Meta-analysis of factors predicting resistance to intravenous immunoglobulin treatment in patients with Kawasaki disease

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Purpose: Studies have been conducted to identify predictive factors of resistance to intravenous immunoglobulin (IVIG) for Kawasaki disease (KD). However, the results are conflicting. This study aimed to identify laboratory factors predictive of resistance to high-dose IVIG for KD by performing meta-analysis of available studies using statistical techniques.

Methods: All relevant scientific publications from 2006 to 2014 were identified through PubMed searches. For studies in English on KD and IVIG resistance, predictive factors were included. A meta-analysis was performed that calculated the effect size of various laboratory parameters as predictive factors for IVIG-resistant KD.

Results: Twelve studies comprising 2,745 patients were included. Meta-analysis demonstrated significant effect sizes for several laboratory parameters: polymorphonuclear leukocytes (PMNs) 0.698 (95% confidence interval [CI], 0.469–0.926), C-reactive protein (CRP) 0.375 (95% CI, 0.086–0.663), pro-brain natriuretic peptide (pro-BNP) 0.561 (95% CI, 0.261–0.861), total bilirubin 0.859 (95% CI, 0.582–1.136), alanine aminotransferase (AST) 0.503 (95% CI, 0.313–0.693), aspartate aminotransferase (ALT) 0.436 (95% CI, 0.275–0.597), albumin 0.427 (95% CI, −0.657 to −0.198), and sodium 0.604 (95% CI, −0.839 to −0.370). Particularly, total bilirubin, PMN, sodium, pro-BNP, and AST, in descending numerical order, demonstrated more than a medium effect size.

Conclusion: Based on the results of this study, laboratory predictive factors for IVIG-resistant KD included higher total bilirubin, PMN, pro-BNP, AST, ALT, and CRP, and lower sodium and albumin. The presence of several of these predictive factors should alert clinicians to the increased likelihood that the patient may not respond adequately to initial IVIG therapy.

Key words: Mucocutaneous lymph node syndrome, Intravenous immunoglobulins, Predictive value of tests, Meta-analysis

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Introduction

Kawasaki disease (KD) is the most common cause of acquired cardiac disease in children. It can cause systemic vasculitis and lead to serious coronary complications.

Although high-dose intravenous immunoglobulin (IVIG) treatment in the acute stage of KD has shown to be effective, 10% to 20% of patients are resistant to initial IVIG treatment. These patients are at the greatest risk of developing coronary artery aneurysm, coronary artery stenosis, myocardial infarction and other serious complications[1].

IVIG resistance is defined as needing second dose of IVIG because of persistent or recrudescent fever, despite initial IVIG treatment. Recent studies have investigated factors

for predicting resistance to IVIG for KD, but their results have been conflicting.

The aim of this study was to find laboratory factors predicting resistance to high-dose IVIG for KD by searching PubMed and performing meta-analysis on the data using statistical techniques.

Materials and methods

All relevant scientific publications were identified through PubMed searches. Search terms included "Kawasaki disease, IVIG resistance" or "IVIG resistant Kawasaki disease" combined with a second identifying phrase, "predictive factors or risk factors" Studies spanned the period from 2006 to 2014. Before including a study in our meta-analysis, we applied several inclusion and exclusion criteria

1. Inclusion criteria

To be included in the meta-analysis of this study, all articles had to meet the following criteria:

(1) Retrospective or prospective cohort study design investigating KD.

(2) A population focus on children (aged 0–18 years) receiving IVIG therapy within a hospital setting.

(3) Study reporting on one of the identified predictive factors of IVIG resistance or a combination thereof: white blood cell count, polymorphonuclear leukocyte (PMN), platelet count, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), pro-brain natriuretic peptide (pro-BNP), total bilirubin aspartate aminotransferase (AST), alanine aminotransferase (ALT), albumin, sodium.

(4) Laboratory values before IVIG therapy compared in each group; variables before IVIG compared between groups.

(5) Kawasaki disease diagnosed according to the criteria published by the American Heart Association in 2004.

2. Exclusion criteria

We excluded studies by title, then abstract, then full text. Exclusion criteria included papers that were not available in English. Initially, 25 abstracts were excluded owing to duplications, leav-
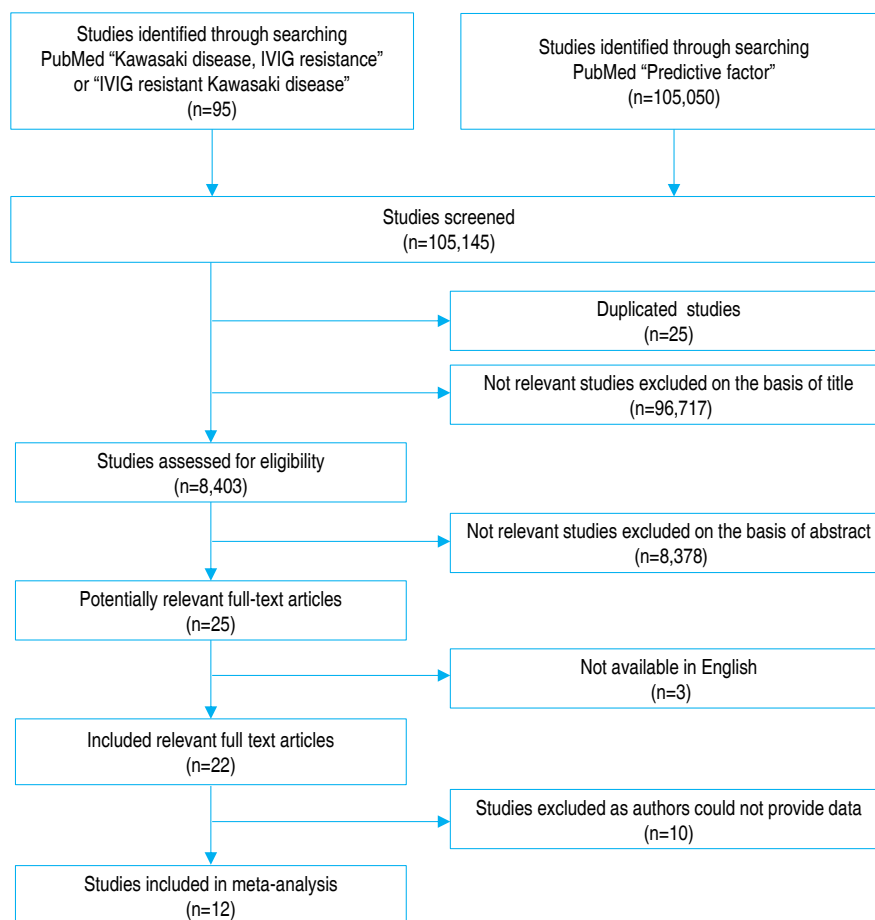

Fig. 1. Flow of studies through the review process. IVIG, intravenous immunoglobulin.

ing 8,403 abstracts to be reviewed. Three abstracts were excluded because they were not available in English.

