Research Square

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Prediction of Repeated Intravenous Immunoglobulin Resistance in Children With Kawasaki Disease

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Abstract

Background: Repeated intravenous immunoglobulin (IVIG) resistance prediction is one of the pivotal topics in Kawasaki disease (KD). Those non-responders of repeated IVIG treatment might be improved by an early-intensified therapy to reduce coronary artery lesion and medical costs. This study investigated predictors of resistance to repeated IVIG treatment in KD.

Methods: A total of 94 children with IVIG-resistant KD treated at our hospital between January 2016 and August 2020 were retrospectively analyzed. According to the therapeutic effect of a second dose IVIG treatment, the children were divided into repeated IVIG-responsive group and repeated IVIG-resistant group, and the clinical and laboratory data were compared. Predictors of repeated IVIG resistance and the optimal cut-off value were determined by multiple logistic regression analysis and receiver operating characteristic (ROC) curve analysis.

Results: The laboratory data of the percentage of neutrophils (N%) and levels of serum procalcitonin (PCT), N-terminal pro-brain natriuretic peptide (NT-proBNP) on admission were significantly higher in repeated IVIG-resistant group compared with repeated IVIG-responsive group, while levels of serum sodium (Na+) and albumin (ALB) were significantly lower (P<0.05). The clinic data showed no significant differences between the two groups. PCT exhibited the largest AUC (0.751) in predicting repeated IVIG resistance in KD compared with N%, Na+, ALB, and NT-proBNP. PCT>1.81ng/ml was an independent predictor of repeated IVIG resistance in KD (OR 4.161, 95% CI 1.441~12.017, P=0.008).

Conclusions: Our study illustrates the serum PCT level before initial IVIG treatment could be used to predict repeated IVIG resistance in KD.

Introduction

Kawasaki disease (KD) is an acute febrile systemic vasculitis syndrome and intravenous immunoglobulin (IVIG) combined with aspirin is the standardized regimen [1]. Approximately 10%-20% of the KD children have a recrudescence or persistent fever at least 36 h following completion of the first dose of IVIG, which is called IVIG-resistant [2]. Japanese risk-scoring systems are used for predicting IVIG-resistance, but it seems irreproducible outside Japan, and attempts to develop similar algorithms have been unsuccessful in Chinese populations [3–5]. As yet, treatment of resistant KD remains a challenge that needs to be solved [6, 7].

The mechanism of IVIG resistance is not entirely clear now and maybe related to the putative dose-response effect of immunoglobulin [8, 9]. A second dose of IVIG at 2 g/kg is suggested as the first choice for resistant KD in current American Heart Association (AHA) guidelines [1]. However, approximately 10% of KD children might develop to both initial and repeated IVIG resistance [10], and often require additional interventions, such as corticosteroid, infliximab, plasma exchange and cytotoxic agents [11, 12]. An intensified initial rescue therapy may reduce the occurrence of repeated IVIG resistance, but whether apply to every resistant KD child is controversial when taking into account potential adverse outcomes and the

economic cost of the treatment [13–17]. It seems more reasonable to consider intensified therapy if KD children with repeated IVIG resistance,that have high risk of coronary artery aneurysm (CAA) [18]. Therefore, early identification of repeated IVIG resistance could help physicians make smarter therapeutic decisions to reduce CAA and medical costs. Herein, we performed this study to explore predictors of repeated IVIG resistance.

Material And Methods

Study subjects

From January 2016 to August 2020, 940 children with KD were admitted and managed at Chengdu Women's and Children's Central Hospital, School of Medicine, University of Electronic Science and Technology of China (UESTC). The diagnosis of complete and incomplete KD was established according to the American Heart Association guideline in 2004 [19]. Among them, 112 KD children developed resistance to initial standard IVIG (2g/kg/d for 1 day) therapy. Initial IVIG resistance was defined as recurrent or persistent fever for at least 36 hours but not longer than 7 days after initial IVIG treatment. Of the 112 initial IVIG-resistant KD children, 9 patients that received steroids as initial rescue therapy instead of a second dose IVIG treatment were excluded, and another 9 children were excluded because of incomplete laboratory data (n = 5) or accompanying infectious diseases (n = 4). Finally, 94 initial IVIG-resistant KD children were included in the study (Fig. 1).

