# Predictive value of coagulation profiles for both initial and repeated immunoglobulin resistance in Kawasaki disease: a prospective cohort study

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**Abstract**

Background: Intravenous immunoglobulin (IVIG) resistance prediction remains substantial in Kawasaki disease (KD), with limited data on the predictive value of coagulation profile for IVIG resistance, particularly for repeated IVIG resistance. Therefore, the aim of our study was to testify the predictive validity of coagulation profile for both initial and repeated IVIG resistance in KD. Methods: A total of 385 KD patients were prospectively recruited between April in 2015 and May in 2019. Coagulation and other profiles were evaluated between IVIG-responsive and IVIG-resistant groups. Multivariate logistic regression analysis was applied to determine the association between coagulation profiles and IVIG resistance. ROC curves analysis was further performed to assess validity of coagulation profiles in predicting both initial and repeated IVIG resistance. Results: PT, APTT and D-dimer were significantly increased in initial IVIG-resistant group with ATIII significantly reduced. Meanwhile, ATIII was declined markedly in repeated IVIG-resistant patients. PT, APTT, D-dimer and ATIII cutoff values of 13.95 s, 41.15 s, 1.48 mg/l, and 89.5% yielded sensitivities of 73%, 32%, 71%, 81%; specificities of 55%, 88%, 62%, 51% for predicting initial IVIG resistance, respectively. The cutoff value of ATIII for predicting repeated IVIG resistance was 68.5%, with sensitivity of 71% and specificity of 55%. Multivariate logistic regression analysis showed that PT, APTT, D-dimer and ATIII were independent risk factors for initial IVIG resistant patients with KD. Conclusions: Coagulation profiles were significantly dysregulated in KD patients. Some of them particularly ATIII may serve as complementary laboratory markers for prediction of both initial and repeated IVIG resistance.

## Introduction

Kawasaki disease (KD) is an acute vasculitis that is the leading cause of acquired heart disease in children, with approximately 15-20% of patients with KD suffering intravenous immunoglobulin (IVIG) resistance[1]. For children who do not respond to initial IVIG treatment, repeated IVIG infusion is recommended by many experts[2]. However, approximately 10% of patients are resistant to both initial and repeated IVIG therapy[3], and thus have a higher risk of coronary artery lesions (CALs). Therefore, early identification of both initial and repeated IVIG resistance is of great importance to reduce CALs, and most importantly, lower medical costs.

It has long been known that inflammation triggered by acute infection can lead to activation of the coagulation system by upregulating the expression of cytokines[4]. In an investigation of critically ill patients, Ogura et al. found that abnormal coagulation was associated with increased systemic inflammatory response syndrome scores[5]. In addition, the relationship between the activation of the immune system and coagulation system is evident in systemic autoimmune or immune-mediated diseases[6]. Therefore, the balance between coagulation and the fibrinolytic system may be disturbed during the acute stages of KD, particularly in

patients with IVIG resistance, since KD vasculitis is accompanied by an increase in inflammatory cells and cytokines, and IVIG resistance may reflect a more severe inflammatory immune condition. Unfortunately, few reports analyze the correlation between coagulopathy and IVIG resistance in KD.

Therefore, a large prospective cohort study was conducted to assess the predictive validity of the serum coagulation profile, including prothrombin time (PT), activated partial thromboplastin time (APTT), thrombin time (TT), international normalized ratio (INR), and fibrinogen, D-dimer, fibrin degradation products (FDP), and antithrombin III (ATIII) levels for identifying patients with KD at risk for both initial and repeated IVIG resistance.

## Materials and Methods

### Subjects

Patients with KD were prospectively recruited between April 2015 and May 2019 at our hospital. A diagnosis of KD relied on the standards recommended by the American Heart Association's Scientific Statement for the diagnosis, treatment, and long-term management of KD[7] and was confirmed by two experienced pediatricians (at least one was a KD specialist). Informed written consent was obtained from the parents after the nature of the study had been fully explained to them. The University Ethics Committee on Human Subjects at Sichuan University approved the study.