A total of 96,717 abstracts were excluded because the topic did not include KD. Another 10 studies were excluded because their authors could not provide data. Details of the abstract review process are presented in, a flow diagram (Fig. 1).

3. Statistics

Meta-analysis was performed using the comprehensive meta-analysis software (Biostat, Englewood, NJ, USA). Heterogeneity was quantified using the I^2 test, which describes the percentage of total variation across the studies that is the result of heterogeneity rather than chance. In the absence of heterogeneity, studies were combined using the Mantel-Haenszel fixed or random effects method of meta-analysis. If visual inspection of the forest plot or a high I^2 value suggested heterogeneity, potential causes were explored using subgroup analyses, mixed-effects (fixed or random) models, and by looking for methodological differences between the studies. If no explanation could be found, random effects meta-analysis was performed.

In addition, the Q test was performed to determine whether studies were homogenous:

$$Q = \sum_{i=1}^{k} W_i (Y_i - M)^2$$

where W_i = investment. In the formula for weight ($1/V_i$), Y_i = the effect size of the study, M = the overall effect size, k = the number of investment.

In this study, we calculated the "standardized mean difference" effect size (d). Calculation of normalized average difference effect of (d) the size and distribution (V_d) is as follows: the investment.

$$d = \frac{\overline{Y_{diff}}}{S_{within}} = \frac{\overline{Y_1} - \overline{Y_2}}{S_{within}} \qquad S_{within} = \frac{S_{diff}}{\sqrt{2(1-r)}}$$

$$V_d = \left(\frac{1}{n} + \frac{d^2}{2n} \right) 2(1-r)$$

R was the correlation coefficient between the pre and post mean average presented in the paper analyzed. All summary effects were presented with a 95% confidence interval (CI).

Results

Our review included data from 2,735 patients comprising; 12 randomized controlled studies reporting patient cohort sizes from 77 to 1,177. Studies were published over the period from 2006 to 2014, and took place across 4 countries, with the largest number of studies originating from South Korea, Japan, United States, China, and Taiwan (1–5 studies each). These studies' characteristics are summarized in Tables 1 and 2.

1. Effect size of white blood cells

Twelve included studies calculated the effect size of the white blood cell as predictive factors of IVIG-resistant KD. No significant heterogeneity of these studies was observed (Q=12.446, P>0.001, I^2=11.619). Meta-analysis demonstrated a small effect size for white blood cells (fixed effects, 0.121; 95% CI, 0.02–0.222; z=2.337; P=0.019). Therefore, this factor had no effect in our analysis (Fig. 2).

2. Effect size of PMNs

Ten included studies calculated the effect size of PMNs as a

Table 1. Study characteristics

Study	Year	Country	No. of patients (control/study)	IVIG-responsive		IVIG-resistant	
				Age (mo)	Sex, male/female	Age (mo)	Sex, male/female
Lee et al.[2]	2014	Korea	91 (80/11)	3.1±1.8	41/39	3.8±3.0	6/5
Cho et al.[3]	2014	Korea	152 (135/17)	34.035±30.15	75/60	35.845±21.65	9/8
Sato et al.[4]	2013	Japan	105 (84/21)	23.0±16.9	51/33	41.5±33.5	11/10
Fu et al.[5]	2013	China	1,177 (966/211)	-	602/364	-	144/67
Yoshimura et al.[6]	2013	Japan	80 (63/17)	2.3±1.6	46/17	1.3±1.0	8/9
Park et al.[7]	2013	Korea	309 (279/30)	26 (13–44)*	142/137	27.5 (16.8–38.3)*	19/11
Kim et al.[8]	2011	Korea	129 (107/22)	29.0±20.8	57/50	35.9±28.6	15/7
Do et al.[9]	2010	Korea	77 (64/13)	30.5±22.5	43/21	32.6±25.3	8/5
Kuo et al.[10]	2010	Taiwan	131 (111/20)	1.60±1.38	78/33	1.63±0.87	15/5
Sleeper et al.[11]	2010	USA	198 (171/27)	3.7±2.5	103/68	3.2±2.2 (2.8)	22/5
Sano et al.[12]	2006	Japan	112 (90/22)	2.2±1.6	-	2.3±1.8	-
Kobayashi et al.[13]	2006	Japan	204 (162/42)	28.4±20.5	102/102	28.4±20.5	21/21

Values are presented as mean±standard deviation unless otherwise indicated.
IVIG, intravenous immunoglobulin.
*Range.

Table 2. Meta-analysis of the effect size for predictive factors of resistance to intravenous immunoglobulin therapy in Kawasaki disease

Variable	No. of studies	Type	ES	95% CI	Heterogeneity	
					P value	I²
WBC count (/mm³)	12	Fixed	0.121	0.02–0.222	0.331	11.619
PMN (%)	10	Random	0.698	0.469–0.926	0.001	68.829
Platelet count (×10³/mm³)	10	Fixed	−0.176	−0.282 to −0.070	0.716	<0.0001
ESR (mm/hr)	7	Random	0.150	−0.056–0.355	0.088	45.459
CRP (mg/dL)	12	Random	0.375	0.086–0.663	<0.001	83.543
Pro-BNP (pg/mL)	5	Random	0.561	0.261–0.861	0.125	44.481
Sodium (meq/L)	10	Random	−0.604	−0.839 to −0.370	<0.001	70.149
Total bilirubin (mg/dL)	8	Random	0.859	0.582–1.136	<0.001	75.014
AST (IU/L)	10	Random	0.503	0.313–0.693	0.022	53.575
ALT (IU/L)	10	Random	0.436	0.275–0.597	0.115	36.728
Albumin (g/dL)	12	Random	−0.427	−0.657 to −0.198	<0.001	73.424

ES, effect size (point estimate); CI, confidence interval; I², I-squared statistic (measure of heterogeneity); WBC, white blood cell; Fixed, fixed-effects analysis; PMN, polymorphonuclear leukocyte; Random, random-effects analysis; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; Pro-BNP, pro-brain natriuretic peptide; AST, aspartate aminotransferase; ALT, alanine aminotransferase.

Fig. 2. The effect size of white blood cells (WBC) as a predictive factor of resistance to intravenous immunoglobulin therapy in Kawasaki disease. CI, confidence interval.

predictive factor of IVIG-resistant KD. However, heterogeneity of these studies was significant (Q (9)=28.873, P<0.001, I²=68.829). Meta-analysis demonstrated a significant effect size for PMN (random effects, 0.698; 95% CI, 0.469–0.926; z=5.979; P<0.001). Therefore, we conclude that PMN had an effect (Fig. 3).

