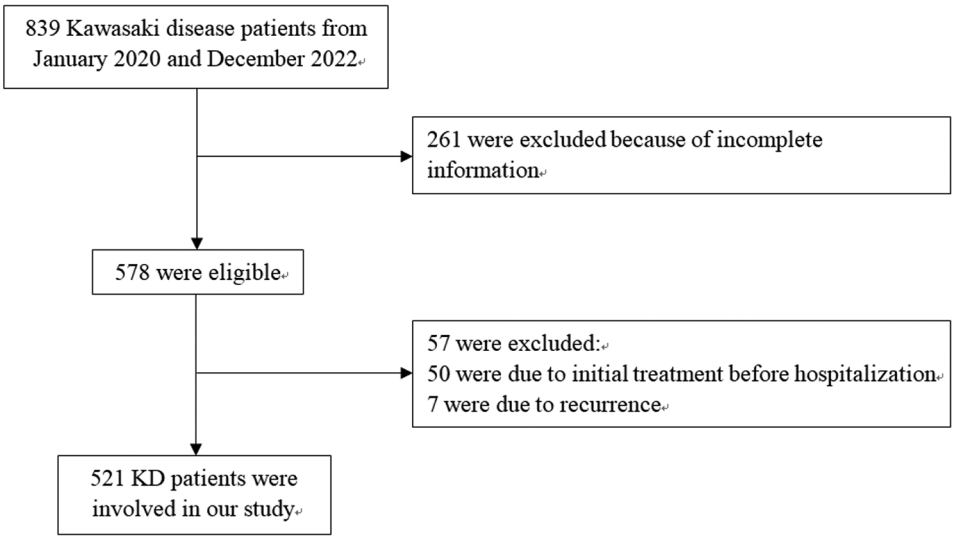

Fig. 1 Numbers of patients with Kawasaki disease who were eligible for the study

with KD classified as IVIG-resistant and those classified as nonresistant. IVIG resistance was defined in patients with KD who developed recurrent or persistent fever (≥38 °C) at least 36 h after completion of the initial IVIG infusion. Patients with incomplete data, recurrent cases, those who had received initial treatment prior to hospitalization, and patients who tested positive for coronavirus disease 2019 (COVID-19) by antibody test were excluded.

Treatment protocol

All patients included in this study were treated with IVIG (2 g/kg as a single infusion) in addition to aspirin (30 ~ 50 mg/kg/d) during the acute phase. The aspirin dosage was subsequently reduced to 3 ~ 5 mg/kg/d once the patient was afebrile for 48–72 h. Patients with IVIG resistance received a second dose of IVIG (2 g/kg as a single infusion) or IVIG (2 g/kg as a single infusion) combined with methylprednisolone (2 mg/kg/d).

Data collection

The medical records of KD patients, including demographic information such as age, weight, sex, fever duration prior to IVIG, CALs and clinical manifestations, were reviewed. Additionally, laboratory parameters, including white blood cell count (WBC), platelet count (PLT) and neutrophilic granulocyte percentage (NE%) as well as the levels of hematocrit (HCT), CRP, alanine aminotransferase (ALT), aspartate aminotransferase (AST), albumin (ALB), total bilirubin (TBIL), serum sodium, serum IL-1β, sIL-2R, serum IL-6, serum tumor necrosis factor-alpha (TNF-α) and serum IL-10, were analyzed. All the laboratory indicators were collected for assessment during the acute febrile period and prior to initial IVIG therapy. The study considered the highest values for WBC, NE%, CRP, AST, ALT, TBIL, IL-1β, sIL-2R, IL-6, TNF-α and IL-10, whereas the lowest values were considered for PLT, HCT, ALB, and serum sodium. Echocardiography was performed both at the time of diagnosis and during the subacute phase. The luminal diameters of the left and right coronary arteries were adjusted to body surface area-specific Z scores according to the 2017 AHA guidelines. CALs were defined when the Z score of any coronary vessel was ≥2.5. Small CALs were defined when the Z score of any coronary vessel was ≥2.5 to <5, medium CALs were defined when the Z score of any coronary vessel was ≥5 to <10, and large or giant aneurysms were defined when the Z score of any coronary vessel was ≥10. CALs were determined to have progressed when the Z score of the coronary artery (left or right) was increased compared with baseline echocardiographic records. CALs were determined to have improved when no coronary artery showed an increased Z score and when at least one coronary artery showed a reduced Z score compared with baseline echocardiographic records. CALs were unchanged if the coronary arteries initially involved showed the same Z scores.

