

Original Article



Factors Predicting Resistance to Intravenous Immunoglobulin Treatment and Coronary Artery Lesion in Patients with Kawasaki Disease: Analysis of the Korean Nationwide Multicenter Survey from 2012 to 2014

Min Kyu Kim, MD¹, Min Seob Song, MD², and Gi Beom Kim, MD³

¹Department of Pediatrics, Good Moonwha Hospital, Busan, Korea

²Department of Pediatrics, Inje University Haeundae Paik Hospital, Busan, Korea

³Department of Pediatrics, Seoul National University Children's Hospital, Seoul, Korea

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Correspondence to

Min Seob Song, MD

Department of Pediatrics, Inje University
Haeundae Paik Hospital, 875, Haeun-daero,
Haeundae-gu, Busan 48108, Korea.
E-mail: msped@hanmail.net

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Conflict of Interest

The authors have no financial conflicts of
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GB; Data curation: Song MS, Kim MK, Kim GB;
Formal analysis: Song MS; Investigation: Song
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MK; Supervision: Song MS; Validation: Song
MS, Kim MK, Kim GB; Visualization: Song MS,
Kim MK, Kim GB; Writing - original draft: Kim
MK, Song MS; Writing - review & editing: Song
MS, Kim MK, Kim GB.

ABSTRACT

Background and Objectives: Approximately 10–15% of children with Kawasaki disease (KD) do not respond to initial intravenous immunoglobulin (IVIG) and have higher risk for coronary artery lesion (CAL). The aim of this study was to identify predictive factors from laboratory findings in patients who do not respond to IVIG treatment and develop CAL from KD.

Methods: We retrospectively collected nationwide multicenter data from the Korean Society of Kawasaki Disease and included 5,151 patients with KD between 2012 and 2014 from 38 hospitals.

Results: Among 5,151 patients with KD, 524 patients belonged to the IVIG-resistant group. The patients in the IVIG-resistant group had a significantly higher serum N-terminal pro-brain natriuretic peptide (NT-proBNP) level ($1,573.91 \pm 3,166.46$ vs. $940.62 \pm 2,326.10$ pg/mL; $p < 0.001$) and a higher percentage of polymorphonuclear neutrophils (PMNs) ($70.89 \pm 15.75\%$ vs. $62.38 \pm 32.94\%$; $p < 0.001$). Multivariate logistic regression analyses revealed that significantly increased PMN, NT-proBNP, C-reactive protein (CRP), aspartate aminotransferase (AST), and alanine aminotransferase (ALT) were the predictors of IVIG resistance ($p < 0.05$). Multivariate logistic regression analyses also showed that only CRP was associated with the risk of CAL ($p < 0.01$), while PMN, NT-proBNP, AST, and ALT were not.

Conclusions: Elevated PMN, serum NT-proBNP, CRP, AST, and ALT levels are significantly associated with IVIG resistance in patients with KD. Moreover, serum CRP is significantly increased in patients with KD with CAL.

Keywords: Mucocutaneous lymph node syndrome; Intravenous immunoglobulins; Coronary artery disease; Natriuretic peptide; Brain; Neutrophils

INTRODUCTION

Kawasaki disease (KD) is an acute febrile pediatric illness, a vasculitis of unknown etiology, and is the most common cause of acquired cardiac disorders in pediatric patients.¹⁾²⁾ KD has no specific diagnostic laboratory markers.³⁾

Coronary artery complications develop in 20% to 25% of patients with untreated KD.⁴⁾ High-dose intravenous immunoglobulin (IVIG) therapy has decreased the risk of development of coronary artery lesions (CALs) in patients with KD,⁵⁻⁷⁾ whereas approximately 10% to 15% of patients showing resistance to initial IVIG have higher risk for CAL.⁸⁻¹⁰⁾ Since the first retrospective study that investigated risk factors for refractory KD used in the database of the 2003 to 2004 nationwide survey of KD in Japan,¹¹⁾ studies have identified that non-responders to initial IVIG therapy had a higher risk for CAL, including aneurysms, compared with responders. Early detection and treatment reduce the occurrence of serious coronary artery complications.

