Predictive Value of Albumin-Bilirubin Grade For Intravenous Immunoglobulin Resistance In A Large Cohort Of Patients With Kawasaki Disease: A Prospective Study

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Abstract

Background: Intravenous immunoglobulin (IVIG) resistance, which defined that Kawasaki disease (KD) patients have recrudescence fever more than 36 hours after IVIG infusion, and its prediction is one of the primary clinical issues and study hotspots in KD. This study aimed to prospectively investigated the value of albumin-bilirubin grade (ALBI) in predicting IVIG resistance in KD, and assessed whether ALBI has more predictive value or accuracy than either ALB or TBil alone in predicting IVIG resistance.

Methods: A total of 823 patients with KD were prospectively enrolled. The clinical and laboratory data were compared between IVIG-response group (n=708) and IVIG-resistance group (n=115). Multivariate logistic regression analysis was performed to identify the independent risk factors of IVIG resistance. Receiver operating characteristic (ROC) curves analysis was applied to assess the validity of ALBI, ALB, and TBil in predicting IVIG resistance.

Results: ALBI was significantly higher in patients with IVIG resistance and was identified as an independent risk factor for IVIG resistance in KD. The parameter of ALBI ≥ −2.57 (AUC: 0.705, 95%CI: 0.672–0.736), ALB ≤ 33.0g/L (AUC: 0.659, 95%CI: 0.626–0.692), and TBil ≥16.0μmol/L (AUC: 0.626, 95%CI: 0.592–0.659), produced a sensitivity, specificity, PPV, and NPV of 0.617, 0.657, 0.226, 0.914, and 0.651; 0.374, 0.850, 0.289, 0.893, and 0.783; 0.269, 0.941, 0.425, 0.888, and 0.847, respectively.

Conclusion: A higher ALBI was an independent risk factor for IVIG resistance. It yielded better predictive ability than ALB and TBil alone for initial IVIG resistance.

Introduction

Kawasaki disease (KD) is an acute systemic vasculitis predominantly affecting children, with coronary artery lesions (CALs) as the most severe sequela[1]. However, approximately 10–20% of patients with KD are resistant to intravenous immunoglobulin(IVIG) treatment and develop a risk of CALs[2] even though timely IVIG treatment is substantially effective. It has been proven that IVIG-resistant patients may benefit from adjunctive therapies for primary treatment, including corticosteroids[3, 4], infliximab[5, 6], plasma exchange[7, 8], and cytotoxic agents[9, 10]. Thus, early prediction of IVIG resistance is of paramount importance for patients since they may benefit from early-intensified therapy.

It has been proven that patients with KD undergo a systemic inflammatory reaction. The liver is one of the immunoregulatory cornerstones and is characterized by small-medium vessels. Thus, in patients with KD, the elevated total bilirubin (TBil) levels may be attributed to liver cell damage for acute hepatic vascular inflammation[11, 12]. Additionally, serum albumin (ALB) decreases due to increased permeability and leakage due to vascular inflammation[12]. Indicators of ALB and TBil were found to be associated with IVIG resistance; however, neither was suitable alone as a predictor of IVIG resistance. Even though both indicators were included in several risk-scoring systems for IVIG resistance prediction in KD[13–18], these risk-scoring systems are based on individual parameters that are scored based on arbitrarily defined predetermined cut-off values, producing variable predictive ability for IVIG resistance in different populations[19–21]. Inevitably, these risk-scoring systems or single indicators stratified patients into distinct groups, resulting in information loss. It was notable that patients who fall around the cut-off point (i.e., just below or above the discriminating value) may be classified as having different

risk levels. Therefore, the predictive ability of ALB, TBil, or available risk-scoring systems comprising of ALB and/or TBil, seems to be limited and unsatisfactory for IVIG resistance.

Recently, a parameter known as the ALBI grade [$0.66\times\log10^{TBil}-0.085\times ALB$], providing information on both ALB and TBil, which reflect systemic inflammatory response and/or the degree of liver damage. ALBI has been proposed as a powerful prognostic indicator of poor outcomes in patients with hepatocellular carcinoma (HCC) [22–26], hepatitis virus infection and acute pancreatitis[27–29]. This parameter positively correlates with inflammatory markers [28]. The systemic inflammatory response is the central pathological process of KD; however, the usefulness of ALBI as a predictor of prognosis has not been evaluated in patients with KD.