3. Effect size of platelets

Ten included studies calculated the effect size of platelets as predictive factors of IVIG-resistant KD. No significant heterogeneity was observed among the studies (Q (9) =6.236, P>0.001,

I²<0.0001). Meta-analysis demonstrated a small effect size in the platelet (fixed effects, −0.176; 95% CI, −0.282 to −0.070; z= −3.262; P=0.001). Therefore, we conclude that platelets had no effect (Fig. 4).

4. Effect size of ESR

Seven included studies calculated the effect size of ESR as a predictive factor of IVIG-resistant KD. Heterogeneity among these studies was low (Q (6)=11.001, P>0.001, I²=45.459). Meta-analysis demonstrated a small effect size for ESR (random effects, 0.150;

PMN

Model		Effect size and 95% confidence interval					Test of null (2-Tail)		Heterogeneity				Tau-squared			
Model	Number Studies	Point estimate	Standard error	Variance	Lower limit	Upper limit	Z-value	P-value	Q-value	df (Q)	P-value	I-squared	Tau Squared	Standard Error	Variance	Tau
Fixed	10	0.530	0.055	0.003	0.423	0.637	9.697	0.000	28.873	9	0.001	68.829	0.084	0.069	0.005	0.290
Random	10	0.698	0.117	0.014	0.469	0.926	5.979	0.000								

Forest plot

Model	Study name	Outcome	Statistics for each study							Std diff in means and 95% CI
			Std diff in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value	
	Sang Min Lee(2014)	PMN	0.763	0.327	0.107	0.123	1.403	2.337	0.019	
	Kee Hyun Cho(2014)	PMN	1.265	0.280	0.079	0.715	1.814	4.510	0.000	
	S. Sato(2013)	PMN	1.340	0.261	0.068	0.828	1.851	5.135	0.000	
	Fu(2013)	PMN	0.337	0.076	0.006	0.188	0.487	4.419	0.000	
	HM Park(2013)	PMN	0.618	0.194	0.038	0.238	0.998	3.189	0.001	
	Hyun Kwon Kim(2011)	PMN	0.842	0.240	0.058	0.371	1.312	3.508	0.000	
	Young-Sun Do(2010)	PMN	0.587	0.308	0.095	-0.017	1.190	1.906	0.057	
	Kuo(2010)	PMN	0.641	0.246	0.061	0.158	1.123	2.603	0.009	
	Sleeper(2010)	PMN	0.232	0.207	0.043	-0.175	0.638	1.117	0.264	
	Tohru Kobayashi(2006)	PMN	0.731	0.177	0.031	0.384	1.077	4.131	0.000	
Fixed			0.530	0.055	0.003	0.423	0.637	9.697	0.000	
Random			0.698	0.117	0.014	0.469	0.926	5.979	0.000	

-2.00 -1.00 0.00 1.00 2.00

Fig. 3. The effect size of polymorphonuclear leukocytes (PMN) as a predictive factor of resistance to intravenous immunoglobulin therapy in Kawasaki disease. CI, confidence interval.

Platelet

Model		Effect size and 95% confidence interval					Test of null (2-Tail)		Heterogeneity				Tau-squared			
Model	Number Studies	Point estimate	Standard error	Variance	Lower limit	Upper limit	Z-value	P-value	Q-value	df (Q)	P-value	I-squared	Tau Squared	Standard Error	Variance	Tau
Fixed	10	-0.176	0.054	0.003	-0.282	-0.070	-3.262	0.001	6.236	9	0.716	0.000	0.000	0.017	0.000	0.000
Random	10	-0.176	0.054	0.003	-0.282	-0.070	-3.262	0.001								

Forest plot

Model	Study name	Outcome	Statistics for each study							Std diff in means and 95% CI
			Std diff in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value	
	Sang Min Lee(2014)	Platelet	0.006	0.322	0.103	-0.624	0.637	0.020	0.984	
	Kee Hyun Cho(2014)	Platelet	-0.250	0.267	0.071	-0.772	0.272	-0.938	0.348	
	S. Sato(2013)	Platelet	-0.214	0.244	0.060	-0.693	0.265	-0.877	0.380	
	Fu(2013)	Platelet	-0.178	0.076	0.006	-0.327	-0.029	-2.340	0.019	
	HM Park(2013)	Platelet	-0.352	0.193	0.037	-0.730	0.025	-1.829	0.067	
	Hyun Kwon Kim(2011)	Platelet	-0.321	0.235	0.055	-0.782	0.139	-1.367	0.172	
	Young-Sun Do(2010)	Platelet	-0.437	0.306	0.094	-1.037	0.164	-1.425	0.154	
	Kuo(2010)	Platelet	0.293	0.244	0.059	-0.185	0.770	1.202	0.229	
	Sleeper(2010)	Platelet	-0.172	0.207	0.043	-0.578	0.235	-0.828	0.407	
	Tohru Kobayashi(2006)	Platelet	-0.106	0.173	0.030	-0.446	0.233	-0.612	0.540	
Fixed			-0.176	0.054	0.003	-0.282	-0.070	-3.262	0.001	
Random			-0.176	0.054	0.003	-0.282	-0.070	-3.262	0.001	

-2.00 -1.00 0.00 1.00 2.00

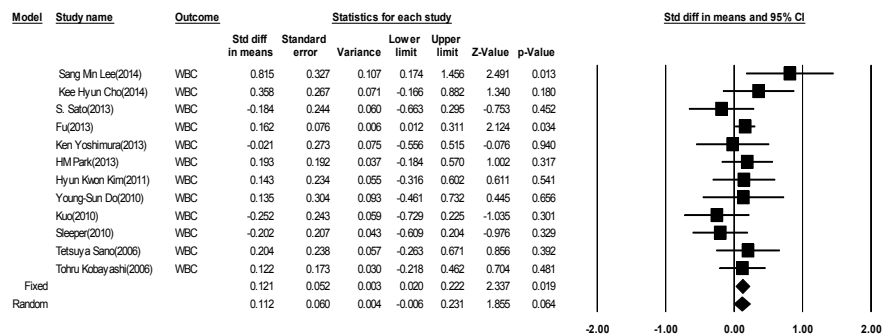**Fig. 4.** The effect size of platelets as a predictive factor of resistance to intravenous immunoglobulin therapy in Kawasaki disease. CI, confidence interval.

95% CI, −0.056 to 0.355; z=1.428; P=0.153). Therefore, ESR showed no effect (Fig. 5).

5. Effect size of CRP

Twelve included studies calculated the effect size of CRP as a predictive factor of IVIG-resistant KD. However, heterogeneity among these studies was significant (Q (11)=66.841 P<0.001, I^2=85.543). Meta-analysis demonstrated a significant effect size for CRP (random effects, 0.375; 95% CI, 0.086–0.663; z=2.546;

P=0.011). Therefore, CRP did show an effect (Fig. 6).