For 94 KD children with initial IVIG resistance, a second dose IVIG (2g/kg/d for 1 day) was administered according to expert consensus on the diagnosis and treatment of KD in China, and 40 of them developed repeated IVIG resistance. Repeated IVIG resistance was defined as recurrent or persistent fever for at least 36 hours after the second IVIG administration. At last, the initial IVIG-resistant KD children were divided into repeated IVIG-responsive group (n = 54) and repeated IVIG-resistant group (n = 40).

This retrospective study was approved by the Ethics Committee of Chengdu Women's and Children's Central Hospital, School of Medicine, UESTC, and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The requirement for informed patient consent was waived.

Data collection

Clinical and laboratory data were collected through medical record review. Clinical data such as age, sex, diagnosis of incomplete KD, time of first and second dose IVIG were collected. Laboratory data on admission before the initial IVIG treatment were collected, including white blood cell count (WBC), platelet (PLT), hemoglobin (Hb), percentage of neutrophils (N%), C-reactive protein (CRP), total bilirubin (TB), serum albumin (ALB), erythrocyte sedimentation rate (ESR), serum alanine aminotransferase (ALT), serum aspartate transaminase (AST), serum sodium (Na+), serum creatinine, blood urea nitrogen, activated partial thromboplastin time (APTT), prothrombin time (PT), D-dimer, procalcitonin (PCT), N-terminal pro-brain natriuretic peptide (NT-proBNP).

The value of coronary artery diameter measured by echocardiography before initial IVIG treatment and at discharge was selected and used to calculate the z score using the formula by Dallaire and Dahdah [20]. CAA was defined as Z score of ≥ 2.5 in at least one of the following coronary arteries: right, left anterior descending, and left main[20].

Statistical analysis

All statistical analyses were performed using IBM SPSS Statistics ver. 21.0 (IBM Co., Armonk, NY, USA).SPSS 20.0. All continuous variables are described as median with interquartile range (25–75% percentile). All categorical variables are described as a frequency with percentage. A $\chi 2$ test was performed to compare categorical variables. Student's t-test was used for normally distributed continuous variables. The Mann-Whitney U-test was used when the distribution was skewed. Receiver operating characteristic curve (ROC) analysis for the predictor was performed, the sensitivity and specificity were calculated, and the cutoff value was determined by the Youden index. Multivariate logistic regression analyses were performed to determine predictors of repeated IVIG resistance. Statistical significance was defined as a $P < 0.05$.

Results

Table 1 exhibits baseline characteristics of the repeated IVIG-responsive group and repeated IVIG-resistant group. Of the 54 patients in the repeated IVIG-responsive group, male outnumbered female by 44:10, the range of age was 2 months–84 months, 4 patients presented with incomplete KD, 12 patients had CAA before initial IVIG treatment and at discharge. Of the 40 patients in the repeated IVIG-resistant group, male outnumbered female by 26:14, the range of age was 9 months–120 months, 4 patients presented with incomplete KD, 12 had CAA before initial IVIG treatment and 14 had CAA at discharge. The median time of the first IVIG treatment for both groups was about 5–6 days after onset of illness, the second dose IVIG was administrated on a median time of 9–10 days. The clinical variables of sex, age, the proportion of incomplete KD, the incidence of CAA, and the time of IVIG treatment showed no significant differences between the two groups ($P > 0.05$). Among the laboratory data on admission, N% and levels of serum PCT, NT-proBNP were significantly higher in the repeated IVIG-resistant group compared with repeated IVIG-responsive group, while levels of serum sodium (Na+) and albumin (ALB) were significantly lower ($P < 0.05$).