Thus, in this cohort, we prospectively evaluated the predictive ability of ALBI for IVIG resistance in patients with KD and assessed whether ALBI has more predictive value or accuracy than either ALB or TBil alone in predicting IVIG resistance.

Patients And Methods

Patients with KD were prospectively recruited between March 2015 and September 2020 at our hospital. KD was diagnosed based on the AHA scientific statement's standards for diagnosis, treatment, and long-term management of KD[1] and confirmed by two experienced pediatricians (including ≥ 1 KD specialist). Structured questionnaires with pre-coded questions, including basic demographic information, clinical manifestations, hematological examination results, treatment, and follow-up outcomes, were used for data collection. All questionnaires were pretested and revised accordingly. Two well-trained doctors conducted data collection. The questionnaires were double-checked to ensure completeness. Informed written consent was obtained from the parents after this study's nature was fully explained to them. The University Ethics Committee approved the study on Human Subjects at Sichuan University. All research was performed following the relevant guidelines and regulations.

Exclusion criteria included known patients with congenital or chronic liver disease affecting the levels of ALB and/or TBil levels. In total, 1196 patients were diagnosed with KD upon admission. Those who had received IVIG treatment in other medical facilities (n = 180) or did not receive IVIG treatment before 10 days from fever onset (n = 97) were excluded. Additionally, 43 patients were excluded due to lack of data regarding complete blood count (CBC) or C-reactive protein(CRP) (n = 17) or serum ALB (n = 26) levels prior to initial IVIG treatment. We also excluded 53 patients because other laboratory data (n = 28) or follow-up results (n = 25) were incomplete. Finally, 823 patients were enrolled for analysis, including 708 initial IVIG responders and 115 initial IVIG non-responders. Of the 115 patients with initial IVIG resistance, 45 did not respond to repeated IVIG treatment and received pulse intravenous methylprednisolone infusion (Fig. 1). No patients received additional treatment such as infliximab, plasma exchange, or cytotoxic agents. The ALBI grade was defined as $0.66\times\log10^{TBil}-0.085\times ALB$ before the initial IVIG infusion.

All patients received the same standard treatment regimen for KD. Aspirin (30–50 mg/kg/day) and IVIG (2 g/kg given as a single intravenous infusion) were administered within the first ten days of illness from fever onset. After patients were treated for 48–72 hours, a tapered dose of aspirin (3–5 mg/kg/day) was administered for 6–8 weeks. If patients had CALs, aspirin was continued until there was no evidence of CALs. The initial IVIG resistance was defined as recurrent or persistent fever or other clinical signs of KD for at least 36 hours but not longer than seven days after initial IVIG [30]. If the patient had initial IVIG resistance, a second IVIG (2 g/kg given as a single intravenous infusion) was administered. Furthermore, if the patient had repeated IVIG resistance defined as having

recurrent or persistent fever after the second IVIG infusion, tapered administration of pulse intravenous methylprednisolone (20–30 mg/kg/day for three consecutive days) followed by oral prednisone (2 mg/kg/day) for seven days was given as adjunctive therapy.

During the acute and sub-acute phase of KD, CALs were based on the normalization of dimensions for body surface area (BSA) as Z scores (standard deviation units from the mean, normalized for BSA) by the AHA scientific statement's standards for diagnosis, treatment, and long-term management of KD[1]. According to the institutional protocol, patients underwent standardized echocardiograms by two pediatric ultrasonologists during the acute phase and 6–8 weeks during the cardiology clinic follow-up evaluations until the resolution of CALs. BSA and Z scores were calculated using the Haycock[31] and the Kobayashi equations[32], respectively.

3. Statistical Analyses

Categorical variables are described as frequencies and percentages (n/%) where appropriate, and quantitative data are presented as the median with the 25th and 75th percentiles (interquartile range (IQR)) in square brackets. The Shapiro-Wilk test and homogeneity test of variance were used to confirm that quantitative data from different groups were normally distributed and met the homogeneity of variance. The chi-squared test, unpaired Student's t-test, and Mann-Whitney U test were applied to compare demographic characteristics, clinical manifestations, and laboratory data between groups. Numerical variables that showed statistical significance in the univariate analysis were transformed into dichotomous variables. Cut-off values corresponding to the maximum Youden's index for sensitivity and specificity were selected based on the receiver operating characteristic (ROC) curve.. These crucial indicators from univariate analysis were then subjected to multivariate logistic regression analysis to identify independent predictors of IVIG resistance. The best cut-off values of the multivariable model for IVIG resistance prediction and its corresponding predictive power were further assessed using the ROC curve. To compare the predictive value of ALBI and ALB, or TBil for IVIG resistance, ROC analysis was conducted to determine the best cut-off values and their corresponding predictive validities. Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and diagnostic accuracy were assessed. A De Long test was used to compare the ROC curves. P values <0.05 were considered statistically significant. All data analyses were performed using SPSS 21.0 (IBM SPSS Statistics version 21.0, Armonk, NY, IBM Corp.).