Outcome measures and definitions

A multivariate logistic regression analysis was employed to assess the significance of various indicators in identifying risk factors, with scores assigned based on odds ratio (OR) values to establish a novel predictive scoring system. The receiver operating characteristic (ROC) curve was used to identify the maximum Youden index corresponding to the total score cutoff, sensitivity, and specificity. Internal validation was performed using the bootstrapping method with 1000 repetitions. The area under the ROC curve was calculated to evaluate the discrimination of the model, while the calibration was

Table 1 Demographic and clinical features of IVIG-resistant and non-resistant patients

	Total (*n* = 521)	IVIG-resistant patients (*n* = 42)	Nonre-sistant patients (*n* = 479)	*P* value*
Demographic features				
Age, y, (mean ± SD)	2.16 ± 1.73	2.15 ± 1.55	2.16 ± 1.74	0.974
Weight, kg, (mean ± SD)	13.45 ± 0.23	13.52 ± 0.89	13.44 ± 0.24	0.925
Male, n (%)	316 (60.65)	28 (66.67)	288 (60.13)	0.407
Fever duration before IVIG, d, (mean ± SD)	5.56 ± 0.08	4.74 ± 0.16	5.63 ± 0.08	0.001
CALs, n (%)				
All	89 (17.08)	15 (35.71)	74 (15.45)	0.001
Samll	65 (12.48)	12 (28.27)	53 (11.06)	0.001
Medium	17 (3.26)	3 (7.14)	14 (2.92)	0.140
Large or giant	7 (1.34)	1 (2.38)	6 (1.25)	0.543
Progressed	21 (4.03)	8 (19.05)	13 (2.71)	0.000
Improved	30 (5.76)	4 (9.52)	26 (5.43)	0.275
Unchanged	38 (7.29)	3 (7.14)	35 (7.31)	0.969
Clinical features, n (%)				
Oral changes	496 (95.20)	42 (100.00)	454 (94.78)	0.985
Conjunctivitis	498 (95.59)	41 (97.62)	457 (95.41)	0.542
Presence of lymphadenopathy	499 (95.78)	42 (100.00)	457 (95.41)	0.986
Rash	422 (81.00)	33 (78.57)	389 (81.21)	0.676
Peripheral extremity changes	373 (71.59)	37 (88.10)	336 (70.15)	0.018

CALs: coronary artery lesions; *P value between IVIG-resistant and nonresistant patients

assessed via calibration curves and the Hosmer–Lemeshow test. Additionally, the validity of the predictions was determined by calculating the area under the ROC curve (AUC), sensitivity and specificity of the six established scoring systems.

Statistical analyses

SPSS Statistics version 26.0 and R software version 4.3.2 were used for the statistical analyses. Categorical variables were summarized using frequencies (%). Continuous variables are expressed as the means ± SDs for normally distributed data or as medians (IQRs) for nonnormally distributed data. The Shapiro–Wilk test was used to examine whether the data were normally distributed. We used the χ^2 test to compare categorical data. The independent samples t test was used to compare groups of normally distributed data, while the Mann–Whitney U test was used for nonnormally distributed data. Statistical significance was set at $P<0.05$.