Recent studies have investigated factors for predicting resistance to IVIG and CAL in patients with KD, but the results have been conflicting. According to one article, higher polymorphonuclear neutrophil (PMN) percentage, C-reactive protein (CRP), and N-terminal-pro-brain natriuretic peptide (NT-proBNP) were considered predictive factors for patients with KD resistant to IVIG treatment,¹²⁾ whereas higher total bilirubin, PMN percentage, NT-proBNP, aspartate aminotransferase (AST), and alanine aminotransferase (ALT); and lower sodium and albumin were reported to be predictors in other studies.¹³⁾ The predictors for the development of CAL in patients with KD have been reported to be male sex, fever duration, and increased serum CRP level and white blood cell (WBC) count as per some studies, whereas other studies reported higher NT-proBNP levels as a predictor.¹⁴⁾¹⁵⁾

The purpose of our study was to determine the factors that can be useful as predictive markers for patients with KD who are at higher risk for IVIG resistance and developing CAL.

METHODS

In the 8th nationwide survey of KD between 2012 and 2014 conducted in the Republic of Korea, a questionnaire on the clinical characteristics of patients was sent to 116 hospitals. Among the 12,292 patients with KD, 5,151 patients from 38 hospitals who were administered IVIG with available serum NT-proBNP data were enrolled in this study. All patients were administered 30–100 mg/kg/day acetylsalicylic acid until they were afebrile and 2 g/kg of IVIG over 12 hours. This study was approved by the Ethics Committee of Inje University Haeundae Paik Hospital (HPIRB201602004001).

KD was diagnosed based on the criteria published by the American Heart Association (AHA) in 2004.²⁾ KD onset was defined as the day of fever onset.

IVIG resistance was defined as needing a second dose of IVIG because of persistent or recrudescence fever, despite initial IVIG treatment.

CALs were assessed by performing serial echocardiography and were defined as dilatations or aneurysms based on the Japanese Ministry of Health criteria¹⁶⁾: a maximum absolute internal diameter >3 mm in children <5 years of age, or >4 mm in children 5 years and older.

SPSS version 21.0 (IBM Corp., Armonk, NY, USA) was used for statistical calculations. Groups of patients emerged within the IVIG-treated patients (IVIG-responsive group vs. IVIG-resistant group and CAL group vs. no CAL group). Laboratory data and patient characteristics were compared between the 2 groups.

A univariate analysis was performed on the clinical data of the KD patients in the IVIG-resistant and CAL groups, wherein categorical data were presented as percentages and were analyzed using the Student's t-test. Quantitative data with normal distribution were presented as mean±standard deviation. Statistical significance was defined as $p < 0.05$. Multivariate logistic regression analyses were performed on the IVIG-resistant factors obtained from the univariate analysis. To assess the ability of laboratory factors for predicting IVIG resistance and CAL development, receiver operating characteristic (ROC) curves were constructed, and the cut-off values were identified.

RESULTS

This study included 5,151 patients with KD (2,733 male patients, 2,008 female patients, 410 no available data), age range was 1 to 159 months (mean age: 33 months).

Of the 5,151 patients who were administered IVIG, 4,627 (89.8%) responded to IVIG treatment, whereas 524 (10.2%) were non-responders. Significant differences were found between the IVIG-resistant and IVIG-responsive groups based on sex, except for 410 patients whose sex were unidentified (male/female: 317/181 and 2,416/1,827, respectively; $p < 0.01$). No significant differences were found between the IVIG-resistant and IVIG-responsive groups based on age (32.20 ± 24.22 and 33.04 ± 23.68 months; $p = 0.447$). No significant differences were found for fever duration before IVIG treatment (6.56 ± 3.84 and 6.86 ± 3.53 days; $p = 0.088$). The number of patients who developed CAL was significantly higher in the IVIG-resistant group, 17% (90 of 524) in the IVIG-resistant group vs. 9.4% (435 of 4,627) in the IVIG-responsive group ($p < 0.05$).

