The Combined Usefulness of the Neutrophil-to-Lymphocyte and Platelet-to-Lymphocyte Ratios in Predicting Intravenous Immunoglobulin Resistance with Kawasaki Disease

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The laboratory records of 405 patients with Kawasaki disease before and after intravenous immunoglobulin (IVIG) therapy were compared between the IVIG-responsive (n = 320) and IVIG-resistant (n = 85) groups. A high neutrophil-to-lymphocyte ratio and a high platelet-to-lymphocyte ratio before IVIG, especially when combined, were useful predictors for IVIG resistance in Kawasaki disease. *(J Pediatr 2016;178:281-4).*

Kawasaki disease (KD) is an acute febrile illness characterized by systemic vasculitis.[1] Although intravenous immunoglobulin (IVIG) is an effective treatment for KD,[2] approximately 10%-20% of patients are resistant to IVIG therapy and, therefore, at higher risk of developing coronary artery abnormalities (CAAs) than responders to IVIG therapy.[2,3] Although several risk-scoring systems using usual laboratory data to predict patients who are IVIG resistant have been developed in Japan,[4-6] these systems do not accurately predict nonresponders among North American patients.[7] Alternatively, inflammatory cytokines and T-cell surface markers have been reported to predict IVIG resistance in patients with KD,[8,9] but these markers are costly and unavailable in routine laboratory data.

The white blood cell count and its subpopulations in the peripheral blood are classic indicators of inflammation. Recent studies have indicated that the neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) are useful as systemic inflammatory markers and prognostic indicators of adverse cardiovascular events and cancers.[10,11] Furthermore, there are several reports that indicate that the combination of NLR and PLR was useful for predicting the risk of cardiac events and mortality in patients undergoing percutaneous coronary intervention[12] and of poor prognosis in patients with malignant diseases.[13] Recently, the NLR value 2 days after IVIG has been reported to predict CAA development and IVIG resistance in KD,[14] but the usefulness of the PLR or the combination of NLR and PLR has not been evaluated to identify patients with refractory KD. We investigated whether or not NLR, PLR, or a combination of both could predict IVIG resistance in patients with KD.

Methods

We retrospectively reviewed the clinical records of patients with KD hospitalized at the National Defense Medical College hospital between April 2005 and August 2015. Our diagnostic criteria for KD were the Diagnostic Guidelines for Kawasaki Disease (5th revision),[15] and the first day of illness was defined as the first day a fever was present. The present study was approved by the institutional review board at National Defense Medical College. All of the patients were treated with oral aspirin (30 mg/kg/d), IVIG (2 g/kg/d), and intravenous ulinastatin (15 000 U/kg in 3 divided doses).[16] IVIG resistance was defined as a persistent fever lasting >24 hours after the completion of IVIG or recrudescent fever associated with KD symptoms after an afebrile period. Serial blood samples were obtained during the acute febrile phase before IVIG and 1 day after IVIG. Echocardiography was performed on admission, before and after IVIG, and subsequently once every 2-4 days until discharge. CAAs were diagnosed in accordance with the Japanese Ministry of Health criteria: an internal lumen diameter >3.0 mm in children <5 years of age (>4.0 mm in children ≥5 years of age) or an internal segment diameter at least 1.5 times larger than that of the adjacent segment. The statistical analyses were performed using an EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan),[17] which is a graphic user interface for R (The R Foundation for Statistical Computing, Vienna, Austria). To assess the ability of NLR and PLR to predict IVIG resistance, receiver operating characteristic curves were constructed, and the most discriminating cut-off values were determined. To identify the independent predictors of IVIG resistance, a multivariate logistic regression analysis was performed including the variables that had shown significant differences on comparison between IVIG-responsive and IVIG-resistant groups. A *P* value of <.05 was considered to be statistically significant.

CAAs	Coronary artery abnormalities
IVIG	Intravenous immunoglobulin
KD	Kawasaki disease
NLR	Neutrophil-to-lymphocyte ratio
PLR	Platelet-to-lymphocyte ratio

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Results

Of the 405 patients enrolled in the present study, 85 (21.0%) were resistant to initial IVIG therapy. On comparison of the clinical and laboratory data between the IVIG-responsive and IVIG-resistant groups (**Table I**), the IVIG-resistant group had a higher percentage of CAA and higher levels of NLR and PLR before IVIG than the IVIG-responsive group. Receiver operating characteristic curve analysis showed that before IVIG therapy, the best NLR and PLR cut-off values were 3.83 and 150, respectively, and the areas under the curve were 0.75 and 0.73 (95% CI 0.70-0.81 and 0.68-0.79), respectively. One day after IVIG therapy, the best NLR and PLR cut-off values were 1.27 and 201, respectively, and the areas under the curve were 0.86 and 0.53 (95% CI 0.81-0.91 and 0.45-0.60), respectively. The sensitivity, specificity, positive predictive value, negative predictive value, and diagnostic accuracy are shown in **Table II** (available at www.jpeds.com). The proportions of patients with an NLR ≥3.83, PLR ≥150, and combined NLR ≥3.83 and PLR ≥150 before IVIG and with NLR ≥1.27, PLR ≥201, and combined NLR ≥1.27 and PLR ≥201 after IVIG were significantly higher in the IVIG-resistant group than in the IVIG-responsive group (**Table III**; available at www.jpeds.com).