6. Effect size of Pro-BNP

Five included studies calculated the effect size of pro-BNP as a predictive factor of IVIG-resistant KD. Heterogeneity among these studies was low (Q (4)=7.205, P>0.001, I^2=44.481). Meta-analysis demonstrated a significant effect size for pro-BNP (random effects, 0.561; 95% CI, 0.261–0.861; z=3.665; P<0.001). Therefore, pro-BNP did have an effect (Fig. 7).

ESR

Model	Number Studies	Point estimate	Standard error	Variance	Lower limit	Upper limit	Z-value	P-value	Q-value	df (Q)	P-value	I-squared	Tau Squared	Standard Error	Variance	Tau
			Effect size and 95% confidence interval				Test of null (2-Tail)		Heterogeneity				Tau-squared			
Fixed	7	0.111	0.060	0.004	-0.008	0.229	1.835	0.067	11.001	6	0.088	45.459	0.031	0.043	0.002	0.177
Random	7	0.150	0.105	0.011	-0.056	0.355	1.428	0.153								

Forest plot

Model	Study name	Outcome	Std diff in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
	Sang Min Lee(2014)	ESR	0.918	0.329	0.108	0.273	1.562	2.792	0.005
	Kee Hyun Cho(2014)	ESR	-0.222	0.266	0.071	-0.744	0.300	-0.833	0.405
	Fu(2013)	ESR	0.080	0.076	0.006	-0.069	0.229	1.049	0.294
	HM Park(2013)	ESR	0.231	0.192	0.037	-0.146	0.608	1.203	0.229
	Young-Sun Do(2010)	ESR	0.211	0.305	0.093	-0.386	0.808	0.693	0.488
	Sleeper(2010)	ESR	-0.155	0.207	0.043	-0.561	0.251	-0.748	0.455
	Tetsuya Sano(2006)	ESR	0.362	0.239	0.057	-0.107	0.830	1.514	0.130
Fixed			0.111	0.060	0.004	-0.008	0.229	1.835	0.067
Random			0.150	0.105	0.011	-0.056	0.355	1.428	0.153

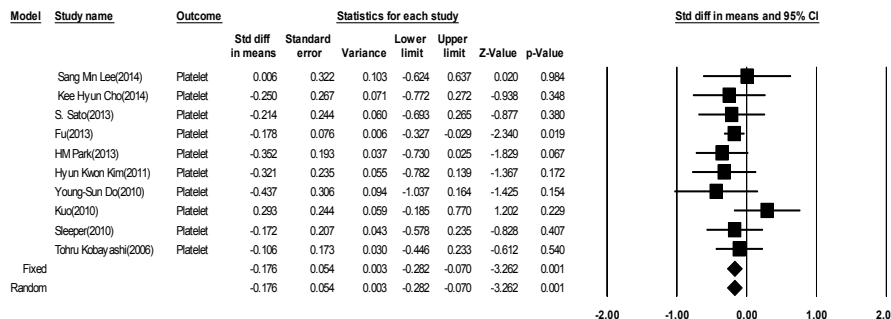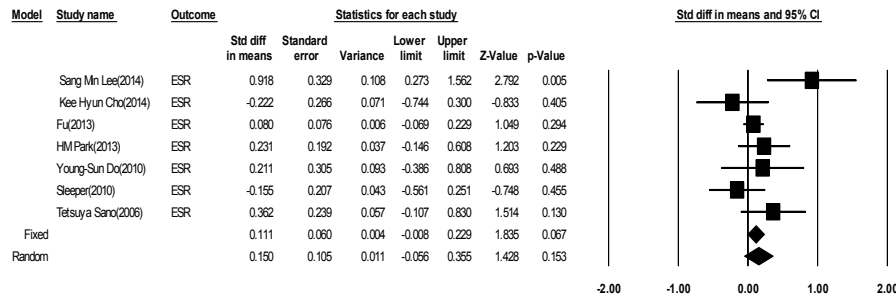Fig. 5. The effect size of erythrocyte sedimentation rate (ESR) as a predictive factor of resistance to intravenous immunoglobulin therapy in Kawasaki disease. CI, confidence interval.

CRP

Model	Number Studies	Point estimate	Standard error	Variance	Lower limit	Upper limit	Z-value	P-value	Q-value	df (Q)	P-value	I-squared	Tau Squared	Standard Error	Variance	Tau
			Effect size and 95% confidence interval				Test of null (2-Tail)		Heterogeneity				Tau-squared			
Fixed	12	0.434	0.052	0.003	0.331	0.536	8.286	0.000	66.841	11	0.000	83.543	0.203	0.134	0.018	0.451
Random	12	0.375	0.147	0.022	0.086	0.663	2.546	0.011								

Forest plot

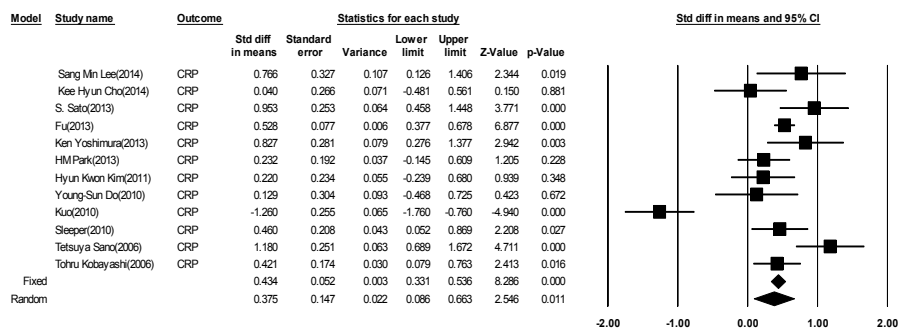| Model	Study name	Outcome	Std diff in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
	Sang Min Lee(2014)	CRP	0.766	0.327	0.107	0.126	1.406	2.344	0.019
	Kee Hyun Cho(2014)	CRP	0.040	0.266	0.071	-0.481	0.561	0.150	0.881
	S. Sato(2013)	CRP	0.953	0.253	0.064	0.458	1.448	3.771	0.000
	Fu(2013)	CRP	0.528	0.077	0.006	0.377	0.678	6.877	0.000
	Ken Yoshimura(2013)	CRP	0.827	0.281	0.079	0.276	1.377	2.942	0.003
	HM Park(2013)	CRP	0.232	0.192	0.037	-0.145	0.609	1.205	0.228
	Hyun Kwon Kim(2011)	CRP	0.220	0.234	0.055	-0.239	0.680	0.939	0.348
	Young-Sun Do(2010)	CRP	0.129	0.304	0.093	-0.468	0.725	0.423	0.672
	Kuo(2010)	CRP	-1.260	0.255	0.065	-1.760	-0.760	-4.940	0.000
	Sleeper(2010)	CRP	0.460	0.208	0.043	0.052	0.869	2.208	0.027
	Tetsuya Sano(2006)	CRP	1.180	0.251	0.063	0.689	1.672	4.711	0.000
	Tohru Kobayashi(2006)	CRP	0.421	0.174	0.030	0.079	0.763	2.413	0.016
Fixed			0.434	0.052	0.003	0.331	0.536	8.286	0.000
Random			0.375	0.147	0.022	0.086	0.663	2.546	0.011

Fig. 6. The effect size of C-reactive protein (CRP) as a predictive factor of resistance to intravenous immunoglobulin therapy in Kawasaki disease. CI, confidence interval.