Table 2 Laboratory values of IVIG-resistant and non-resistant patients

	IVIG-resistant patients (*n* = 42)	Nonresistant patients (*n* = 479)	*P* value
WBC, 10^9/L, (mean ± SD)	15.90 ± 0.95	15.09 ± 0.36	0.521
PLT, 10^9/L, (mean ± SD)	275.67 ± 19.91	342.25 ± 5.81	0.000
NE%, (mean ± SD)	77.61 ± 1.87	62.58 ± 0.75	0.000
HCT, %, (mean ± SD)	33.54 ± 0.50	33.72 ± 0.15	0.764
CRP, mg/L, (mean ± SD)	95.23 ± 7.21	61.99 ± 2.05	0.000
ALT, U/L, (mean ± SD)	120.10 ± 22.74	52.26 ± 3.44	0.000
AST, U/L, (mean ± SD)	97.21 ± 22.35	41.57 ± 2.66	0.000
ALB, g/L, (mean ± SD)	34.51 ± 0.67	36.70 ± 0.21	0.001
TBIL, μmol/L, (mean ± SD)	18.70 ± 3.03	7.98 ± 0.40	0.000
Sodium, mmol/L, (mean ± SD)	133.53 ± 0.43	135.10 ± 0.12	0.306
IL-1β, pg/mL, (mean ± SD)	15.09 ± 1.49	14.08 ± 0.68	0.663
sIL-2R, U/mL, (mean ± SD)	4435.98 ± 338.44	2461.85 ± 73.96	0.000
IL-6, pg/mL, (mean ± SD)	155.52 ± 32.58	37.82 ± 3.49	0.000
TNF-α, pg/mL, (mean ± SD)	31.02 ± 1.56	22.97 ± 0.44	0.000
IL-10, pg/mL, (mean ± SD)	79.29 ± 16.82	21.58 ± 2.13	0.000

ALB: albumin; ALT: alanine aminotransferase; AST: aspartate aminotransferase; CRP: C-reactive protein; HCT: hematocrit; IL-1β: interleukin-1β; IL-6: interleukin-6; IL-10: interleukin-10; NE%: neutrophilic granulocyte percentage; PLT: platelet count; sIL-2R: soluble interleukin-2 receptor; TBIL: total bilirubin; TNF-α: tumor necrosis factor α; WBC: white blood cell count

Results

Baseline characteristics

In all, 839 patients diagnosed with KD were treated at the cardiovascular medical ward of our institution between January 2020 and December 2022. Among these patients, 261 were excluded because of incomplete data, 50 were excluded because they received initial treatment before hospitalization, and 7 were excluded because of disease recurrence. Ultimately, 521 KD patients (Fig. 1) with an average age of 2.16 ± 1.73 years were included in our study, and of these, 42 patients (8.06%) were classified as IVIG-resistant. The demographic and clinical characteristics of the IVIG-resistant (66.67% male) and nonresistant patients (60.13% male) are shown in Table 1. No statistically significant differences in demographic or clinical characteristics were observed between the IVIG-resistant and nonresistant groups, with the exception of fever duration before IVIG (4.74 ± 0.16 vs. 5.63 ± 0.08; $P=0.001$), the occurrence rate of CALs (15 (35.71%) vs. 74 (15.45%); $P=0.001$), and the occurrence rate of peripheral extremity changes (37 (88.10%) vs. 336 (70.15%); $P=0.018$). The laboratory values of the IVIG-resistant and nonresistant patients are shown in Table 2. Compared with IVIG-nonresistant patients, IVIG-resistant patients had a significantly greater NE% (77.61 ± 1.87 vs. 62.61 ± 0.75; $P<0.001$), CRP level (95.23 ± 7.21 vs. 61.99 ± 2.05; $P<0.001$), ALT level (120.10 ± 22.74 vs. 52.26 ± 3.44; $P<0.001$), AST level (97.21 ± 22.35

vs. 41.57±2.66; $P<0.001$), TBIL level (18.70±3.03 vs. 7.98±0.40; $P<0.001$), sIL-2R (4435.98±338.44 vs. 2461.85±73.96; $P<0.001$), IL-6 (155.52±32.58 vs. 37.82±3.49; $P<0.001$), TNF-α (31.02±1.56 vs. 22.97±0.44; $P<0.001$) and IL-10 (79.29±16.82 vs. 21.58±2.13; $P<0.001$). PLT (275.67±19.91 vs. 342.25±5.81; $P<0.001$) and ALB levels (34.51±0.67 vs. 36.70±0.21; $P=0.001$) were significantly lower in resistant patients than in nonresistant patients.