Results

4.1 Comparison of Clinical Data Between Initial IVIG-Response Group and IVIG-Resistance Group

Table 1 shows no significant differences between groups regarding sex, fever duration before IVIG treatment, the occurrence of incomplete KD, and typical clinical manifestations of KD ($p > 0.05$). The incidence of CALs was relatively higher in the IVIG-resistance group, but the difference was not statistically significant (13.0% vs10.0%, $p = 0.325$). Compared with patients from the IVIG-responsive group, patients from the IVIG-resistant group were older, presenting substantially higher levels of neutrophil percentage (N%), alanine aminotransferase (ALT), TBil, and ALBI, but lower levels of hemoglobin, platelet (PLT), ALB and sodium (Na^+) ($p < 0.005$).

Table 1
Comparison of clinical data between the groups of initial IVIG-response and IVIG-resistance in KD

	IVIG-responsive (n = 708)	IVIG-resistance (n = 115)	*p* value
Male	403(56.9)	59(51.3)	0.267
Age, years	2.1(1.2–3.6)	2.3(1.3–4.5)	0.026
Clinical manifestations			
Rash	549(77.5)	96(83.5)	0.190
Extremity changes	393(55.5)	65(57.4)	0.762
Conjunctivitis	651(91.9)	103(89.6)	0.368
Oral changes	639(90.3)	108(93.9)	0.296
Cervical lymphadenopathy	310(43.8)	62(53.9)	0.055
Fever duration before initial IVIG, days	5.0(5.0–6.0)	5.0(4.0–6.0)	0.212
Incomplete KD	275(38.8)	36(31.3)	0.146
CALs in the acute phase of KD	71(10.0)	15(13.0)	0.325
Before initial IVIG			
Time of blood test from fever onset, days	5.0(4.0–6.0)	4.0(3.0–5.0)	0.558
WBC, $\times 10^9$/L	13.2(10.7–16.6)	13.6(10.0-16.9)	0.515
Neutrophil, %	66.2(77.0–56.0)	77.5(66.2–84.0)	<0.001
Lymphocyte, %	24.6(16.0–33.0)	15.0(9.6–24.0)	<0.001
Hemoglobin, g/L	109(102–117)	107(101–114)	0.036
PLT, $\times 10^9$/L	316(259–387)	290(196–348)	<0.001
CRP, mg/L	71.0(43.0-107.0)	92.1(62.0-144.0)	<0.001
ESR, mm/h	64.0(46.0–81.0)	67.0(48.0–87.0)	0.152
AST, U/L	33.0(25.0–49.0)	37.0(25.0–73.0)	0.161
ALT, U/L	36.0(20.0-77.7)	54.0(27.0-125.0)	0.006
ALB, g/L	38.0(35.0–41.0)	36.0(30.3–39.0)	0.004
TBil, μmol/L	6.0(4.0-8.5)	7.0(5.0–19.0)	<0.001

Abbreviations: ALB, Albumin; AST, aspartate aminotransferase; ALT, alanine aminotransferase; CRP, C-reactive protein; CALs, coronary artery lesions; ESR, erythrocyte sedimentation rate; IVIG, intravenous immunoglobulin; KD, Kawasaki disease; TBil, total bilirubin; Na^+, sodium; WBC, white blood cell; ALBI, albumin-bilirubin index;

The data are presented as the median with the 25th and 75th percentiles in square brackets for continuous variables and as the percentage for the categorical variables.