Multiple logistic regression analyses were performed to determine whether or not the above cut-off values and their combinations were significant predictors for IVIG resistance in KD (**Table IV**). Before IVIG therapy, the ORs of NLR ≥3.83 and PLR ≥150 adjusted for age, number of days of illness at IVIG administration, and aspartate aminotransferase, alanine aminotransferase, sodium, and C-reactive protein levels were 2.96 (95% CI 1.26-6.97; $P = .01$) and 2.27 (1.08-4.73; $P = .03$), respectively. The OR of the combination of both NLR ≥3.83 and PLR ≥150 (3.59, 95% CI 1.91-6.77; $P < .001$) was higher than those of either NLR ≥3.83 or PLR ≥150 alone. After IVIG therapy, the OR of NLR ≥1.27 (22.6, 95% CI 9.57-53.4; $P < .001$) was significantly higher than before therapy, and the OR of PLR ≥201 (0.97, 95% CI 0.46-2.05; $P = .95$) was not significantly so. The OR of the combination of both NLR ≥1.27 and PLR ≥201 was 2.76 (95% CI 1.31-5.80; $P = .007$), which was lower than that of NLR ≥1.27 alone.

Discussion

Neutrophil counts increase in response to inflammation and infection. The severity of the clinical course in critically ill patients with shock and sepsis has been reported to be correlated with marked neutrophilia and lymphocytopenia in white blood cells.[18] Thus, the NLR is an inflammation-based marker, and its increase reflects an accelerated inflammatory response. In the acute phase of KD, the number of circulating neutrophils increases, and their function is enhanced with the markedly increased production of oxygen intermediate,[19] neutrophil elastase, and myeloperoxidase,[20] which may lead to tissue self-destruction. For these reasons, the activated neutrophil-mediated endothelial cell injury is believed to be involved in the pathogenesis of KD vasculitis. The present study revealed that the NLR was an independent predictor of IVIG

Table I. Comparison of clinical data among the IVIG-responsive and IVIG-resistant groups in KD

	IVIG-responsive (n = 320)	IVIG-resistant (n = 85)	*P* value
Male (%)	185 (57.8%)	49 (57.6%)	1.00*
Age (mo at onset)	25 (13-42)	34 (17-54)	.01
Days of illness at diagnosis	5 (4-5)	4 (3-5)	<.001
Days of illness at IVIG administration	5 (5-6)	4 (4-5)	<.001
CAA (+)	1 (0.3%)	9 (10.6%)	<.001*
Before IVIG therapy			
WBCs, $\times 10^3/mm^3$	13.45 (11.02-16.70)	13.50 (10.90-17.20)	0.91
Neutrophils, $\times 10^3/mm^3$	9.10 (6.98-11.76)	10.52 (8.74-14.65)	<.001
Lymphocytes, $\times 10^3/mm^3$	2.89 (1.73-4.47)	1.44 (1.07-2.33)	<.001
Others, $\times 10^3/mm^3$	1.03 (0.63-1.41)	0.72 (0.40-1.06)	<.001
Platelet count, $\times 10^4/mm^3$	33.50 (28.50-39.30)	30.70 (23.90-36.20)	.003
NLR	3.06 (1.75-5.94)	7.80 (4.38-13.46)	<.001
PLR	111.12 (81.22-182.80)	207.11 (150.34-277.98)	<.001
T-Bil, mg/dL	0.6 (0.4-0.8)	0.9 (0.5-2.5)	0.17
AST, IU/L	38 (29-75.5)	60 (30-158)	.006
ALT, IU/L	26 (14-99)	73 (16-224)	.005
Albumin, g/dL	3.8 (3.5-4.0)	3.7 (3.3-4.0)	0.13
Sodium, mmol/L	135 (133-136)	132 (130-135)	<.001
CRP, mg/dL	6.8 (4.2-10.5)	10.0 (6.8-14.74)	<.001
After IVIG therapy			
WBCs, $\times 10^3/mm^3$	7.00 (5.40-8.53)	10.25 (8.08-13.00)	<.001
Neutrophils, $\times 10^3/mm^3$	2.50 (1.74-3.95)	7.36 (4.69-9.59)	<.001
Lymphocytes, $\times 10^3/mm^3$	2.95 (2.18-4.24)	2.22 (1.47-3.16)	<.001
Others, $\times 10^3/mm^3$	0.82 (0.59-1.13)	0.76 (0.51-1.02)	.07
Platelet count, $\times 10^4/mm^3$	40.30 (32.75-48.95)	29.00 (23.90-34.85)	<.001
NLR	0.83 (0.52-1.34)	3.40 (1.99-5.77)	<.001
PLR	131.97 (96.43-185.21)	147.46 (96.03-208.98)	0.49

ALT, alanine aminotransferase; *AST*, aspartate aminotransferase; *CRP*, C-reactive protein; *T-Bil*, total bilirubin; *WBC*, white blood cell.
The data are presented as the median (25th-75th percentile) for the continuous variables and as the number of patients (%) for the categorical variables.
The *P* values were obtained using the Mann-Whitney U test or *Fisher exact test.