

# Impact of D-Dimer on the Resistance to Intravenous Immunoglobulin Therapy in Kawasaki Disease

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## Abstract

**Aim:** To investigate the impact of D-dimer on the resistance to intravenous immunoglobulin therapy (IVIG) in Kawasaki Disease

**Patients:** From 2013 through 2016, 225 patients were newly diagnosed as Kawasaki Disease at our institute. Among them, Kobayashi score (K-score) was available for 203 patients, and D-dimer before treatment was measured in 131 patients, in which 119 patients were initially treated with IVIG. These 119 patients were analyzed.

**Results:** K-score was not associated with IVIG resistance efficiently (odds ratio of 1.78, 95%CI: 0.68-4.69,  $p = 0.24$ ). However, odds ratio was improved to 2.52 (95%CI: 0.88-7.25,  $p = 0.08$ ) for 101 patients in which D-dimer was  $< 2.5\mu\text{g/mL}$ . On the contrary, D-dimer value  $\geq 2.5\mu\text{g/mL}$  was associated with IVIG resistance with odds ratio of 3.26 (95%CI: 1.17-9.10,  $p = 0.02$ ) and D-dimer value  $\geq 4.0\mu\text{g/mL}$  with odds ratio of 5.98 (95%CI: 1.10-32.42,  $p = 0.02$ ) as an independent factor.

**Conclusion:** Association of K-score with IVIG resistance is limited, and elevated D-dimer before treatment is a significant independent risk factor for IVIG resistance even in the patients with low K-score.

**Keywords:** Kasawaki Disease, intravenous immunoglobulin therapy, D-dimer, Kobayashi score

**Abbreviations:** ASA: acetylsalicylic acid; CAL: coronary artery lesions; IVIG: intravenous high dose immunoglobulin; KD: Kawasaki disease; K-score: Kobayashi score; PSL: prednisolone

## Introduction

Kawasaki Disease (KD) is an inflammatory disease of unknown etiology and is diagnosed based on six main clinical symptoms and develops mostly in children less than four years old [1,2].

The Coronary Artery Lesions (CAL) during the acute phase is well known serious complications.

Although the precise long term prognosis of CAL is yet to be determined, it is known to cause acute myocardial ischemia or infarction eventually and the subsequent sudden death in some cases [3].

The incidence of CAL has been decreased from 20% to less than 3% dramatically through the early introduction of intravenous high dose immunoglobulin (2g/kg) therapy (IVIG) in combination with oral Acetylsalicylic Acid (30mg/kg/day) (ASA) during the past three decades [4].

Furthermore, more intensive therapy is applied primarily to high risk group to reduce CAL based on the prognostic risk scoring systems such as Kobayashi score system (K-score), because CAL is more frequently observed in high risk group which tends to show resistance to IVIG [5,6]. Recently, targeting therapy to TNF- $\alpha$  has been shown effective to refractory KD [7]. However, the usefulness and effectiveness of K-score system have been argued recently by several reports from different countries [8-10].

KD is classified in medium vessel vasculitis pathologically. In general, primary treatment for vasculitis is based on the control of inflammation with corticosteroid [11]. D-dimer is regarded as a useful and sensitive indicator of vasculitis and widely used clinically [12]. On the contrary, the widely used K-score system does not include the factor that directly reflects the progression of vasculitis.

We investigated the impact of D-dimer on the resistance to initial IVIG therapy and evaluated the usefulness of K-score system.