Exclusion criteria included known patients with congenital or chronic hematologic disease affecting the coagulation cascade; patients with end-stage renal disease requiring dialysis, acute or chronic liver failure, and autoimmune disease; patients who had undergone surgery recently; patients with infectious or inflammatory diseases, and patients who received oral anticoagulant or heparin therapy. A total of 520 patients diagnosed with KD were initially screened for participation in this study. Of these, patients who had received initial IVIG treatment at other medical facilities (n=87), received IVIG treatment within 10 days of fever onset (n=12), or cases where IVIG treatment was initiated before blood sampling (n=17) were excluded. Another 19 patients were excluded because of incomplete laboratory data or lack of follow-up results (Figure 1). Finally, data from 385 patients were analyzed.

All patients received 2 g/kg of IVIG for 24 hours and 30–50 mg/kg/day of aspirin until they were afebrile. 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 7 days after initial IVIG treatment. For patients with initial IVIG resistance, the second IVIG dose (2 g/kg given as a single intravenous infusion) was administered according to expert consensus on the diagnosis and treatment of KD in China. Furthermore, pulse intravenous methylprednisolone (10-30 mg/kg/day for three consecutive days) followed by oral prednisone (2 mg/kg/day) tapered over seven days were additionally administered if the patient had recurrent or persistent fever even after the second IVIG administration. No patients received any additional treatment such as infliximab, plasma exchange, or cytotoxic agents. Coronary artery lesions (CALs) were defined on the normalization of dimensions for BSA as Z scores, according to the AHA scientific statement of KD[7].

Patients were subsequently categorized into two groups depending on whether they responded to the initial IVIG treatment (initial IVIG-responsive group, n=326; initial IVIG-resistant group, n=59). The initial IVIG-resistant group was further divided into two subgroups based on the effectiveness of repeated IVIG treatment [repeated IVIG-responsive group (n=36) and repeated IVIG-resistant group (n=23)].

### Laboratory measurements

Coagulation analyses of the patient's plasma, including PT, APTT, TT, fibrinogen, D-dimer, FDP, international normalized ratio, and ATIII activity, were performed before initial IVIG within 10 days from fever onset. Standard coagulation measurements were performed with a CoagXL-automated coagulometer (Diagon Ltd., Budapest, Hungary) using reagents from Diagon.

### Statistics

Data analyses were performed using SPSS version 21.0 (SPSS Inc. Chicago, IL, USA). Quantitative data are presented as the medians with the 25th and 75th percentiles in square brackets, while qualitative data are expressed as the number or percentage as appropriate. A chi-squared test and unpaired Student's t-test or Mann–Whitney U test were used to compare the demographic characteristics, clinical manifestations, and laboratory data. Significant indicators from univariate analysis were then subjected to multivariate logistic regression analysis to identify independent predictors of IVIG resistance. Receiver operating characteristic (ROC) curve analysis was used to evaluate the value of coagulative biomarkers for predicting the development of initial and repeated IVIG resistance. A P-value <0.05 was considered statistically significant.

## Results

### Subjects

CALs were observed in 47 patients (12.2%), while transient pericardial effusion, valve regurgitation, cardiac enlargement, and ventricular systolic dysfunction were noted in 11, 40, 38, and 2 children, respectively. No significant difference was found in serum coagulation profiles between the CALs and non-CALs groups. (Supplemental material 1).

### Serum coagulation levels for predicting initial IVIG resistance

As shown in Table 1, there were no significant differences in age, sex, the day of illness before IVIG treatment, sampling day of illness, and typical clinical manifestations between the initial IVIG-responsive and IVIG-resistant groups. As for other cardiac complications, the percentage of patients with cardiac enlargement and pericardial effusion was found to be significantly higher in the initial IVIG-resistant group (p=0.003 and p=0.016, respectively). Initial IVIG-resistant patients had much higher incidence of CALs, with substantial higher level of serum C-reactive protein (CRP), neutrophil-lymphocyte ratio (NLR), serum total bilirubin (TB), serum alanine aminotransferase (ALT), creatinine, urea nitrogen, but with lower hemoglobin, platelet count, albumin, sodium, potassium before the initial IVIG treatment (all $P < 0.005$). No significant differences were found in the white blood cell count, erythrocyte sedimentation rate, and aspartate aminotransferase between the two groups.