Laboratory data showed significant differences between the IVIG-responsive and IVIG-resistant groups (Table 1). Compared with the IVIG-responsive group, the IVIG-resistant group had higher NT-proBNP levels (IVIG-resistant group vs. IVIG-responsive group, $1,573.91 \pm 3,166.46$ vs. $940.62 \pm 2,326.10$ pg/mL; $p < 0.001$), higher serum CRP levels (10.32 ± 8.74 vs. 7.81 ± 10.15 mg/dL; $p < 0.001$), higher PMN percentage ($70.89 \pm 15.75\%$ vs. $62.38 \pm 32.94\%$; $p < 0.001$), higher AST (140.83 ± 228.48 vs. 76.08 ± 136.73 IU/L; $p < 0.001$), and higher ALT (153.14 ± 209.55 vs. 84.50 ± 136.22 IU/L; $p < 0.001$). Serum albumin (3.75 ± 0.52 vs. 4.17 ± 8.94 g/dL; $p = 0.287$), and total bilirubin levels (1.23 ± 1.55 vs. 0.78 ± 5.55 mg/dL; $p = 0.068$) were insignificant.

Table 1. Demographic, laboratory characteristics of patients with KD during diagnosis in the IVIG-responsive and IVIG-resistant groups

	IVIG responsive	IVIG resistant	p value
Sex Male	2,416 (52.2)	317 (60.5)	<0.001
Female	1,827 (39.5)	181 (34.5)	
Not identified	384 (8.3)	26 (5.0)	
Age (months)	32.20 ± 24.22	33.04 ± 23.68	0.447
Duration of fever before IVIG treatment	6.56 ± 3.84	6.86 ± 3.53	0.088
PMN (%)	62.38 ± 32.94	70.89 ± 15.75	<0.001
Albumin (g/dL)	4.17 ± 8.94	3.75 ± 0.52	0.287
Total bilirubin (g/dL)	0.78 ± 5.55	1.23 ± 1.55	0.068
AST (IU/L)	76.08 ± 136.73	140.83 ± 228.48	<0.001
ALT (IU/L)	84.50 ± 136.22	153.14 ± 209.55	<0.001
CRP (mg/dL)	7.81 ± 10.15	10.32 ± 8.74	<0.001
NT-proBNP (pg/dL)	$940.62 \pm 2,326.10$	$1,573.91 \pm 3,166.46$	<0.001

Values are presented as number (%) or mean±standard deviation.

ALT = alanine aminotransferase; AST = aspartate aminotransferase; CRP = C-reactive protein; IVIG = intravenous immunoglobulin; KD = Kawasaki disease; NT-proBNP = N-terminal-pro-brain natriuretic peptide; PMN = polymorphonuclear neutrophil.

Multivariable logistic regression analysis between KD patients with and without IVIG resistance and with and without CAL was performed to evaluate the relative risk of each laboratory parameters that had statistical differences (**Table 2**). The multivariate logistic regression analyses showed that the PMN, AST, ALT, CRP, and NT-proBNP levels were significantly higher in the IVIG-resistant group compared with the IVIG-responsive group in patients with KD. The albumin level in the IVIG-resistant group was significantly lower than that in the IVIG-responsive group in patients with KD. The multivariate logistic regression analyses showed that only CRP was associated with risk for CAL, while PMN, NT-proBNP, AST, ALT, and albumin were not.

Despite administering IVIG, 524 of 5,151 patients developed CAL. Significant differences were found between the CAL and non-CAL groups based on sex, except for 410 patients whose sex cannot be identified (male/female: 336/146 and 2,397/1,862, respectively; $p < 0.001$). Significant differences were found between the CAL and non-CAL groups (31.78 ± 24.29 and 36.57 ± 22.61 months; $p < 0.001$) with respect to age. The patients in the CAL group had higher serum CRP levels (9.79 ± 14.25 vs. 7.86 ± 9.42 mg/dL; $p = 0.002$) (**Table 3**).