Multivariate logistic regression analysis

Fever duration before IVIG, the occurrence rate of peripheral extremity changes, PLT, NE%, and the levels of CRP, ALT, AST, ALB, TBIL, sIL-2R, IL-6, TNF-α and IL-10 were included as independent variables in the multivariate analysis, while the response to IVIG was the dependent variable. While the occurrence of CALs was statistically significant, data collection for this variable did not occur prior to initial treatment with immunoglobulin; therefore, it was not included in the regression analysis. Finally, the results of logistic regression analyses revealed that the PLT, NE%, AST level and sIL-2R level were independent predictors of IVIG resistance (Table 3).

Table 3 Results of logistic regression analyses of intravenous immunoglobulin resistance in KD patients

Variables	Logistic coefficient(β)	Odds ratio (95% CI)	*P* value
Fever duration before IVIG	-0.306	0.737 (0.480, 1.077)	0.140
Peripheral extremity changes	0.656	1.927 (0.691, 6.393)	0.240
PLT	-0.005	0.995 (0.991, 0.999)	0.011
NE%	0.044	1.045 (1.008, 1.083)	0.016
CRP	0.004	1.004 (0.996, 1.013)	0.309
ALT	-0.001	0.999 (0.994, 1.005)	0.860
AST	0.006	1.006 (1.001, 1.012)	0.021
TBIL	0.003	1.003 (0.974, 1.034)	0.836
ALB	-0.064	0.938 (0.863, 1.018)	0.125
sIL-2R	0.000	1.000 (1.000, 1.000)	0.020
IL-6	0.001	1.001 (0.999,1.004)	0.327
TNF-α	-0.005	0.995 (0.956, 1.035)	0.796
IL-10	0.005	1.005 (1.000, 1.010)	0.052

Development of a new prediction model

A novel scoring system was developed utilizing OR values of four independent predictors (PLT, NE%, AST level and sIL-2R level) to determine the risk for IVIG resistance: PLT≤282×10^9/L (1 point), NE% ≥ 72% (1 point), AST level≥80 U/L (1 point), and sIL-2R level≥2400 U/mL (1 point). A cutoff point≥3 was considered a high risk factor for IVIG resistance.

Predictive model validation

The novel scoring system demonstrated a sensitivity of 69.29% and a specificity of 83.91% in identifying the IVIG-resistant group. The area under the ROC curve (Fig. 2a) was 0.889. Following 1000 bootstrap resampling internal validations, both the predictive model and the validation set showed a high degree of fit, as illustrated by the calibration curves (Fig. 2b and c). The Hosmer–Lemeshow statistic was 0.476.

Comparison of the predictive performance

The sensitivity and specificity, with respect to the IVIG response, of six previously established scoring systems and the new system are summarized in Table 4. The Egami score demonstrated a high specificity of 88.52% but a low sensitivity of 38.10%. Conversely, the Formosa score and Harada score had high sensitivity (95.24% and 78.57%) but low specificity (41.13% and 43.22%). The Kobayashi score, Lan score, Yang score and the new system score all had high sensitivities of 66.67%,