Table 1
Comparison of characteristics between repeated IVIG-responsive group and repeated IVIG-resistant group in KD

Parameter	repeated IVIG-responsive group (n = 54)	repeated IVIG-resistant group (n = 40)	$t/Z/\chi^2$	*p*
Age(months)	35.0(13.0 ~ 60.0)	38.5(19.0 ~ 50.7)	0.245	0.807
Boys (%)	44(81.48%)	26(65.00%)	3.283	0.070
iKD[(%)]	4(7.40%)	4(10.00%)	0.198	0.656
Time of first IVIG (day)	6.0(5.0 ~ 6.0)	5.5(5.0 ~ 6.0)	0.620	0.535
Time of second IVIG (day)	10.0(8. 0 ~ 12.0)	9.00(8.0 ~ 12.7)	1.022	0.307
NO. of CAA before initial IVIG (%)	12(22.2%)	12(30.0%)	0.731	0.393
NO. of CAA at discharge (%)	12(22.2%)	14(35.0%)	1.875	0.171
WBC count ($\times 10^9$ /L)	16.51(10.25 ~ 20.59)	15.39(11.07 ~ 17.74)	0.245	0.807
N%	73.50(70.50 ~ 86.60)	84.60(74.97 ~ 89.15)	2.386	0.017*
Hb (g/L)	110(96 ~ 121)	103(92 ~ 115)	1.899	*0.061*
PLT ($\times 10^9$ /L)	284(215 ~ 381)	264(190 ~ 339)	1.361	0.173
CRP (mg/L)	106.5(73.0 ~ 141.0)	114.0(83.8 ~ 166.5)	1.573	*0.119*
ESR(mm/h)	81.0(52.0 ~ 100.0)	86.5(65.8 ~ 119.5)	0.964	*0.338*
ALT (U/L)	61.4(17.0 ~ 153.6)	66.0(28.0 ~ 136.9)	0.704	0.482
AST (U/L)	67.1(35.9 ~ 133.9)	41.5(33.2 ~ 97.7)	1.346	0.178
Na+ (mmol/L)	135.0(133.8 ~ 137.8)	133.0(130.3 ~ 136.9)	2.754	0.006*
ALB (g/L)	33.5(30.2 ~ 37.1)	30.2(29.3 ~ 33.3)	3.494	*0.001**
TB (umol/L)	12.6(9.8 ~ 17.8)	14.9(11.4 ~ 18.9)	1.380	0.167
Creatinine (umol/L)	30.8(26.7 ~ 35.0)	32(29.0 ~ 35.8)	1.197	*0.234*

*Statistically significant ($P < 0.05$)

IVIG: intravenous immunoglobulin; iKD: incomplete kawasaki disease; CAA: coronary artery aneurysm; NO.: number; WBC: white blood cell; Hb: hemoglobin; PLT: platelet; N%: percentage of neutrophils; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; ALT: alanine aminotransferase; AST: aspartate transaminase; Na+: serum sodium;ALB: albumin; TB: total bilirubin; APTT: activated partial thromboplastin time; PT: prothrombin time; PCT: procalcitonin; NT-proBNP: N-terminal pro-brain natriuretic peptide.

Parameter	repeated IVIG-responsive group (n = 54)	repeated IVIG-resistant group (n = 40)	$t/Z/X^2$	*p*
Urea nitrogen (mmol/L)	3.19(2.79 ~ 3.49)	3.33(2.83 ~ 3.90)	1.883	*0.063*
APTT(s)	47.8(43.5 ~ 52.5)	44.6(41.2 ~ 52.5)	0.933	0.351
PT(s)	15.3(14.5 ~ 16.8)	16.0(15.4 ~ 16.7)	1.945	0.052
D-dimer (ug/ml)	1.92(1.36 ~ 3.88)	2.34(1.44 ~ 3.89)	1.270	0.204
PCT (ng/ml)	1.40(0.99 ~ 2.84)	3.81(1.90 ~ 10.51)	4.153	< 0.001*
NT-proBNP(pg/ml)	487.1(182.3 ~ 763.9)	669.8(303.5 ~ 1493.8)	2.433	0.015*
*Statistically significant ($P < 0.05$)				
IVIG: intravenous immunoglobulin; iKD: incomplete kawasaki disease; CAA: coronary artery aneurysm; NO.: number; WBC: white blood cell; Hb: hemoglobin; PLT: platelet; N%: percentage of neutrophils; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; ALT: alanine aminotransferase; AST: aspartate transaminase; Na+: serum sodium;ALB: albumin; TB: total bilirubin; APTT: activated partial thromboplastin time; PT: prothrombin time; PCT: procalcitonin; NT-proBNP: N-terminal pro-brain natriuretic peptide.				