## Methods and Patients

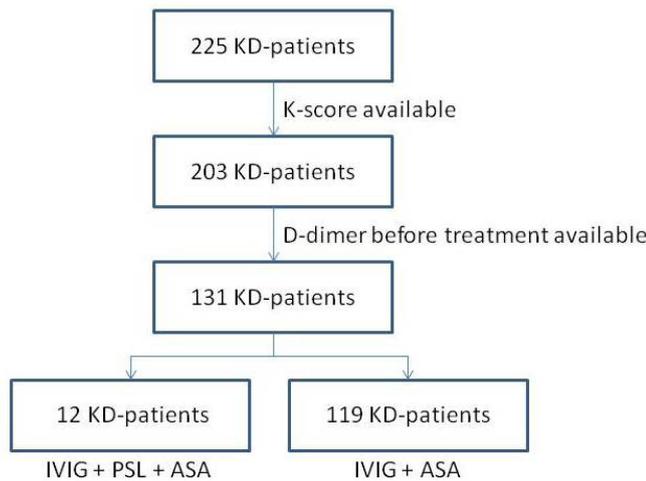
From 2013 through 2016, 225 patients were newly diagnosed as KD at our institute. Diagnosis of KD was performed according to the Diagnostic Guidelines for Kawasaki Disease (the 5<sup>th</sup> revised edition) [13]. Among them, K-score was available for 203 patients before IVIG therapy, and D-dimer before treatment was measured in 131 patients (Figure 1). From January, 2013 to June, 2016, IVIG plus ASA therapy was performed to KD patient primarily. From July, 2016, we conducted risk stratification by the K-score system, and Prednisolone (PSL) 2mg/kg/day was added together to 12 high-risk group (K-score $\geq 5$ ) patients as an initial treatment according to the report [6]. Clinical feature and evaluation of this cohort have been reported in detail elsewhere [10]. We investigated the relation of K-score and D-dimer with initial resistance to IVIG plus ASA therapy, retrospectively.

Statistical analysis was performed by  $\chi^2$  test and  $p < 0.05$  was determined statistically significant.

Resistance to IVIG plus ASA therapy was defined as follows; decline of fever ( $< 37.5^\circ\text{C}$ ) was not obtained or fever was re-increased again more than  $37.5^\circ\text{C}$  within 24 to 36 hours after IVIG injection. The second IVIG therapy with or without Prednisolone (PSL) was applied to resistant patients.

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**Figure 1:** Flow chart of patient recruitment.

**Results**

Flow chart of patient recruitment is presented in Figure 1. In the previous study, 203 KD patients in which K-score was available were analyzed for the relation of IVIG resistance with K-score [10]. D-dimer before treatment was available in 131 KD patients.

Among 131 patients, D-dimer value was within normal range (<1µg/mL) in 35 patients (26.7%), and below 2.5µg/mL in 113 patients (86.3%). In 119 patients who received initial IVIG plus ASA therapy, D-dimer value was within normal range in 32 cases (26.9%), and less than 2.5 µg/mL in 101 cases (84.9%). In these 119 patients, K-score was not associated with IVIG resistance significantly (odds ratio of 1.78, 95%CI: 0.68-4.69, P = 0.24 by  $\chi^2$  test) with sensitivity of 0.24 and specificity of 0.30. However, K-score was associated with IVIG resistance relatively well (odds ratio of 2.52, 95%CI: 0.88-7.25, P = 0.08 by  $\chi^2$  test) in 101 patients in which D-dimer was less than 2.5µg/mL with sensitivity of 0.29 and specificity of 0.74. In 18 cases with D-dimer  $\geq$  2.5µg/mL before the treatment, 10 patients showed IVIG resistance (55.6%), and the K-score was  $\geq$ 5 in only one patient in them (Table1-a).

D-dimer value of more than 2.5µg/mL was significantly associated with IVIG resistance (odds ratio of 3.26, 95%CI: 1.17-9.10, P = 0.02 by  $\chi^2$  test) as an independent factor, with sensitivity of 0.26 and specificity of 0.72. In cases with D-dimer  $\geq$ 4.0µg/mL, odds ratio of IVIG resistance was increased up to 5.98 (95%CI: 1.10-32.4, P=0.02 by  $\chi^2$  test) (Table 2).