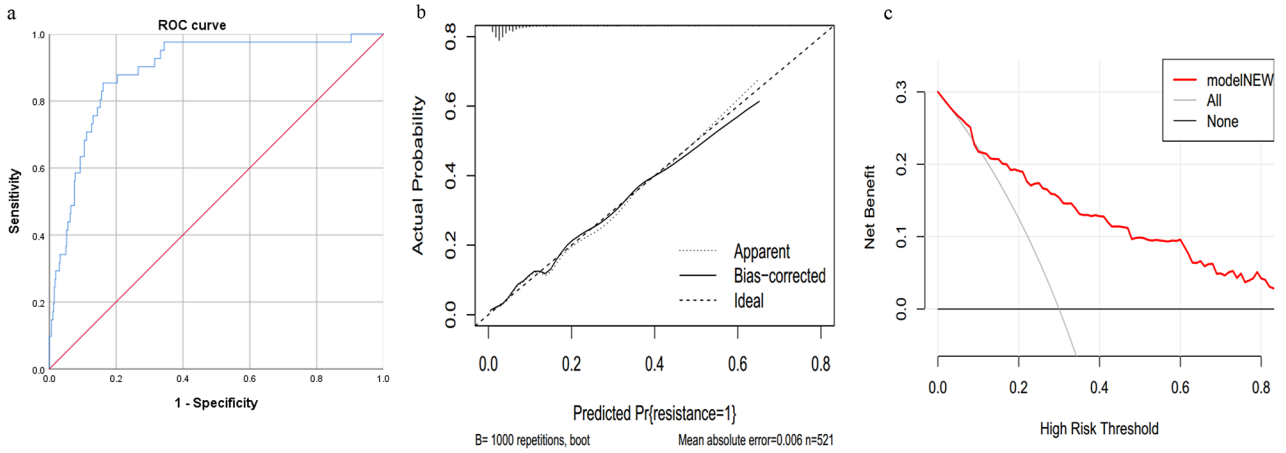

Fig. 2 Performance and validation of the new model. **a**: ROC curve of the new model; **b**: Calibration curve of the new model; **c**: Decision curve analysis (DCA) curve of the new model

Table 4 Data used to evaluate the different scoring systems to predict IVIG resistance in patients with KD

	Egami	Formosa	Harada	Kobayashi	Lan	Yang	New
SE (%)	38.10	95.24	78.57	66.67	66.67	69.05	69.29
SP (%)	88.52	41.13	43.22	74.95	73.49	77.24	83.91
AUC	0.797	0.799	0.762	0.874	0.846	0.832	0.889