The ROC curves using N%, Na+, ALB, PCT and NT-proBNP to predict repeated IVIG resistance were analyzed (Fig. 2; Table 2). PCT exhibited the largest AUC (0.751) compared with other indicators. The classical cutoff points for PCT, N%, Na+, ALB, and NT-proBNP was 1.81 ng/ml, 133.8mmol/l, 32.2U/L, 965.8pg/dl, respectively. The sensitivity of PCT was revealed to be the highest, with values of 80.00%, compared with that of 75.00, 65.00, 70.00 and 45.00% for N%, Na+, ALB, and NT-proBNP at their classical cutoff points. The specificity of NT-proBNP was determined to be the highest, with a value of 85.19%, compared with that of 59.26, 74.07, 66.67 and 64.80% for N%, Na+, ALB, and PCT at their classical cutoff points.

Table 2
Receiver operating characteristic analysis to predict repeated IVIG resistance in KD

Indicator	AUC	P-value	95% CI	Cut-off	Sensitivity (%)	Specificity (%)	Youden index
N%	0.644	0.016	0.539 ~ 0.741	76.5 [a]	75.00	59.26	0.3426
Na+	0.667	0.005	0.562 ~ 0.761	133.8 [b]	65.00	74.07	0.3907
ALB	0.690	< 0.001	0.586 ~ 0.781	32.2 [c]	70.00	66.67	0.3667
PCT	0.751	< 0.001	0.710 ~ 0.879	1.81 [d]	80.00	64.80	0.4481
NT-proBNP	0.647	0.012	0.542 ~ 0.743	965.8 [e]	45.00	85.19	0.3019

[a] Values are ng/ml; [b] Values are mmol/l; [c] Values are U/L ; [d] Values are ng/ml; [e] Values are pg/ml.

N%: percentage of neutrophils; Na+: serum sodium; ALB: albumin; PCT: procalcitonin; NT-proBNP: N-terminal pro-brain natriuretic peptide; AUC, area under curve.

Using N%>76.5%, Na + ≤ 133.8mmol/l, ALB ≤ 32.2ng/ml, PCT > 1.81ng/ml, NT-proBNP > 965.8 pg/ml as binary independent variable, multivariate logistic regression analysis for repeated IVIG resistance in KD was analyzed (Table 3). The results showed that PCT > 1.81ng/ml was an independent predictor for repeated IVIG resistance (OR 4.161, 95% CI 1.441 ~ 12.017, $P = 0.008$).

Table 3
A multivariate logistic regression model for repeated IVIG resistance in KD

Indicator	*β*	*Wald*	*P*	*OR*	*95%CI*
N%>76.5%	0.781	1.808	0.179	2.183	0.699 ~ 6.815
Na + ≤ 133.8mmol/l	0.477	0.646	0.421	1.611	0.504 ~ 5.153
ALB ≤ 32.2ng/ml	0.800	2.117	0.146	2.226	0.758 ~ 6.541
PCT > 1.81ng/ml	1.426	6.943	0.008	4.161	1.441 ~ 12.017
NT-proBNP > 965.8 pg/ml	0.824	1.826	0.177	2.281	0.690 ~ 7.541

N%: percentage of neutrophils; Na+: serum sodium;ALB: albumin; PCT: procalcitonin; NT-proBNP: N-terminal pro-brain natriuretic peptide; AUC, area under curve.

Discussion

There have been numerous studies of initial IVIG resistance in KD, but few reports on repeated IVIG resistance [21–26]. In our retrospective investigation, the incidence of initial IVIG resistance was about 11.91% (112/940), and the rate of repeated IVIG resistance was about 4.25% (40/940). It has been reported that age less than 3 months, incomplete KD, incidence of CAA and initial administration of IVIG ≤ 4.0 days were associated with initial IVIG resistance [27–31]. The hypercoagulation of increased APTT, PT and D-dimer and the abnormal liver function of increased ALT, AST, TB were confirmed as the risk factors favor initial IVIG resistance [22, 32–35]. The raise of WBC, PLT, CRP, ESR, creatinine, blood urea nitrogen and the decline of Hb were also observed in KD children with initial IVIG resistance [35–38]. But, these clinical data and laboratory data were not associated with repeated IVIG resistance, since there were no differences between the repeated IVIG-responsive group and repeated IVIG-resistant group in our research. These differences have not been found in other studies either[21–24].