7. Effect size of total bilirubin

Seven included studies calculated the effect size of total bilirubin as a predictive factor of IVIG-resistant KD. However, heterogeneity among these studies was significant (Q (7)=28.015, $P<0.001$, I^2=75.014). Meta-analysis demonstrated a significant effect size for total bilirubin (random effects, 0.859; 95% CI, 0.582–1.136; z=6.081; $P<0.001$). Therefore, total bilirubin had the greatest effect (Fig. 8).

8. Effect size of AST

Ten included studies calculated the effect size of AST as a predictive factor of IVIG-resistant KD. Heterogeneity among these studies was significant (Q (9)=19.386 $P<0.001$, I^2=53.575). Meta-analysis demonstrated a significant effect size for AST (random effects, 0.503; 95% CI, 0.313–0.693; z=5.190; $P<0.001$). Therefore, AST had an effect (Fig. 9).

9. Effect size of ALT

Ten included studies calculated the effect size of ALT as a pre-

Pro-BNP

Model	Number Studies	Point estimate	Standard error	Variance	Lower limit	Upper limit	Z-value	P-value	Q-value	df (Q)	P-value	I-squared	Tau Squared	Standard Error	Variance	Tau
		Effect size and 95% confidence interval					Test of null (2-Tail)		Heterogeneity				Tau-squared			
Fixed	5	0.586	0.112	0.012	0.368	0.805	5.257	0.000	7.205	4	0.125	44.481	0.051	0.082	0.007	0.227
Random	5	0.561	0.153	0.023	0.261	0.861	3.665	0.000								

Forest plot

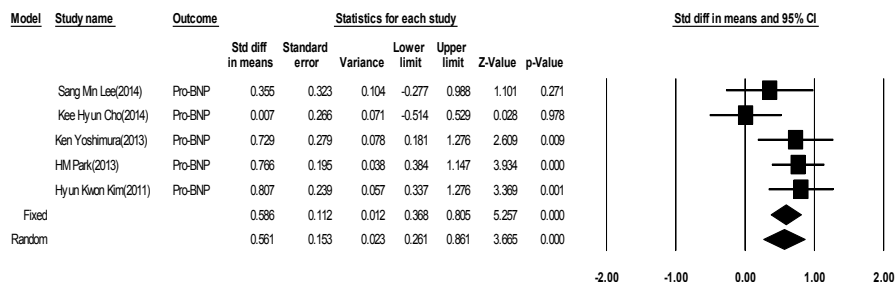| Model	Study name	Outcome	Std diff in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value	Std diff in means and 95% CI
	Sang Min Lee(2014)	Pro-BNP	0.355	0.323	0.104	-0.277	0.988	1.101	0.271	
	Kee Hyun Cho(2014)	Pro-BNP	0.007	0.266	0.071	-0.514	0.529	0.028	0.978	
	Ken Yoshimura(2013)	Pro-BNP	0.729	0.279	0.078	0.181	1.276	2.609	0.009	
	HM Park(2013)	Pro-BNP	0.766	0.195	0.038	0.384	1.147	3.934	0.000	
	Hyun Kwon Kim(2011)	Pro-BNP	0.807	0.239	0.057	0.337	1.276	3.369	0.001	
Fixed			0.586	0.112	0.012	0.368	0.805	5.257	0.000	
Random			0.561	0.153	0.023	0.261	0.861	3.665	0.000	

Fig. 7. The effect size of pro-brain natriuretic peptide (pro-BNP) as a predictive factor of resistance to intravenous immunoglobulin therapy in Kawasaki disease. CI, confidence interval.

Total bilirubin

Model	Number Studies	Point estimate	Standard error	Variance	Lower limit	Upper limit	Z-value	P-value	Q-value	df (Q)	P-value	I-squared	Tau Squared	Standard Error	Variance	Tau
		Effect size and 95% confidence interval					Test of null (2-Tail)		Heterogeneity				Tau-squared			
Fixed	8	0.672	0.058	0.003	0.559	0.786	11.620	0.000	28.015	7	0.000	75.014	0.109	0.094	0.009	0.330
Random	8	0.859	0.141	0.020	0.582	1.136	6.081	0.000								

Forest plot

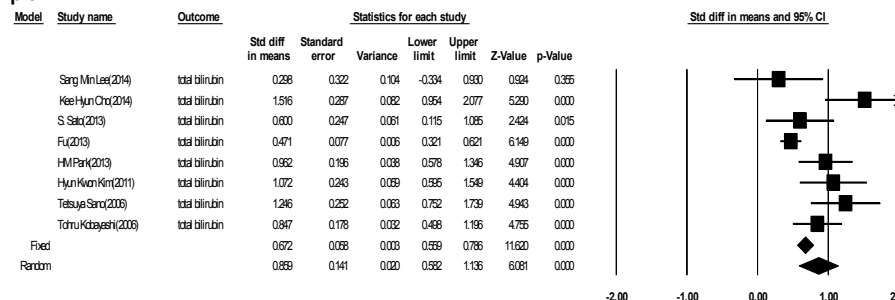| Model	Study name	Outcome	Std diff in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value	Std diff in means and 95% CI
	Sang Min Lee(2014)	total bilirubin	0.298	0.322	0.104	-0.334	0.930	0.924	0.355	
	Kee Hyun Cho(2014)	total bilirubin	1.516	0.287	0.082	0.954	2.077	5.290	0.000	
	S. Sato(2013)	total bilirubin	0.600	0.247	0.061	0.115	1.085	2.424	0.015	
	Fu(2013)	total bilirubin	0.471	0.077	0.006	0.321	0.621	6.149	0.000	
	HM Park(2013)	total bilirubin	0.962	0.196	0.038	0.578	1.346	4.907	0.000	
	Hyun Kwon Kim(2011)	total bilirubin	1.072	0.243	0.059	0.595	1.549	4.404	0.000	
	Tetsuya Sano(2008)	total bilirubin	1.246	0.252	0.063	0.752	1.739	4.943	0.000	
	Tohru Kobayashi(2006)	total bilirubin	0.847	0.178	0.032	0.498	1.196	4.755	0.000	
Fixed			0.672	0.058	0.003	0.559	0.786	11.620	0.000	
Random			0.859	0.141	0.020	0.582	1.136	6.081	0.000	

Fig. 8. The effect size of total bilirubin as a predictive factor of resistance to intravenous immunoglobulin therapy in Kawasaki disease. CI, confidence interval.

dictive factor of IVIG-resistant KD. Heterogeneity among these studies was low (Q (9)=14.224, P>0.001, I^2=36.728). Meta-analysis demonstrated a significant effect size for ALT (random effects, 0.436; 95% CI, 0.275–0.597; z=5.303; P<0.001). Therefore, ALT had an effect (Fig. 10).