SE: sensitivity; SP: specificity; AUC: area under the curve

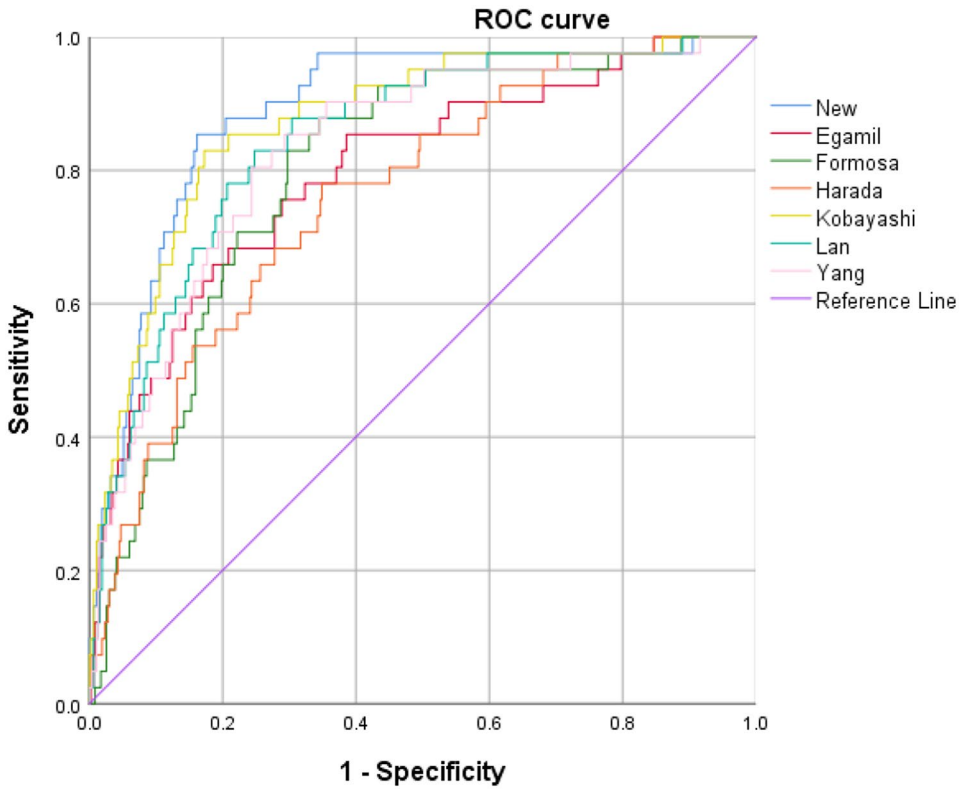

Fig. 3 ROC curves for the different scoring systems

66.67%, 69.05% and 69.29%, respectively. However, the new system exhibited a higher specificity (83.91%) than the other three scoring systems (Kobayashi 74.95%, Lan 73.49% and Yang 77.24%), which indicates its potential to reduce misdiagnosis rates in IVIG-resistant patients. The ROC curves for the various scoring systems are shown in Fig. 3. The areas under the ROC curves are shown in Table 4.

Discussion

To the best of our knowledge, this study represents a novel contribution to the field of KD research, as it is the first to report a scoring system utilizing sIL-2R levels to predict IVIG resistance in KD patients. Our findings indicate that the PLT, NE% and the levels of AST and sIL-2R are independent risk factors for IVIG resistance in KD patients. Furthermore, our scoring system demonstrated superior accuracy in identifying IVIG-resistant KD patients compared to six already existing scoring systems.

KD is an acute febrile systemic vasculitis that primarily affects small- to medium-sized arteries, particularly coronary arteries. In China, the incidence of CALs in KD patients ranges from 9.1 to 21.5% [27–30]. Our study revealed that 17.08% of KD patients developed CALs. Previous studies have shown that IVIG-resistant KD patients are at an increased risk for the development of CALs [3, 5, 31]. Our research confirmed this association, as the incidence of CALs in the IVIG-resistant group (35.71%) was significantly higher than that in the non-resistant group (15.45%) ($P=0.001$). Moreover, our study revealed that the IVIG-resistant group (19.05%) presented a greater likelihood of developing subsequent progression of CALs than the non-resistant group (2.71%) ($P<0.001$). Consequently, the timely and precise identification of IVIG resistance in KD patients holds paramount importance.

This study evaluated the effectiveness of six popular scoring systems for predicting IVIG resistance among KD patients in eastern China. Moreover, a novel scoring

system based on sIL-2R levels was developed. The results indicated that, compared with the Kobayashi scoring system proposed in Japan, as well as the Lan and Yang scoring systems from China, our newly developed scoring system demonstrated superior performance in Chinese pediatric patients. Furthermore, our new scoring system exhibited the highest levels of sensitivity and specificity.

The Kobayashi scoring system, initially proposed in Japan with a study population of 528 KD patients, demonstrated a sensitivity of 86% and a specificity of 68% for predicting IVIG resistance. However, when applied to Caucasian children [32, 33], the efficacy of this scoring system was found to be suboptimal, potentially due to genetic factors. Several studies have highlighted the association between KD and genetic variants in the inositol 1,4,5-trisphosphate 3-kinase C (ITPKC) gene [34, 35]. Therefore, KD patients with different genetic backgrounds may exhibit differing susceptibilities to IVIG resistance. When applied to Chinese KD patients, the Kobayashi scoring system has shown inconsistent efficacy across different studies. Huang et al. [36] retrospectively analyzed 84 KD patients in Taiwan, China using the Kobayashi score and reported a sensitivity and specificity of 37.5% and 86.8%, respectively. Song et al. [25] conducted a study of 1163 KD patients in Beijing, China using the Kobayashi score and reported a sensitivity and specificity of 16% and 85%, respectively. These findings suggest that IVIG resistance may remain undetected in a significant number of children with KD in similar populations. Nevertheless, a study by Liu et al. [37] involving 346 Chinese patients revealed that the Kobayashi score was significantly higher in the IVIG-resistant KD group than in the non-resistant group. Our study revealed that the Kobayashi scoring system performs relatively well in Chinese KD patients, with a sensitivity of 66.67% and a specificity of 74.95%. In conclusion, the inconsistency of the Kobayashi scoring system within the Chinese population raises concerns about its reliability.