The effect of KD on the coagulation system was evaluated by assessing the coagulation profiles of initial IVIG-responsive and IVIG-resistant subjects. The PT (14.3 [13.6-15.5] s vs. 13.8 [13-14.4] s, p=0.005) and APTT (35.3 [31.9-44.7] s vs. 34.2 [30.7-38.1] s, p=0.006) were significantly longer in the initial IVIG-resistant group, with significantly higher D-dimer levels (2.1 [1.20-2.82] mg/l vs. 1.2 [0.8-2.07] mg/l, p=0.020) as well as ATIII activity (81% [65-88%] vs. 89% [81-100%], p<0.001) (Table 1).

### Multivariate logistic regression and ROC curve analysis for predicting initial IVIG resistance

To not affect the prediction efficiency, the correlation between univariate factors and coagulation profiles were tested by Pearson analysis. The strong variables were removed from the model (Supplemental material 2). Multivariate logistic regression analysis showed that longer PT, APTT, higher D-dimer and lower ATIII activity were independent risk factors for initial IVIG resistance in patients with KD (Table 2).

The validity of the serum coagulation profile in predicting initial IVIG resistance in patients with KD was assessed using ROC curve analysis. The areas under the curve (AUC) of the various variables for predicting IVIG resistance were 0.662, 0.599, 0.684, and 0.706 for PT, APTT, D-dimer, and ATIII, respectively. The PT, APTT, D-dimer and ATIII cutoff values of 13.95 s, 41.15 s, 1.48 mg/l, and 89.5% yielded sensitivities of 73%, 32%, 71%, 81%; specificities of 55%, 88%, 62%, 51% for predicting initial IVIG resistance, respectively (Table 3 and Figure 2A).

### Serum coagulation levels for predicting repeated IVIG resistance

A comparison of clinical data between the repeated IVIG-responsive (n=33) and repeated IVIG-resistant (n=26) groups is shown in Table 4. The repeated IVIG-resistant subjects had lower ATIII activity than those of repeated IVIG-responsive subjects (65% [60-81%] vs. 84% [76.23-89.75%], p=0.001). There was no significant difference in any other examined parameters between the two groups.

ROC curve analysis for predicting repeated IVIG resistance

ROC curves were used to calculate the AUC and predictive values of each coagulation parameter (Table 3 and Figure 2B). The AUC of ATIII for predicting repeated-KD patients was 0.753. In repeated-KD patients, the cutoff value of ATIII was 68.5%, which yielded a sensitivity of 71%, specificity of 55% for predicting repeated-IVIG resistance.

Discussion

To the best of our knowledge, this is the first study to clarify the association between coagulation and IVIG resistance in patients with KD based on a relatively large clinical dataset. In this prospective study, we support the hypothesis that there are marked differences in coagulation profiles, including longer PT and APTT, higher D-dimer levels, and lower ATIII activity, that may predict initial IVIG resistance. In addition, using multivariate logistic regression analysis, we found that longer PT, APTT, higher D-dimer and lower ATIII activity before initial IVIG were significant independent risk factors for initial IVIG resistance. Furthermore, significantly lower ATIII activity was found in patients with repeated IVIG resistance. Our results suggest that patients with impaired coagulation who are resistant to IVIG (initial and/or repeated) may need more aggressive treatment to reduce the likelihood of developing CALs.

Previous evidence has shown that coagulative profiles play an important role in sepsis and are associated with severe outcomes[8]. However, whether coagulative biomarkers can predict the development of IVIG resistance in KD remains unclear as few studies have been published to date. Recently, Chen et al. compared the changes in coagulation between acute KD patients and healthy controls[9]. The authors showed higher D-dimer levels and prolonged APTT and PT in KD, suggesting hypercoagulation as a common complication of KD. However, the results were limited by the small sample size (n=20) and retrospective nature of the study. Unlike previous studies, we found the predictive validity of coagulation biomarkers in IVIG resistance based on a relatively larger sample size. Severe infection and inflammation might be the possible pathomechanisms for impaired coagulation in IVIG-resistant patients[10]. First, infection is one of the most recognized causes in patients with KD[11]. In our preliminary study, we found that serum procalcitonin was significantly elevated in both the initial and repeated IVIG-resistant groups compared to that in non-responders[12]. Procalcitonin has been widely proven to be a significant biomarker for severe bacterial infection and sepsis[13]. In addition, cytokine storms, which have been demonstrated in systemic infections, play a central role in the different effects on the coagulation and fibrinolysis pathways[14]. Therefore, longer PT and APTT, higher D-dimer levels, and lower ATIII activity in IVIG-resistant patients with KD in our study may suggest a more noticeable impact of coagulation and reflect more severe inflammation in this population.