	IVIG-responsive (n = 708)	IVIG-resistance (n = 115)	*p* value
Na^+, mmol/L	137.0(135.0-139.0)	135.0(133.0-137.0)	0.001
ALBI	−2.73(−3.00- (−2.46))	−2.38(−2.69- (−1.93))	0.001

Abbreviations: ALB, Albumin; AST, aspartate aminotransferase; ALT, alanine aminotransferase; CRP, C-reactive protein; CALs, coronary artery lesions; ESR, erythrocyte sedimentation rate; IVIG, intravenous immunoglobulin; KD, Kawasaki disease; TBil, total bilirubin; Na^+, sodium; WBC, white blood cell; ALBI, albumin-bilirubin index;

The data are presented as the median with the 25th and 75th percentiles in square brackets for continuous variables and as the percentage for the categorical variables.

4.2 Multivariate logistic regression analysis for IVIG resistance prediction in KD

As shown in Table 2, multivariate logistic regression analysis was performed to investigate whether SII was an independent risk factor for IVIG resistance in KD. Statistically significant variables including age, N%, PLT, hemoglobin, CRP, ALT, Na^+ levels, and ALBI were identified as confounding factors. The multivariate logistic regression model did not comprise the parameters of ALB and TBil since all of them showed strong correlations with ALBI. The results showed that ALBI ≥ − 2.57 were independent risk factors for IVIG resistance (OR: 3.374, 95%CI: 2.016–5.648, $p < 0.001$).

Table 2
A multivariate logistic regression analysis for predicting IVIG resistance in KD

	β	SE	Walds	*P* value	OR	95% CI
Age ≥ 4.42 years	0.265	0.286	0.855	0.355	1.303	0.744–2.284
Neutrophil ≥ 76.2%	0.460	0.256	3.233	0.072	1.585	0.959–2.617
Platelet ≤ 312×10^9/L	0.504	0.232	4.720	0.030	1.655	1.051–2.608
Hemoglobin ≤ 104g/L	0.341	0.226	2.268	0.132	1.406	0.902–2.190
CRP ≥ 57.4mg/L	0.268	0.278	0.934	0.334	1.308	0.759–2.253
ALT ≥ 41U/L	0.260	0.232	1.255	0.263	1.297	0.823–2.044
Na + ≤ 135.4mmol/L	0.752	0.233	10.391	0.001	2.121	1.343–3.350
ALBI≥-2.14	1.216	0.263	21.406	0.000	3.374	2.016–5.648
Interpret	-0.745	0.327	5.185	0.023	0.475	

Abbreviations: ALBI, albumin-bilirubin index; ALT, alanine aminotransferase; ALB, albumin; CRP, C-reactive protein; IVIG, intravenous immunoglobulin; TBil, total bilirubin; KD, Kawasaki disease; Na+, serum sodium;

4.3 Predictive Ability of ALBI, ALB, and TBil in Predicting Initial IVIG Resistance

The parameters of ALBI ≥ − 2.57, ALB ≤ 33.0g/L, and TBil ≥ 16.0μmol/L produced a sensitivity, specificity, PPV, and NPV of 0.617, 0.657, 0.226, 0.914, and 0.651; 0.374, 0.850, 0.289, 0.893, and 0.783; 0.269, 0.941, 0.425, 0.888, and 0.847, respectively (Table 3).

Table 3
Sensitivity, specificity, PPV, NPV, diagnostic accuracy of ALBI, ALB and TBil cut-off values in initial IVIG resistance prediction

	AUC	SE	95%CI	Sensitivity	Specificity	PPV	NPV	Diagnostic accuracy	*p* value
ALB ≤ 33.0g/L	0.659	0.0281	0.626–0.692	0.374	0.850	0.289	0.893	0.783	< 0.001
TBil ≥ 16.0μmol/L	0.626	0.0305	0.592–0.659	0.269	0.941	0.425	0.888	0.847	< 0.001
ALBI≥-2.57	0.705	0.0277	0.672–0.736	0.617	0.657	0.226	0.914	0.651	< 0.001

Abbreviations: ALB, serum albumin; TBil, total bilirubin; ALBI = $0.66\times\log10^{TBil}-0.085\times ALB$; IVIG, intravenous immunoglobulin; NPV, negative predictive value; PPV, positive predictive value.

Pairwise comparison of ROC curves between ALBI and ALB, TBil in predicting IVIG resistance by De Long test, p = 0.001 and 0.012.