The various variables for predicting IVIG resistance in patients with KD were assessed by a ROC curve analysis (**Table 4**). The PMN percentage cut-off value of 72.15% yielded a sensitivity of 55.1%, a specificity of 71.9%, and a positive predictive value of 82% for predicting IVIG resistance. The NT-proBNP cut-off value of 503 pg/mL yielded a sensitivity of 51.9%, a specificity of 61.7%, and a positive predictive value of 87% for predicting IVIG resistance in the acute phase of KD. The CRP cut-off value of 6.88 mg/dL yielded a sensitivity of 63% and a specificity of 59%, and a positive predictive value of 85% for predicting IVIG resistance. The total bilirubin cut-off value of 0.855 yielded a sensitivity of 40%, a specificity

Table 2. Multivariate logistic regression comparison of laboratory data between KD patients with and without IVIG resistance/CAL

Variable	p value	OR	95% CI for OR	
			Lower	Upper
PMN				
IVIG resistance	0.000*	1.005	1.002	1.007
CAL	0.214	1.002	0.999	1.004
Albumin				
IVIG resistance	0.000*	0.619	0.501	0.765
CAL	0.400	1.005	0.993	1.017
Total bilirubin				
IVIG resistance	0.224	1.009	0.995	1.023
CAL	0.137	1.009	0.997	1.021
AST				
IVIG resistance	0.029†	1.001	1	1.002
CAL	0.520	1	0.999	1.001
ALT				
IVIG resistance	0.002†	1.001	1.001	1.002
CAL	0.234	0.999	0.998	1
CRP				
IVIG resistance	0.005†	1.012	1.004	1.020
CAL	0.004†	1.013	1.004	1.022
NT-proBNP				
IVIG resistance	0.002†	1	1	1
CAL	0.172	1	1	1

CI presents the lower and upper values of the estimated parameter, i.e., if the experiment were to be performed 100 times on the same data under the same conditions, then 95% of the time estimate will be in that interval.

ALT = alanine aminotransferase; AST = aspartate aminotransferase; CAL = coronary artery lesion; CI = confidence interval; CRP = C-reactive protein; IVIG = intravenous immunoglobulin; KD = Kawasaki disease; NT-proBNP = N-terminal-pro-brain natriuretic peptide; OR = odds ratio; PMN = polymorphonuclear neutrophil. Statistical significances were * $p < 0.001$, † $p < 0.01$, ‡ $p < 0.05$.

Table 3. Demographic, laboratory characteristics of KD patients during diagnosis in the group with and without CAL

	CAL-	CAL+	p value
Sex Male	2,397 (51.9)	336 (62.7)	<0.001
Female	1,862 (40.3)	146 (27.2)	
Not identified	356 (7.7)	54 (10.1)	
Age (months)	31.78±24.29	36.57±22.61	<0.001
Duration of fever before IVIG treatment	6.62±3.85	6.38±3.46	0.174
PMN (%)	62.97±31.50	65.64±33.48	0.067
Albumin (g/dL)	4.11±8.54	4.29±7.87	0.642
Total bilirubin (g/dL)	0.77±4.77	1.29±8.55	0.038
AST (IU/L)	83.00±150.83	80.05±142.60	0.668
ALT (IU/L)	92.22±148.55	85.62±131.69	0.328
CRP (mg/dL)	7.86±9.42	9.79±14.25	0.002
NT-proBNP (pg/dL)	984.74±2,428.99	1,179.93±2,453.97	0.079

Values are presented as number (%) or mean±standard deviation.

ALT = alanine aminotransferase; AST = aspartate aminotransferase; CAL = coronary artery lesion; CRP = C-reactive protein; IVIG = intravenous immunoglobulin; KD = Kawasaki disease; NT-proBNP = N-terminal-pro-brain natriuretic peptide; PMN = polymorphonuclear neutrophil.