10. Effect size of albumin

Twelve included studies calculated the effect size of albumin as a predictive factor of IVIG-resistant KD. Heterogeneity among these studies was significant (Q (11)=41.391, P<0.001, I^2=73.424). Meta-analysis demonstrated a significant effect size for albumin (random effects, −0.427; 95% CI, −0.657 to −0.198; z=−3.656; P<

0.001). Therefore, albumin had an effect (Fig. 11).

11. Effect size of sodium

Ten included studies calculated the effect size of sodium as a predictive factor of IVIG-resistant KD. Heterogeneity among these studies was significant (Q (9)=30.15, P<0.001, I^2=70.149). Meta-analysis demonstrated a significant effect size for sodium (random effects, −0.604; 95% CI, −0.839 to −0.370; z=−5.047; P<0.001). Therefore, sodium had an effect (Fig. 12).

AST

Model		Effect size and 95% confidence interval					Test of null (2-Tail)		Heterogeneity				Tau-squared			
Model	Number Studies	Point estimate	Standard error	Variance	Lower limit	Upper limit	Z-value	P-value	Q-value	df (Q)	P-value	I-squared	Tau Squared	Standard Error	Variance	Tau
Fixed	10	0.409	0.055	0.003	0.302	0.517	7.460	0.000	19.386	9	0.022	53.575	0.044	0.044	0.002	0.211
Random	10	0.503	0.097	0.009	0.313	0.693	5.190	0.000								

Forest plot

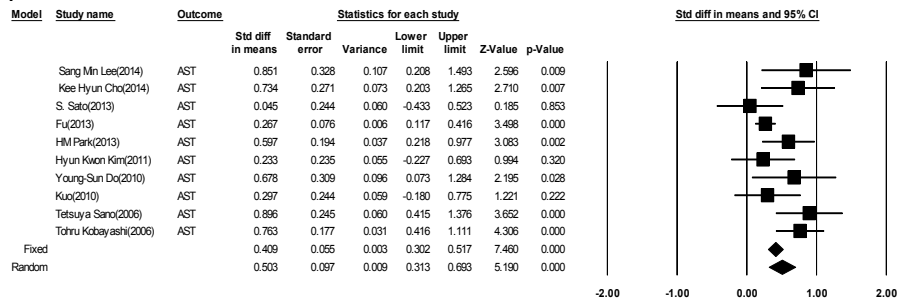| Model	Study name	Outcome	Statistics for each study							Std diff in means and 95% CI
			Std diff in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value	
	Sang Min Lee(2014)	AST	0.851	0.328	0.107	0.208	1.493	2.596	0.009	
	Kee Hyun Cho(2014)	AST	0.734	0.271	0.073	0.203	1.265	2.710	0.007	
	S. Sato(2013)	AST	0.045	0.244	0.060	-0.433	0.523	0.185	0.853	
	Fu(2013)	AST	0.267	0.076	0.006	0.117	0.416	3.498	0.000	
	HM Park(2013)	AST	0.597	0.194	0.037	0.218	0.977	3.083	0.002	
	Hyun Kwon Kim(2011)	AST	0.233	0.235	0.055	-0.227	0.693	0.994	0.320	
	Young-Sun Do(2010)	AST	0.678	0.309	0.096	0.073	1.284	2.195	0.028	
	Kuo(2010)	AST	0.297	0.244	0.059	-0.180	0.775	1.221	0.222	
	Tetsuya Sano(2006)	AST	0.896	0.245	0.060	0.415	1.376	3.652	0.000	
	Tohru Kobayashi(2006)	AST	0.763	0.177	0.031	0.416	1.111	4.306	0.000	
Fixed			0.409	0.055	0.003	0.302	0.517	7.460	0.000	
Random			0.503	0.097	0.009	0.313	0.693	5.190	0.000	

Fig. 9. The effect size of alanine aminotransferase (AST) as a predictive factor of resistance to intravenous immunoglobulin therapy in Kawasaki disease. CI, confidence interval.

ALT

Model		Effect size and 95% confidence interval					Test of null (2-Tail)		Heterogeneity				Tau-squared			
Model	Number Studies	Point estimate	Standard error	Variance	Lower limit	Upper limit	Z-value	P-value	Q-value	df (Q)	P-value	I-squared	Tau Squared	Standard Error	Variance	Tau
Fixed	10	0.355	0.055	0.003	0.248	0.462	6.488	0.000	14.224	9	0.115	36.728	0.022	0.030	0.001	0.149
Random	10	0.436	0.082	0.007	0.275	0.597	5.303	0.000								