The AUC value of ALBI (AUC: 0.705, 95%CI: 0.672–0.736) did significantly differed from that of ALB (AUC: 0.659, 95%CI: 0.626–0.692) and TBil (AUC: 0.626, 95%CI: 0.592–0.659) (p = 0.001 and 0.012, respectively) (Fig. 2). Additionally, diagnostic sensitivity and specificity of CAR, CRP, and ALB according to the ROC optimized decision limits in predicting initial IVIG resistance are shown in Table 4.

Table 4
Diagnostic specificity and sensitivity according to ROC-optimized decision limits for ALBI, ALB, and TBil in predicting initial IVIG resistance among patients with KD

	Estimated specificity at fixed sensitivity (n = 823)				Estimated sensitivity at fixed specificity (n = 823)			
ALBI	Sensitivity(%)	Specificity(%)	Cut-off point	n	Specificity(%)	Sensitivity(%)	Cut-off point	n
	99.0	7.9	-3.29	767	99.0	10.4	-1.58	20
	97.5	13.3	-3.18	727	97.5	13.9	-1.77	35
	95.0	17.2	-3.12	698	95.0	26.1	-1.97	66
	90.0	23.6	-3.02	648	90.0	40.9	-2.15	120
ALB								
	99.0	8.5	43.8	753	99.0	4.4	26.0	12
	97.5	12.6	42.9	713	97.5	15.9	28.8	35
	95.0	16.6	41.9	661	95.0	25.2	30.4	64
	90.0	20.1	41.9	661	90.0	30.7	31.8	93
TBil								
	99.0	1.5	1.91	816	99.0	6.9	47.9	16
	97.5	2.3	1.93	816	97.5	17.4	30.3	38
	95.0	3.5	1.96	816	95.0	24.2	18.6	65
	90.0	11.7	2.94	771	90.0	29.5	12.9	106

Abbreviations: ALBI, albumin-bilirubin index; ALB, albumin; TBil, total bilirubin; IVIG, intravenous immunoglobulin; KD, Kawasaki disease.

4.4 Association of ALBI with repeated IVIG resistance and CALs in KD

The patients were divided into two subgroups according to whether patients with KD presented with repeated IVIG resistance: patients with repeated IVIG resistance (n = 45) and response to the second IVIG (n = 70). There was no significant difference in ALBI between patients with repeated IVIG resistance and IVIG response[− 2.47(−2.8-(−2.02)) *vs.* − 2.27(−2.64-(−1.9)), $p = 0.081$] (Supplementary material 1). The ALBI tended to be higher in the patients with CALs than with non-CALs, but the difference was not statistically significant [− 2.63(−2.92- (−2.19)) *vs.* − 2.70(−3.00- (−2.42)), $p = 0.065$] (Supplementary material 2).

Discussion

The indicators of ALB and TBil were found to be associated with IVIG resistance and included in several risk-scoring systems for IVIG resistance prediction in KD[13, 19–23]; however, neither indicator was ideal. Except for representing liver function[33–36], the ALBI grade calculated using ALB and TBil could reflect systemic inflammatory response[28]. To the best of our knowledge, this cohort was the first to explore the predictive validity of ALBI for IVIG resistance prediction. The present study incorporated data on both ALB and TBil, for IVIG resistance prediction in patients with KD and compared its predictive value with ALB and TBil. Furthermore, the

sensitivity, specificity, PPV, and NPV of all three predictors were also assessed. ALBI was identified as an independent risk factor for IVIG resistance in KD. The discriminating cut-off value of ALBI for predicting IVIG resistance was − 2.57, with moderate sensitivity (0.617) and specificity (0.657). Moreover, the discriminating ability of ALBI was superior to that of ALB and TBil in IVIG resistance based on ROC analysis.