The present study indicated that initial IVIG-resistant patients have longer PT and APTT. The results of our study were consistent with those of Benediktsson et al., who found prolonged APTT and PT in sepsis patients[15]. PT and APTT are traditionally modeled as extrinsic and intrinsic pathways that join to form a common pathway[16]. In the study by Aird et al., inflammation-induced activation of the coagulation system was found to be initiated by the extrinsic pathway and amplified by the intrinsic pathway via crosstalk and a feedback loop[17]. Several studies have revealed that blocking tissue factor activity completely decreases inflammation-induced coagulation activation in models of experimental endotoxemia or bacteremia[14, 18]. Therefore, elevated PT and APTT may be associated with initial IVIG resistance in KD. However, APTT should be cautiously used in clinical settings as a single biomarker for predicting initial IVIG resistance because of the relatively low sensitivity (32.0%).

AT, also called AT III, is the main inhibitor of thrombin and factor Xa, which plays a role in thrombin generation[19]. In our study, significantly lower ATIII activity in the initial and repeated IVIG-resistant patients was observed. This finding is consistent with previous reports[20] and corresponds with the fact that inflammation leads to the activation of coagulation, and coagulation markedly affects inflammatory activity[21]. In the study by Xie et al., ATIII reduction was found to be closely related to the prognosis of patients with sepsis[22]. One possible explanation is that decreased ATIII activity increases fibrin formation and insufficient fibrinolysis, which could cause microvascular thrombus[23]. Therefore, based on the results of

the present study, ATIII activity may be a risk factor for predicting IVIG resistance in patients with KD.

D-dimer is the smallest FDP (molecular weight: 180 kDa) in the process of fibrinolysis, it is relatively stable and considered the final product of fibrinolysis[24].[25]. Previous studies have found that D-dimer is associated with severe sepsis or septic shock[8]. In our study, patients with initial IVIG resistance had higher D-dimer levels. This result was in line with a study by Panigada et al., who found that sepsis patients were characterized by higher levels of D-dimer[8]. Similar results were also reported by Wang et al., who demonstrated that elevated D-dimer was a risk factor for severe outcomes in patients with bacterial infections[26]. The above findings may be explained by the imbalance between the coagulation system and inflammatory pathways in infected patients as fibrinolytic activators and inhibitors modulate the inflammatory response by their effects on inflammatory cell recruitment and migration[27, 28]. In a study by Shorr et al., higher proinflammatory cytokine levels were found in those with higher D-dimer levels, indicating a potential relationship between the coagulation system and inflammation[29]. Therefore, in the acute stage of KD, increased D-dimer levels may be used as a predictor for initial IVIG treatment failure.

The strengths of this study were its prospective design and relatively large sample size. However, the present study has several limitations. First, this study was performed at a single institution. Our hospital is the largest pediatric medical center in Southwest China, which may lead to a selection bias due to a higher number of severely ill patients being admitted to this facility. Second, the present study was a prospective cohort study with strict inclusion and exclusion criteria. The findings of this study are, therefore, applicable only to Chinese patients with KD receiving standardized IVIG treatment (2 g/kg) within 10 days of fever onset.

Despite these limitations, this prospective study is the first to report pronounced changes in PT, APTT, D-dimer levels, and ATIII activity in the acute stage of KD, which may serve as complementary laboratory biomarkers for predicting IVIG resistance. In addition, the predictive validity of ATIII activity as a single biomarker for IVIG resistance may be superior to other coagulation biomarkers with a relatively high sensitivity.

Conclusions

In summary, the inflammatory process mediated by KD is associated with the cause of impaired coagulation, which supports the notion that patients with KD who also have hypercoagulation during the acute phase could be at higher risk of developing IVIG resistance.