Forest plot

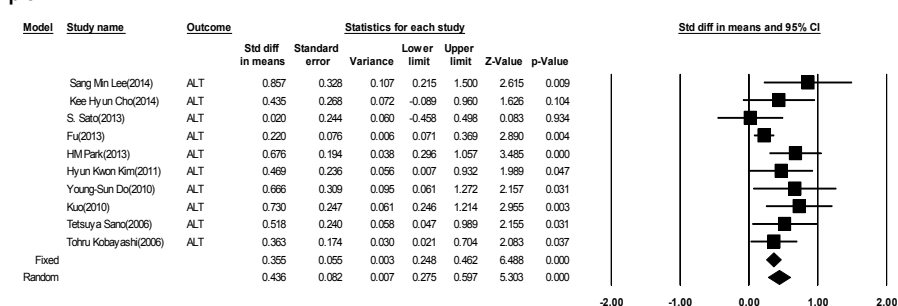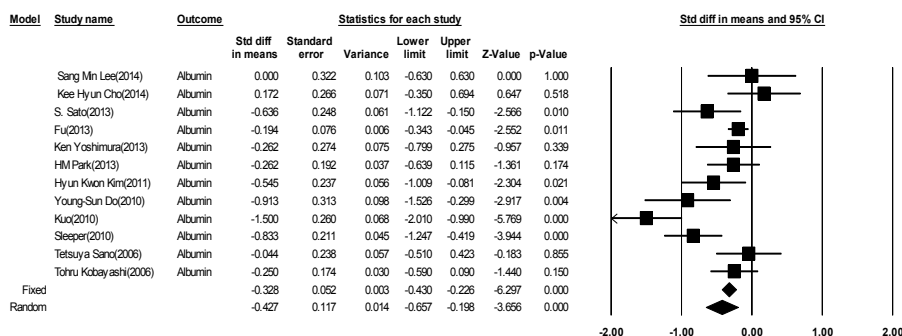| Model	Study name	Outcome	Statistics for each study							Std diff in means and 95% CI
			Std diff in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value	
	Sang Min Lee(2014)	ALT	0.857	0.328	0.107	0.215	1.500	2.615	0.009	
	Kee Hyun Cho(2014)	ALT	0.435	0.268	0.072	-0.089	0.960	1.626	0.104	
	S. Sato(2013)	ALT	0.020	0.244	0.060	-0.458	0.498	0.083	0.934	
	Fu(2013)	ALT	0.220	0.076	0.006	0.071	0.369	2.890	0.004	
	HM Park(2013)	ALT	0.676	0.194	0.038	0.296	1.057	3.485	0.000	
	Hyun Kwon Kim(2011)	ALT	0.469	0.236	0.056	0.007	0.932	1.989	0.047	
	Young-Sun Do(2010)	ALT	0.666	0.309	0.095	0.061	1.272	2.157	0.031	
	Kuo(2010)	ALT	0.730	0.247	0.061	0.246	1.214	2.955	0.003	
	Tetsuya Sano(2006)	ALT	0.518	0.240	0.058	0.047	0.989	2.155	0.031	
	Tohru Kobayashi(2006)	ALT	0.363	0.174	0.030	0.021	0.704	2.083	0.037	
Fixed			0.355	0.055	0.003	0.248	0.462	6.488	0.000	
Random			0.436	0.082	0.007	0.275	0.597	5.303	0.000	

Fig. 10. The effect size of aspartate aminotransferase (ALT) as a predictive factor of resistance to intravenous immunoglobulin therapy in Kawasaki disease. CI, confidence interval.

Discussion

Some patients with KD fail initial IVIG therapy for reasons that are not clear. Retrospective studies have identified potential factors that predict which patients will require further therapy for refractory disease. The presence of one or more of these risk factors for treatment failure should alert clinicians to an increased likelihood that the patient may not respond adequately to the initial IVIG therapy. The ability to predict a lack of response to IVIG before initiating therapy, would allow clinicians to identify these patients because they might benefit from more aggressive treatment.

Several previous studies have published data that could be used for predicting nonresponse to IVIG therapy and patients who are at high risk for coronary artery lesions (CALs)[2-13]. These data include duration of fever, male sex, serum CRP, ESR level, white blood cell count, PMN cell count, hemoglobin, platelet count, transaminase, total bilirubin and pro-BNP, albumin, and sodium levels. However, these studies did not have consistent results, and no single marker proved to be indicative of KD patients who were resistant to IVIG therapy.

In one such study, Kuo et al.[10] reported a univariate analysis of 131 patients. This analysis showed that patients who had initial findings of high neutrophil count, abnormal liver function, low

Albumin

Model		Effect size and 95% confidence interval					Test of null (2-Tail)		Heterogeneity				Tau-squared			
Model	Number Studies	Point estimate	Standard error	Variance	Lower limit	Upper limit	Z-value	P-value	Q-value	df (Q)	P-value	I-squared	Tau Squared	Standard Error	Variance	Tau
Fixed	12	-0.328	0.052	0.003	-0.430	-0.226	-6.297	0.000	41.391	11	0.000	73.424	0.110	0.079	0.006	0.331
Random	12	-0.427	0.117	0.014	-0.657	-0.198	-3.656	0.000								

Forest plot

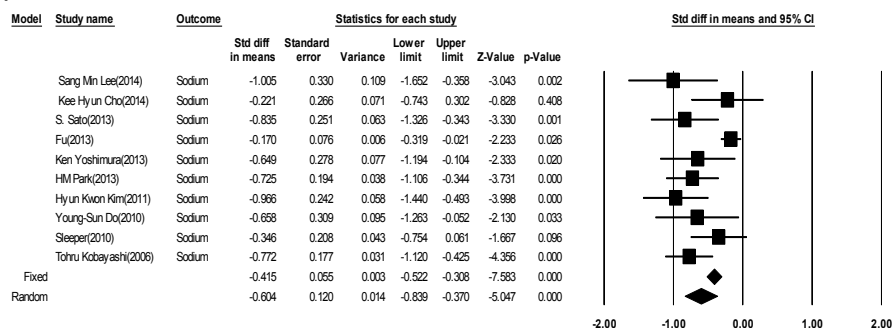| Model	Study name	Outcome	Statistics for each study							Std diff in means and 95% CI
			Std diff in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value	
	Sang Min Lee(2014)	Albumin	0.000	0.322	0.103	-0.630	0.630	0.000	1.000	
	Kee Hyun Cho(2014)	Albumin	0.172	0.266	0.071	-0.350	0.694	0.647	0.518	
	S. Sato(2013)	Albumin	-0.636	0.248	0.061	-1.122	-0.150	-2.566	0.010	
	Fu(2013)	Albumin	-0.194	0.076	0.006	-0.343	-0.045	-2.552	0.011	
	Ken Yoshimura(2013)	Albumin	-0.262	0.274	0.075	-0.799	0.275	-0.957	0.339	
	HM Park(2013)	Albumin	-0.262	0.192	0.037	-0.639	0.115	-1.361	0.174	
	Hyun Kwon Kim(2011)	Albumin	-0.545	0.237	0.056	-1.009	-0.081	-2.304	0.021	
	Young-Sun Do(2010)	Albumin	-0.913	0.313	0.098	-1.526	-0.299	-2.917	0.004	
	Kuo(2010)	Albumin	-1.500	0.260	0.068	-2.010	-0.990	-5.769	0.000	
	Sleeper(2010)	Albumin	-0.833	0.211	0.045	-1.247	-0.419	-3.944	0.000	
	Tetsuya Sano(2006)	Albumin	-0.044	0.238	0.057	-0.510	0.423	-0.183	0.855	
	Tohru Kobayashi(2006)	Albumin	-0.250	0.174	0.030	-0.590	0.090	-1.440	0.150	
Fixed			-0.328	0.052	0.003	-0.430	-0.226	-6.297	0.000	
Random			-0.427	0.117	0.014	-0.657	-0.198	-3.656	0.000	

Fig. 11. The effect size of albumin as a predictive factor of resistance to intravenous immunoglobulin therapy in Kawasaki disease. CI, confidence interval.