The Lan and Yang scoring systems, established in 2018, were tested in 1655 and 2102 Chinese KD patients, respectively. In our study, both methods performed relatively well in Chinese KD patients, with sensitivities of 66.67% and 69.05% and specificities of 73.49% and 77.24%, respectively. The larger sample sizes of these two systems compared with the sample size for the Formosa, another Chinese scoring system with a sample size of only 248, may account for the lower sensitivity and specificity observed with the Formosa system.

Compared with the existing scoring systems, our novel scoring system performed the best. Our new scoring system incorporates the PLT, NE% and the AST and sIL-2R levels as key components. Notably, the PLT included in the Kobayashi score, Egami score and Lan score, was consistent with our findings, with a cutoff value of approximately 300×10^9/L. The PLT is considered a biomarker for the development of CALs in KD patients, typically reaching its nadir within 6 ~ 7 days and peaking after 10 days [38]. Furthermore, the PLT reflects the severity of the underlying inflammation or severity of KD [39]. NE% is also included in the Kobayashi score, Formosa score, Yang score and Lan score, with cutoff values of approximately 60 ~ 80%. In addition, it has been shown to be a predictive risk factor for IVIG resistance in many studies in China [40–42]. An elevated NE% indicates the presence of significant inflammation in KD patients. AST levels are also included in the Kobayashi score and Sano score, with cutoff values of approximately 100 ~ 200 IU/L. Research [43] has demonstrated that the AST level in the KD group with shock was greater than that in the group without shock, which suggests that the AST level may reflect the severity of KD progression. To our knowledge, our study is the first to incorporate sIL-2R into a scoring system for IVIG resistance. SIL-2R is secreted upon T-cell activation. According to previous studies [44–46], blood sIL-2R levels are elevated in various human diseases, including autoimmune and inflammatory diseases, solid cancers, myocardial infarction, and infections. Many studies [15, 21, 47] have shown that elevated sIL-2R levels during the pathological process of KD may serve as a valuable marker for assessing the severity and progression of inflammation in pediatric patients, which contributes to early prediction. Our study further supports this notion and demonstrated a significant increase in sIL-2R levels among IVIG-resistant populations, which suggests its potential utility as an independent risk factor for predicting IVIG resistance.

However, our study was subject to several limitations. First, the sample size was not as large as that in other studies, such as those pertaining to the Lan and Yang scoring systems, which included over 1500 KD patients, and in those studies, these systems performed relatively well in Chinese KD patients. Despite our limited sample population, the incorporation of the novel indicator sIL-2R resulted in the highest sensitivity and specificity of all the scoring systems compared in our study. Additionally, the retrospective nature of our study limited the availability of data on proinflammatory cytokines. In subsequent research, we will expand the study sample size and include more proinflammatory cytokine indicators.

Conclusion

In conclusion, our novel scoring system utilizing sIL-2R performs better than other existing scoring systems and is suitable for predicting IVIG resistance in Chinese patients with KD.

Abbreviations

AHA	American Heart Association
ALB	Albumin

ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
CAL	Coronary artery lesion
COVID-19	Coronavirus disease 2019
CRP	C-reactive protein
ESR	Erythrocyte sedimentation rate
HCT	Hematocrit
IL	Interleukin
ITPKC	Inositol 1,4,5-trisphosphate 3-kinase C
IVIG	Intravenous immunoglobulin
KD	Kawasaki disease
NE%	Neutrophilic granulocyte percentage
OR	Odds ratio
PLT	Platelet count
ROC	Receiver operating characteristic
sIL-2R	Soluble interleukin-2 receptor
TBIL	Total bilirubin
TNF-α	Tumor necrosis factor-alpha
WBC	White blood cell

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Data availability
The datasets used and/or analyzed in the current study are available from the corresponding author upon reasonable request.

Declarations

Ethical approval
This study was approved by the Children's Hospital of Nanjing Medical University Research Ethics Committee (202302036-1). The need for informed consent was waived.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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