Concerning the development and progression of HCC due to chronic viral hepatitis and/or alcoholic or metabolic liver disease, chronic inflammation, and altered immune responses play pivotal roles and are associating with proinflammatory cytokines, such as interleukin(IL)-6 and tumor necrosis factor (TNF)[37, 38]. Besides, the liver is an immunoregulation cornerstone that produces numerous innate and adaptive immune cells and maintains immunotolerance to non-pathological or constant inflammatory stimuli[39]. The ALBI grade, directly calculated from serum ALB and TBil values, was firstly proposed by Johnson et al. to assess liver function in patients with HCC [26]. Accumulating evidences show that higher ALBI grades were associated with poor prognosis, overall survival, and disease-free survival, as well as liver function and liver cancer stage in patients with HCC[33–36], superior to Child-Pugh (CP) score. Moreover, in patients with acute pancreatitis[28], the ALBI grades could reflect serious systemic inflammation associated with the increased levels of various cytokines, such as IL-1, IL-6, IL-8, tumor necrosis factor (TNF)-α, and platelet-activating factor. Serum ALB is involved in managing systemic inflammation reaction and organic oxidation resistance, and elevated serum TBil reflects the degree of liver damage. Considering the accumulating evidences and the vital role of systemic inflammation in the pathology of KD, it is reasonable to believe that the ALBI grade could reflect the inflammatory process in patients with KD. It has been demonstrated that serum ALB decreases because of increased permeability and leakage due to vascular inflammation in patients with KD. TBil levels are increased during hepatic vascular inflammation resulting in liver cell damage. Both parameters are associated with IVIG resistance and included in several risk-scoring systems for IVIG resistance prediction in KD[13, 15, 16, 40–43]. Consistent with findings that the ALBI grade was a powerful prognostic indicator in patients with the disease mentioned above, we found ALBI to be an independent risk factor for IVIG resistance in KD. Moreover, its predictive ability was more valuable and accurate than either ALB or TBil in IVIG resistance prediction. We speculated that the ALBI grade provided information on both ALB and TBil to predict the systemic inflammatory state and prognosis of patients with KD.

Besides, it is crucial to predict the development of CALs in KD. However, the ALBI grade did not differentiate between patients with KD with and without CALs [− 2.63 (−2.92–(−2.19)) vs. − 2.69 (−3.00 −(−2.42)), $p = 0.065$]. Previous findings suggested that persistent chronic inflammation may be more likely associated with the development of CALs. Compared with our baseline ALBI grade, fluctuations in ALBI may possess greater predictive power for CALs in patients with KD. Therefore, further studies that collect ALBI at different time points are necessary to classify its predictive ability and prognosis of CALs.

This study has some potential limitations. First, selective bias may occur as this study was performed in a single institution. Second, the findings may only be applicable to patients with KD receiving standardized IVIG treatment (2 g/Kg) > 10 days from fever onset. Despite the above limitations, this is the first prospective study to determine the predictive value of ALBI for IVIG resistance with large sample size. ALBI was significantly higher in patients with IVIG resistance and an independent risk factor for IVIG resistance. Due to an unknown origin of KD and in light of the above findings, we speculate that a prediction model combined with other specific indicators rather than clinical and routine laboratory variables might have a better outcome.

Conclusions

A higher ALBI was an independent risk factor for initial IVIG resistance, yielding better predictive ability than ALB and TBil alone for initial IVIG resistance. ALBI may provide some valuable references for clinical management in further studies.

Abbreviations

AHA American Heart Association

ALB Albumin

ALBI Albumin-bilirubin

ALT Alanine aminotransferase

BSA Body surface area

CALs Coronary artery lesions

CBC Complete blood count

CP Child-Pugh

CRP C-reactive protein

HCC Hepatocellular carcinoma

IL Interleukin

IQR Interquartile range

IVIG Intravenous immunoglobulin

KD Kawasaki disease

NPV Negative predictive value

PLT Platelet

PPV Positive predictive value

ROC Receiver operating characteristic

TBil Total bilirubin

TNF Tumor necrosis factor

Declarations

Ethics approval and consent to participate: Written informed consent was obtained from the parents following a full explanation of the nature of the study. The University Ethics Committee on Human Subjects at Sichuan

University approved the study.

Consent for publication: Written consent obtained

Availability of data and materials: All data generated or analyzed during this study are included in this published article and the supplementary files.

Competing interests: None of authors declared any conflict of interests.

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Authors' contributions

YY and QLN drafted the manuscript, contributed to the data collection, interpreted the statistical analysis and approved the final manuscript as submitted. SSR drafted the manuscript, provided supplementary materials and approved the final manuscript as submitted. ZNJ provided Figures, contributed to the data collection, study design and as well as approved the final manuscript as submitted. WM provided Tables, contributed to the data collection and approved the final manuscript as submitted. LL contributed to the data collection and approved the final manuscript as submitted. ZKY provided major treatment on these patients while admitted, contributed to the study design, approved financial support and as well as approved the final manuscript as submitted. WC and LXL conceived conception and designed the study, contributed to the data collection and approved the final manuscript as submitted.