Table 4. ROC to compare various variables for resistance to IVIG treatment

	AUC	Cut-off value	Sensitivity	Specificity	PPV	NPV
PMN (%)	0.682	72.15	55.1	71.9	0.82	0.07
NT-proBNP (pg/dL)	0.579	503.00	51.9	61.7	0.87	0.08
CRP (mg/dL)	0.624	6.88	63.0	59.0	0.85	0.07
Albumin (g/dL)	0.438	2.58	99.0	3.0	0.90	0.33
Total bilirubin (g/dL)	0.660	0.86	40.0	87.0	0.78	0.07
AST (IU/L)	0.622	52.50	49.0	72.0	0.83	0.07
ALT (IU/L)	0.622	51.10	57.0	66.0	0.84	0.07

ALT = alanine aminotransferase; AST = aspartate aminotransferase; AUC = area under the curve; CRP = C-reactive protein; IVIG = intravenous immunoglobulin; NPV = negative predictive value; NT-proBNP = N-terminal-pro-brain natriuretic peptide; PMN = polymorphonuclear neutrophil; PPV = positive predictive value; ROC = receiver operating characteristic.

Table 5. ROC to compare various variables for prediction of CAL

	AUC	Cut-off value	Sensitivity	Specificity	PPV	NPV
PMN (%)	0.550	71.95	55.5	71.2	0.87	0.09
NT-proBNP (pg/dL)	0.530	709	41.2	70.5	0.88	0.10
CRP (mg/dL)	0.517	11.71	25.0	81.0	0.87	0.01
Albumin (g/dL)	0.464	4.75	98.0	4.0	0.90	0.20
Total bilirubin (g/dL)	0.500	1.13	84.0	21.0	0.90	0.14
AST (IU/L)	0.493	203.5	91.0	10.0	0.90	0.11
ALT (IU/L)	0.497	11.5	14.0	88.0	0.91	0.11

ALT = alanine aminotransferase; AST = aspartate aminotransferase; AUC = area under the curve; CAL = coronary artery lesion; CRP = C-reactive protein; NPV = negative predictive value; NT-proBNP = N-terminal-pro-brain natriuretic peptide; PMN = polymorphonuclear neutrophil; PPV = positive predictive value; ROC = receiver operating characteristic.

of 87%, and a positive predictive value of 78% for predicting IVIG resistance. The AST cut-off value of 52.5 IU/L yielded a sensitivity of 49%, a specificity of 72%, and a positive predictive value of 83% for predicting IVIG resistance. The ALT cut-off value of 51.5 IU/L yielded a sensitivity of 57%, a specificity of 66%, and a positive predictive value of 84% for predicting IVIG resistance. The albumin cut-off value of 2 g/dL yielded a sensitivity of 99%, a specificity of 3%, and a positive predictive value of 90% for predicting IVIG resistance.

The various variables for predicting CAL in patients with KD was assessed by an ROC curve analysis (**Table 5**). The NT-proBNP cut-off value of 709 pg/mL yielded a sensitivity of 41.2% and a specificity of 70.5% for predicting CAL in the acute phase of KD. The CRP cut-off value of 11.71 mg/dL yielded a sensitivity of 25% and a specificity of 81% for predicting CAL. The PMN percentage cut-off value of 71.95% yielded a sensitivity of 55.5% and a specificity of 71.2% for predicting CAL.

DISCUSSION

Some patients with KD fail to respond to initial IVIG therapy. Retrospective studies have identified potential factors that could predict which patients will require further therapy for refractory disease.¹³⁾¹⁴⁾ 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 judicious and aggressive treatment.

Our study significantly revealed that increased PMN, NT-proBNP, CRP, AST, and ALT levels are predictors for IVIG resistance.

NT-proBNP is released from the heart in response to pressure and volume overload.¹⁷⁾ NT-proBNP elevation is also associated with cytokine reactions.¹⁸⁾ In fact, a linear correlation between NT-proBNP and CRP levels was present in the current study (NT-proBNP=32.224; CRP+741.015; $p<0.001$).