However, we founded that KD children with repeated IVIG resistance had higher N%, PCT, and lower ALB, Na + compared with KD children responding to repeated IVIG treatment, which is also confirmed associating with both initial and repeated IVIG resistance in other studies [21–23, 39–43], indicating more serious inflammation and increased vascular permeability [35, 44, 45]. It suggested these children may require more aggressive anti-inflammatory therapy. Whether enhancing initial anti-inflammatory treatment could decrease the incidence of CAA remains controversial [18, 46–49]. The incidence of CAA during hospitalization was relatively higher in KD children with repeated IVIG resistance in our study, despite lacking statistical differences. Meanwhile, a significantly higher level of NT-proBNP, which is an important cardiac biomarker that associating with ventricular myocyte ischemia and hypoxia [50], was observed in these children, indicating that timely control of inflammation could reduce myocardial injury.

Predictive values of N%, Na+, ALB, PCT and NT-proBNP on repeated IVIG resistance in KD were further explored in our study, and found that PCT > 1.81ng/ml (OR = 4.161) on admission may be an independent predictor of repeated IVIG resistance in KD yielded sensitivity of 80.00% and specificity of 64.80%. NT-proBNP yielded the highest specificity of 85.19% in our study, which was reported to be a predictor of initial IVIG resistance [33, 36, 51, 52], but it failed to predict repeated IVIG resistance, the reason may be due to relatively low sensitivity of 45.00%. At its root, perhaps, the mechanism of IVIG resistance is an immune response that causes systemic vasculitis, not only damage to the coronary arterial wall [53]. Production and secretion of PCT is promoted by inflammatory cytokines such as tumor necrosis factor-α and interleukin-6 [54], which are also major inflammatory factors of KD [55]. Endothelial cell function could be impaired by PCT under an inflammatory state, which leading to loss of an endothelial barrier that may contribute to capillary leakage, hypercoagulation, anti-angiogenic properties and even inducing endothelial cell death in vitro [45, 56–57]. Compared with NT-proBNP, PCT may be a better indicator of KD pathology, which may explain part of the mechanism underlying repeated IVIG resistance.

This study has some limitations. First, the sample size of this study is small, further multicenter prospective studies are needed to confirm our findings. Second, the present study had strict inclusion and exclusion criteria, the findings in our study were only applicable to KD patients receiving standardized IVIG treatment. Third, because laboratory data before repeated IVIG treatment were scarce, we only

investigated the laboratory data on admission. Further studies are needed to look into the laboratory data after the initial IVIG treatment.

Conclusions

KD children with repeated IVIG resistance have more serious inflammation and myocardial injury compared with KD children responding to repeated IVIG treatment. KD patients with PCT > 1.81ng/ml on admission might be at higher risk of developing repeated IVIG resistance, which may require an early-intensified therapy.

Abbreviations

KD: Kawasaki disease; IVIG: Intravenous immunoglobulin; CAA: Coronary artery aneurysm; N%: Percentage of neutrophils; ALB: Albumin; Na+: Serum sodium; PCT: Procalcitonin; NT-proBNP: N-terminal pro-brain natriuretic peptide

Declarations

Ethics approval and consent to participate

This retrospective study is approved by the Ethics Committee of Chengdu Women's and Children's Central Hospital, School of Medicine, UESTC, and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Due to the retrospective nature of the study, informed consent was waived.

Consent for publication

Not Applicable.

Availability of data and material

The datasets used and analyzed during the current study are not publicly available due to limitations of ethical approval involving the patient data and anonymity but are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no conflict of interest.

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Not applicable.

Authors' contributions

Yaheng LU and Yanfeng Yang provided study conception and design, wrote the first draft of the manuscript. Tingting Chen, Yizhou Wen, Feifei Si and Xindan Wu provided data collection and statistical analysis. All authors have revised and edited the manuscript and accepted the final version of the manuscript.