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**Tables**

**Table1.** Comparison of clinical data between the groups of initial IVIG-resistant and IVIG-responsive in KD

**Table2.** A multivariate logistic regression model for initial IVIG resistance in patients with KD

**Table3.** The validity of coagulation profile cut-off values in predicting initial and repeated IVIG resistance.

**Table4.** Comparison of clinical data between the groups of repeated IVIG-resistant and IVIG-responsive in KD

**Figure Legends**

**Figure 1.** The flowchart of our prospective study

A total of 520 patients diagnosed with KD were initially screened for participation in this study. Of these, patients who had received initial IVIG treatment at other medical facilities (n=87), received IVIG treatment within 10 days of fever onset (n=12), or cases where IVIG treatment was initiated before blood sampling (n=17) were excluded. Another 19 patients were excluded because of incomplete laboratory data or lack of follow-up results. Finally, data from 385 patients were analyzed. Of the 385 patients, 326 (84.7%) responded to initial IVIG treatment, whereas 59 (15.3%) did not respond. Of the 59 patients with initial IVIG resistance, 23 did not respond to repeated IVIG treatment and received pulse intravenous methylprednisolone infusion. Then data analysis and multivariate logistic regression analysis were performed in these groups.

**Figure 2.** The receiver-operating characteristic (ROC) curve for coagulation profiles in predicting initial and repeated IVIG resistance. (A) ROC curve for coagulation profiles (PT, APTT, D-dimer, ATIII) in predicting initial IVIG resistance. (B) ROC curve for ATIII in predicting repeated IVIG resistance.

**Supplemental material 1** . Comparison of coagulation profiles between the groups of CALs and non-CALs group in KD

**Supplemental material 2** . Clinical correlation between univariate factors and coagulation profile in the KD subjects

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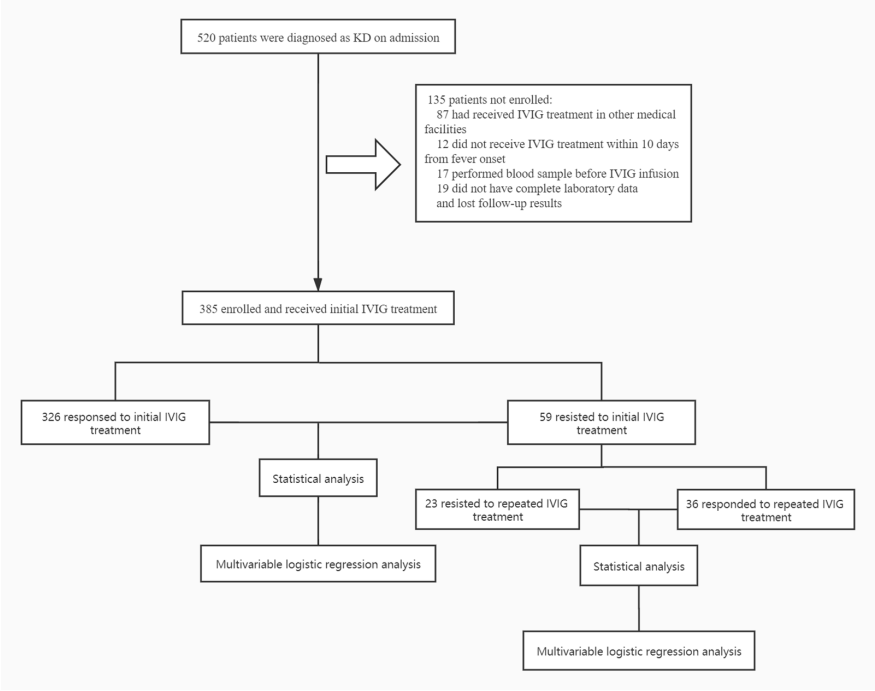


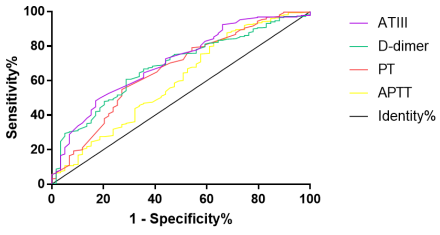


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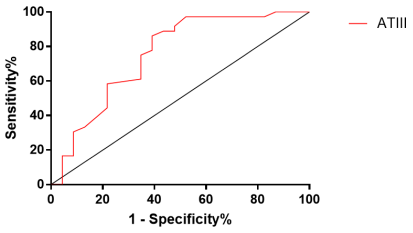


ROC curve for predicting repeated IVIG resistance

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