Several previous studies reported increased patient serum NT-proBNP levels in acute phase of KD, thus providing useful markers for diagnosing KD.¹⁹⁻²³⁾ In addition, several studies have published data that NT-proBNP could be used for predicting resistance to IVIG therapy and patients who are at high risk for CAL. Yoshimura et al.¹⁵⁾ previously reported that serum NT-proBNP level is increased in children with KD with CAL and IVIG resistance and may be useful to predict CAL and IVIG resistance in KD. In that study, serum NT-proBNP level was considered a better single predictor for IVIG non-responders. Kim et al.²⁴⁾ and Cho and Kang¹²⁾ also showed that NT-proBNP is a helpful marker in identifying patients at risk for not responding to initial IVIG treatment. By using larger multicenter data in our study, we further confirmed that serum NT-proBNP levels are also increased in children with KD with IVIG resistance. However, in our study, NT-proBNP is not associated with risk for CAL. These results could have been limited by its retrospective design. Information bias was possibly covered by the time of IVIG administration and timing of measurement of CA lesions. In addition, the cut-off value of NT-proBNP, as well as its sensitivity, for predicting IVIG resistance was lower than that in published studies. These results may have been caused by the data collection from laboratories with different reference ranges.

In our study, multivariate logistic regression analyses showed significantly increased PMN, NT-proBNP, AST, ALT, and CRP levels, and decreased albumin level are associated with risk for IVIG resistance although those were not found as good indicators of IVIG resistance by the area under the curve (AUC).

These values were almost correlated with the results of our previous meta-analysis study of laboratory predictive factors for IVIG-resistant KD. The meta-analysis of 12 studies, comprising 2,745 patients, demonstrated that the laboratory predictive factors for IVIG-resistant KD included higher PMN percentage, NT-proBNP, total bilirubin, ALT, and CRP levels, and lower sodium and albumin levels.¹³⁾ 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 adequately respond to the initial IVIG therapy. Although the multivariate logistic regression analyses showed that only CRP was associated with risk for CAL, the AUC was too low and not regarded as a good predictor.

In our study, PMN percentage was an important laboratory predictive factor in addition to NT-proBNP for IVIG-resistant KD. The findings of Ha et al.²⁵⁾ are comparable to our

research. In their study, in patients with acute febrile phase of KD, IVIG-resistant patients had higher neutrophil-to-lymphocyte ratios (NLR) than IVIG-responsive patients. Kawamura et al.²⁶⁾ also reported recently that high NLR and high platelet-to-lymphocyte ratio before IVIG, especially when combined, were useful predictors for IVIG resistance in KD. Their study revealed that both $NLR \geq 3.83$ before IVIG and $NLR \geq 1.27$ after IVIG were predictive for IVIG resistance. Neutrophil counts increase in response to inflammation and infection. Leliefeld et al.²⁷⁾ showed that in severe inflammation, neutrophils are rapidly activated, which affect their functional capacities, such as chemotaxis, phagocytosis, intracellular killing, neutrophil extracellular traps, and their capacity to modulate adaptive immunity. They reviewed the possible mechanisms of suppression of adaptive immunity by neutrophils and the contribution of neutrophil subsets to immune paralysis. Takeshita et al.²⁸⁾ demonstrated that in patients with CAL, polymorphonuclear cells had higher percentages of vacuolization and increased toxic granulation scores at the time of admission, and these scores remained persistently higher in patients with CALs than in patients without CALs, despite administration of a full-dose of IVIG.

The accurate prediction of potentially IVIG-resistant patients remains a challenge. However, the presence of several predictive factors in our study should alert clinicians to the increased probability of the patient not responding adequately to initial IVIG therapy. Because IVIG-resistant patients have a higher probability for CAL formation, aggressive treatment is important.

The strength of this study is the large number of cases, the data were collected nationwide, and the sample size is the largest in the literature. However, the limitations to this study include the retrospective nature of the study with incomplete data collection. Furthermore, substantial proportions of patients were excluded because of incomplete data. Further weakness might exist because of different sampling times at each institution and data obtained from laboratories with different reference ranges in multicenter clinical studies. Finally, as demonstrated by the poor predictive abilities (low AUC values) of the individual cut-off values of laboratory parameters in this study, multiple factors seem to be associated with IVIG resistance, as well as the development of CALs, in KD. Hence, a comprehensive approach seems necessary.

PMN percentage, serum NT-proBNP, CRP, AST, and ALT levels are significantly increased in patients with KD with IVIG resistance and may be useful for predicting IVIG resistance in KD. Furthermore, serum CRP is significantly increased in patients with KD with CAL.

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