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Figures

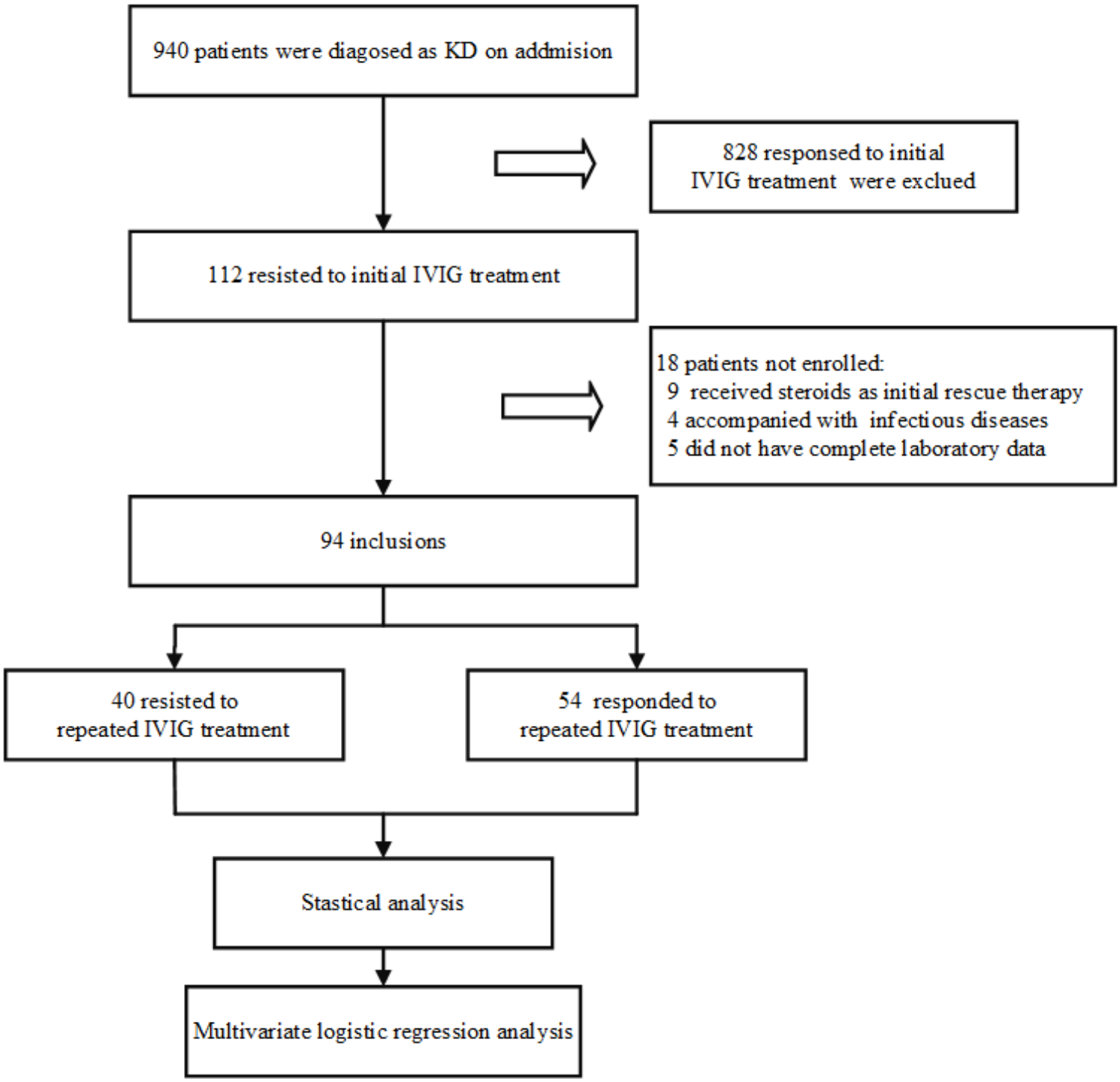

Figure 1

The flowchart of our retrospective study

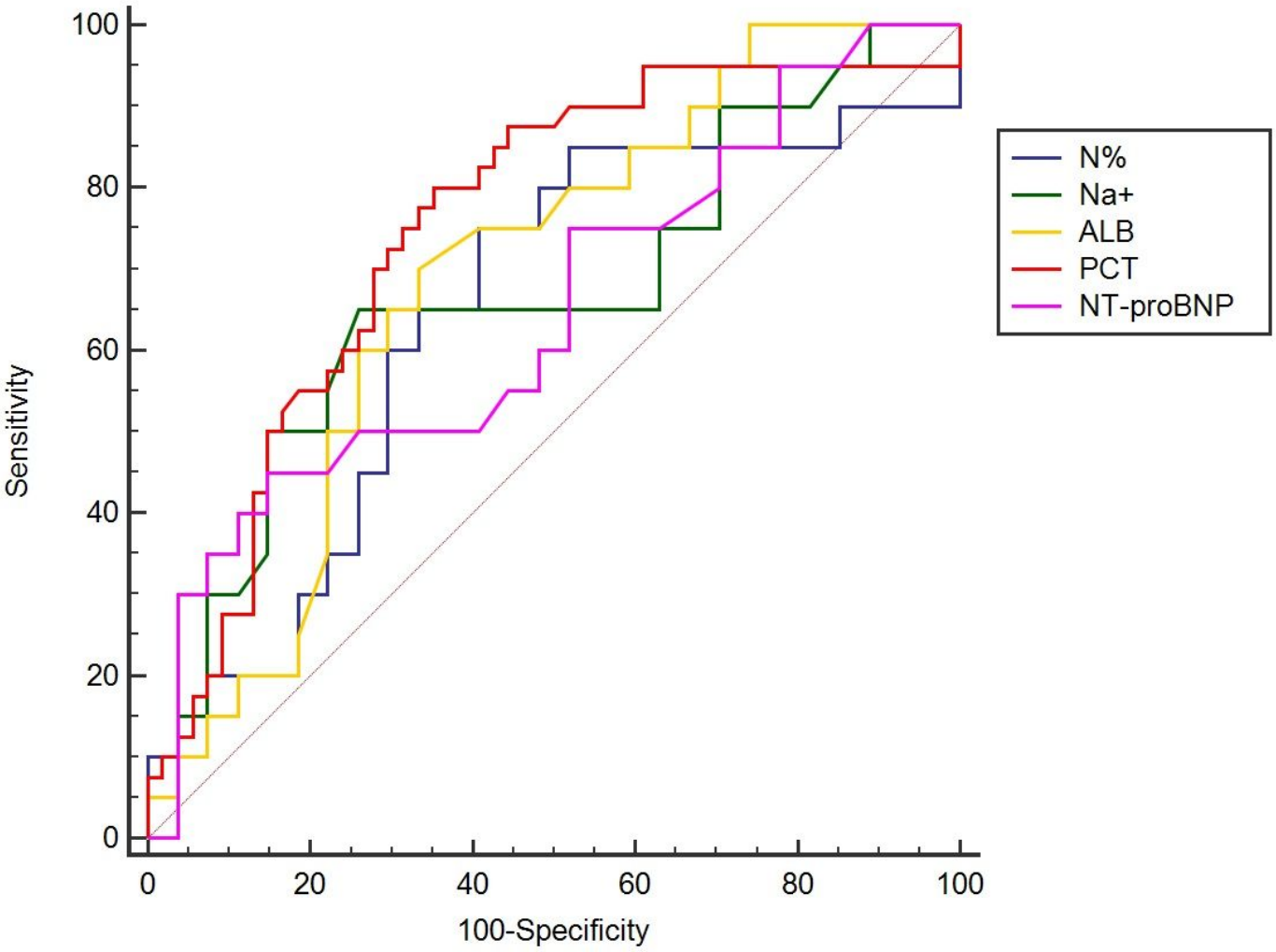

Figure 2

Receiver operating characteristic analysis in predicting repeated IVIG resistance in KD N%: percentage of neutrophils; Na+: serum sodium; ALB: albumin; PCT: procalcitonin; NT-proBNP: N-terminal pro-brain natriuretic peptide; AUC, area under curve.