Sodium

Model		Effect size and 95% confidence interval					Test of null (2-Tail)		Heterogeneity				Tau-squared			
Model	Number Studies	Point estimate	Standard error	Variance	Lower limit	Upper limit	Z-value	P-value	Q-value	df (Q)	P-value	I-squared	Tau Squared	Standard Error	Variance	Tau
Fixed	10	-0.415	0.055	0.003	-0.522	-0.308	-7.583	0.000	30.150	9	0.000	70.149	0.090	0.073	0.005	0.300
Random	10	-0.604	0.120	0.014	-0.839	-0.370	-5.047	0.000								

Forest plot

Model	Study name	Outcome	Statistics for each study							Std diff in means and 95% CI
			Std diff in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value	
	Sang Min Lee(2014)	Sodium	-1.005	0.330	0.109	-1.652	-0.358	-3.043	0.002	
	Kee Hyun Cho(2014)	Sodium	-0.221	0.266	0.071	-0.743	0.302	-0.828	0.408	
	S. Sato(2013)	Sodium	-0.835	0.251	0.063	-1.326	-0.343	-3.330	0.001	
	Fu(2013)	Sodium	-0.170	0.076	0.006	-0.319	-0.021	-2.233	0.026	
	Ken Yoshimura(2013)	Sodium	-0.649	0.278	0.077	-1.194	-0.104	-2.333	0.020	
	HM Park(2013)	Sodium	-0.725	0.194	0.038	-1.106	-0.344	-3.731	0.000	
	Hyun Kwon Kim(2011)	Sodium	-0.966	0.242	0.058	-1.440	-0.493	-3.998	0.000	
	Young-Sun Do(2010)	Sodium	-0.658	0.309	0.095	-1.263	-0.052	-2.130	0.033	
	Sleeper(2010)	Sodium	-0.346	0.208	0.043	-0.754	0.061	-1.667	0.096	
	Tohru Kobayashi(2006)	Sodium	-0.772	0.177	0.031	-1.120	-0.425	-4.356	0.000	
Fixed			-0.415	0.055	0.003	-0.522	-0.308	-7.583	0.000	
Random			-0.604	0.120	0.014	-0.839	-0.370	-5.047	0.000	

Fig. 12. The effect size of sodium as a predictive factor of resistance to intravenous immunoglobulin therapy in Kawasaki disease. CI, confidence interval.

serum albumin level and pericardial effusion were at risk for IVIG treatment failure. Multivariate analysis using a logistic regression procedure showed that serum albumin level (≤2.9 g/dL) was an independent predictive factor of IVIG resistance in patients with KD (*P*=0.006; odds ratio, 40; 95% CI, 52.8–562). In another study, Sano et al.[12] reported a univariate analysis of pre-IVIG data from 112 patients showed that the neutrophil count and serum levels of CRP, total bilirubin, AST, ALT, and lactate dehydrogenase were significantly higher in IVIG-nonresponder than in IVIG-responsive patients. A multivariate analysis selected CRP (*P*=0.009), total bilirubin (*P*=0.001), and AST (*P*=0.002) as independent predictors

of nonresponsiveness to initial IVIG treatment. After defining predictive values, patients with at least 2 of 3 predictors (CRP≥7.0 mg, total bilirubin≥0.9 mg, or AST≥200 IU/L) were considered to be non-responsive to IVIG for acute KD. Kobayashi et al.[13] reported risk predictors such as day of illness at initial treatment, age in months, percentage of white blood cells representing neutrophils, platelet count, and serum AST, sodium, and CRP. Tremoulet et al.[14] mentioned high percentage band cell count, long illness day, high gamma-glutamyl transferase, and low age-adjusted hemoglobin as factors for predicting risk of IVIG-non-response. Park et al.[7] reported that elevated ALT and total biliru-

bin levels were significant in the IVIG-resistant group. Yoshimura et al.[6] reported that 19 of 80 patients developed CAL, despite IVIG administration. These patients had a significantly higher serum N-terminal (NT)-pro-BNP level than patients who did not develop CAL. The NT-pro-BNP cutoff value of 1,300 pg/mL yielded a sensitivity of 95% and a specificity of 85% for predicting CAL. However, 17 of the 80 patients were IVIG nonresponders who also had significantly higher serum NT-pro-BNP than the IVIG responders. The NT-pro-BNP cutoff value of 800 pg/mL yielded a sensitivity of 71% and a specificity of 62% for predicting IVIG nonresponders.

The previous studies had limitations, such as the number of IVIG-nonresponders being too small to represent a sample. In addition, no consensus on risk factors has been reached. Many studies of such risk factors were conducted in Japanese patients, and a scoring system for predicting IVIG-nonresponders using various parameters was proposed. However, when these risk-scoring systems were applied to subjects from other ethnic groups, specificity was high but sensitivity was low, so they had difficulty in screening out high-risk patients[11]. In this meta-analysis, we included studies from South Korea, China, Taiwan, and United States, in addition to Japan.

In this study, we calculated the "standardized mean difference" effect size for various predictive factors. According to one standard proposed by Cohen[15], small effect size=0.3, medium effect size=0.5, and large effect size=0.8. Our meta-analysis demonstrated significant effect sizes for PMN (0.698), CRP (0.375), pro-BNP (0.561), total bilirubin (0.859), AST (0.503), ALT (0.436), albumin (-0.427), sodium (-0.604). Based on the results of this study, we found several predictors (PMN count, CRP, pro-BNP, total bilirubin, AST, ALT, albumin, sodium) for IVIG-resistant KD. In particular, total bilirubin, PMN, sodium, pro-BNP, and AST demonstrated greater than medium effects in descending numerical order.

Earlier and more effective primary therapy in patients who are predicted to be nonresponsive to IVIG might reduce their risk of coronary artery complications. Combining initial therapy with IVIG as usual plus another agent may be a feasible choice for patients who are predicted to have IVIG-resistant KD. At present, controversy remains about whether combination therapy is associated with a better outcome in these patients[1].

It may be also important to determine the effectiveness of IVIG soon after therapy, especially in treatment-resistant cases, to assess the patient's need for additional therapy to prevent further dilatation of the coronary artery. Kim et al.[8] suggested guidelines for retreating KD patients who received IVIG treatment; these authors recommend that, in early-stage disease, additional therapy should be administered for febrile patients who have high values of CRP, NT-pro-BNP, and/or neutrophil counts after IVIG therapy. However, no definitive algorithm exists to determine the effectiveness of IVIG therapy and retreatment. In addition, it is also uncertain which agents are effective alternative treatments after failure to defervesce with initial IVIG treatment[1].

In conclusion, controversy remains as to which risk factors predict patient responding to IVIG and what additional treatments should be applied to reduce the development of CAL. After performing our meta-analysis of large-scale studies, we found several laboratory predictive factors for IVIG-resistant KD. Therefore, in the presence of several such factors, clinicians should be alert to an increased likelihood that the patient may not respond adequately to initial IVIG therapy.

Conflict of interest

No potential conflict of interest relevant to this article was reported

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