Between cases with D-dimer of less than 2.5µg/mL and D-dimer of 2.5µg/mL and more, there was no significant difference in age (35.1+/-30.2 vs 37.2+/-29.6 months old; mean+/-SD), C-reactive protein value (7.68+/-4.76 vs 7.98+/-4.76 mg/dL; mean+/-SD), white blood cell count (13,750+/-5,043 vs 13,624+/-5,307 /µL; mean+/-SD),

**Table 1a:** IVIG resistance in 119 KD patients in whom D-dimer was available before IVIG.

D-dimer range (µg/mL)	n	K-s $\geq$ 5	IVIG resistant	K-s $\geq$ 5 in IVIG resistant
D-d<1	32	2	11	1
1 $\leq$ D-d<2	55	13	15	6
2 $\leq$ D-d<2.5	14	3	2	1
2.5 $\leq$ D-d<3	4	1	3	1
3 $\leq$ D-d<4	7	0	2	0
4 $\leq$ D-d	7	2	5	0

K-s: Kobayashi score; D-d:D-dimer

**Table 1b:** IVIG resistance in 12 KD patients who received IVIG plus PSL as an initial treatment because of K-s $\geq$ 5.

D-dimer range (µg/mL)	K-s $\geq$ 5	resistant to IVIG plus PSL
D-d<1	3	0
1 $\leq$ D-d<2	5	0
2 $\leq$ D-d<2.5	4	3
2.5 $\leq$ D-d<3	0	0
3 $\leq$ D-d<4	0	0
4 $\leq$ D-d	0	0

K-s: Kobayashi score; D-d:D-dimer

**Table 2:** Impact of D-dimer before treatment on IVIG resistance.

Cut off	sensitivity	specificity	positive predictive value	odds ratio	p-value
D-d $\geq$ 1µg/mL	0.71	0.66	0.31	0.86	0.73
D-d $\geq$ 2µg/mL	0.32	0.7	0.38	1.41	0.43
D-d $\geq$ 2.5µg/mL	0.26	0.72	0.56	3.26	0.02*
D-d $\geq$ 3µg/mL	0.18	0.94	0.58	3.43	0.04*
D-d $\geq$ 4µg/mL	0.13	0.98	0.71	5.98	0.02*
K-s $\geq$ 5	0.24	0.3	0.43	1.78	0.24

K-s: Kobayashi score; D-d:D-dimer; \*: statistically significant

serum Na (135.2+/-2.8 vs 134.4+/-3.4 mEq/L; mean+/-SD) and Alanine Aminotransferase (ALT) (103+/-198 vs 114+/-207 IU/L; mean+/-SD) before the treatment.

**Discussion**

In our cohort of 119 KD patients in whom D-dimer was available before IVIG plus ASA therapy, specificity of IVIG resistance by K-score was as low as 0.30, which was extremely worse than 0.80 in the primary report [5]. To reduce the failure of initial treatment, some other factors have to be taken into account for therapy stratification.

Our observation showed that D-dimer value of more than 2.5µg/mL can be a significant risk factor for IVIG resistance regardless of K-score with an odds ratio of 3.26 (95%CI: 1.17-9.10, p = 0.02) and specificity of 0.72.

Furthermore, among 12 patients with K-score  $\geq$  5 who subsequently received IVIG plus PSL plus ASA as an initial treatment, three cases presented resistance to initial treatment, and D-dimer value before treatment was more than 2.0µg/mL in all three resistant cases (Table1-b), and one of three developed coronary artery aneurysm in spite of subsequent infliximab administration.

From the above observation, K-score system was relatively useful for a case with low D-dimer level as a stratification method for an initial treatment of KD, but not useful enough for a case with high D-dimer level.

Recently, the reports from US and UK cohort have shown that sensitivity and specificity of IVIG resistance by K-score system were not as good as previously reported [8,9]. We have also reported that K-score system was not sufficient enough to predict IVIG resistance in Japanese patient cohort [10]. Especially, significant number of IVIG resistant cases was still involved in low K-score group. Other clinical factors that extract IVIG resistant cases efficiently in low K-score group have to be determined to reduce IVIG resistant cases.

It has been reported that D-dimer was associated with a severity or risk for CAL of KD [14,15]. In these papers, elevation of D-dimer

was speculated to be an early sign of coronary aneurysm formation and subsequent micro-thrombosis. Our study indicates that high D-dimer value itself also works as an independent risk factor to predict resistance to IVIG in low K-score group.

The conventional K-score system might underestimate the severity or progression of vasculitis in some cases of KD, especially with high D-dimer value. D-dimer value before IVIG therapy should be taken into account for the evaluation of severity and treatment stratification of KD.

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