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Figures

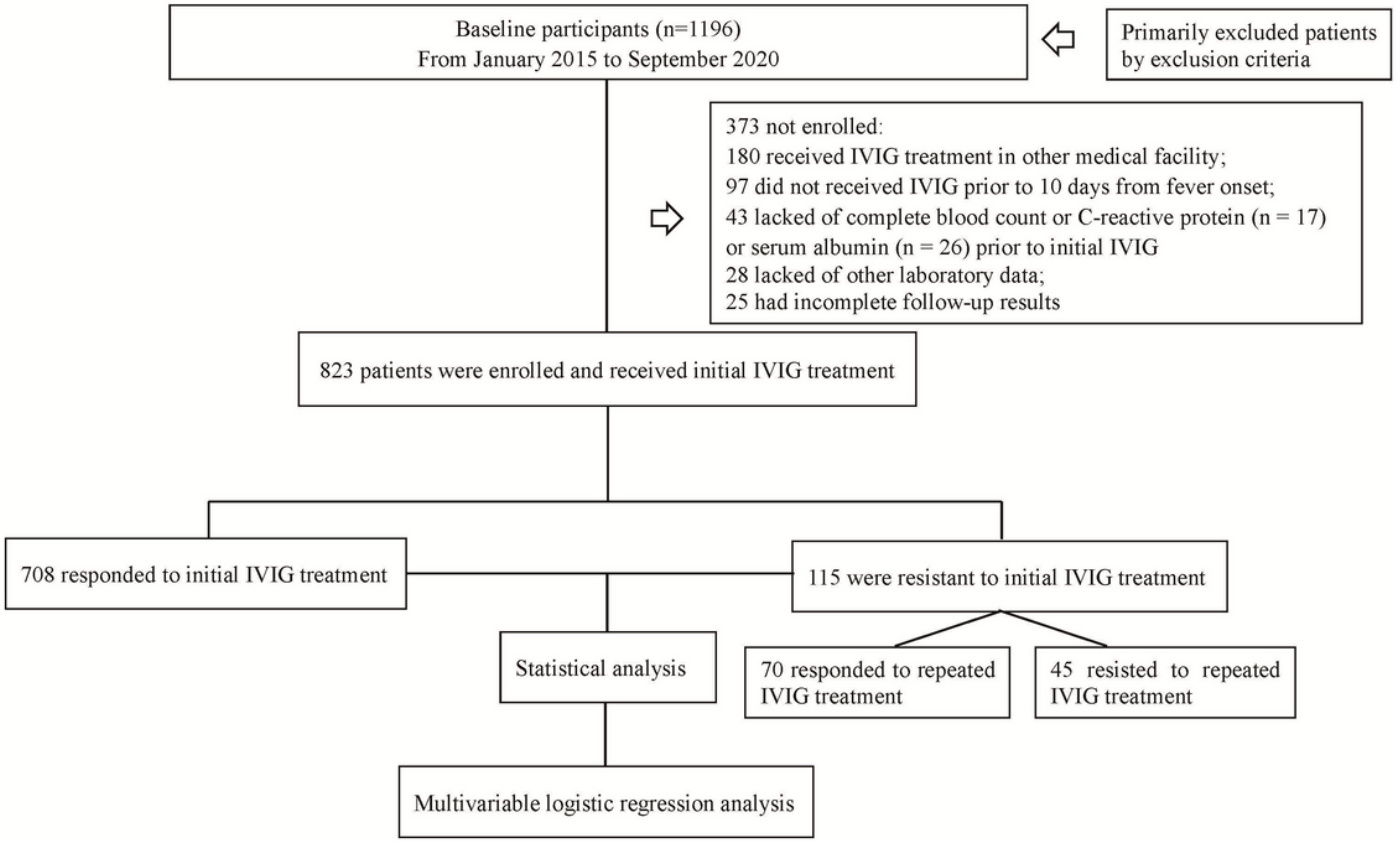

Figure 1

The flowchart of our prospective cohort study. From January 2018 to September 2020, 1196 patients were diagnosed with KD upon admission. Those who had received IVIG treatment in other medical facilities (n = 180) or did not receive IVIG treatment prior to 10 days from fever onset (n = 97) were excluded. Additionally, 43 patients were also excluded due to lack of data regarding complete blood count (CBC) or C-reactive protein(CRP) (n = 17) or serum ALB (n = 26) levels prior to initial IVIG treatment. We also excluded 53 patients because other laboratory data (n = 28) or follow-up results (n = 25) were incomplete. Finally, 823 patients were enrolled for analysis, including 708 initial IVIG responders and 115 initial IVIG non-responders. Of the 115 patients with initial IVIG resistance, 45 did not respond to repeated IVIG treatment and received pulse intravenous methylprednisolone infusion (Figure 1). No patients received additional treatment such as infliximab, plasma exchange or cytotoxic agents.

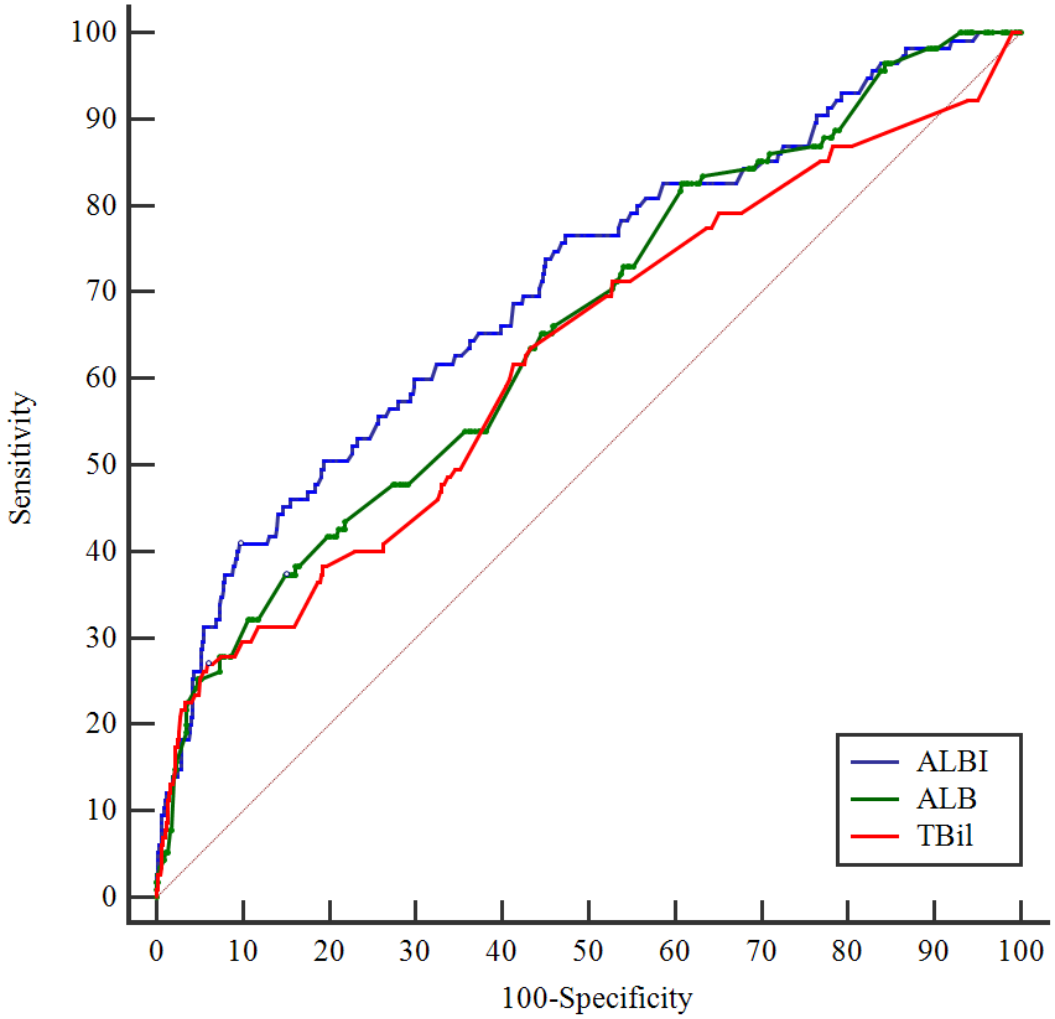

Figure 2

The receiver operating characteristic (ROC) curve for ALBI, ALB, and TBil in predicting initial IVIG resistance.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Supplementarymaterial1repeatedIVIGresistance.docx
- Supplementarymaterial2CALsvsnonCALs.docx