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Platelet Indices as Diagnostic Marker for Kawasaki Disease

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Various candidate biomarkers have been investigated for the early and accurate diagnosis of Kawasaki disease (KD). We aimed to evaluate platelet activity using platelet indices (PI) in patients with KD or simple febrile illness to determine whether these indices might support a diagnosis of KD. Another objective of the study was to delineate the changes in PI from the acute to convalescent phases of KD. A total of 225 patients with complete KD (cKD), 110 with incomplete KD (iKD), and 71 with simple febrile illness (control) were enrolled. PI included mean platelet volume (MPV), platelet distribution width (PDW), and plateletcrit (PCT). We serially measured the serum PI four times for each patient with KD from the acute to convalescent phases: on D0 (day of intravenous immunoglobulin (IVIG) treatment) and repeated on days 2 (D2), 14 (D14), and 56 (D56) after IVIG therapy. Data from the control group were collected during the acute stage of the disease (D0). The platelet counts in the cKD ($341\pm103\times10^3/mm^3$) and iKD ($374\pm135\times10^3/mm^3$) at diagnosis were higher than the control group ($290\pm128\times10^3/mm^3$). The PCT in the cKD (0.284±0.085%) and iKD (0.313±0.109%) groups at diagnosis were also higher than the control group (0.246±0.108%). However, the MPV and PDW levels in the KD group were not statistically significant. Therefore, platelet count and PCT are adjuvant parameters for the differential diagnosis of KD from a simple febrile illness.

Key Words: *Kawasaki Disease; Platelet Indices; Biomarker*

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INTRODUCTION

Kawasaki disease (KD) is characterized by systemic inflammation in medium-sized arteries especially in coronary arteries during acute febrile phase.[1-3] About 15-25% of KD patients develop coronary artery lesions, including coronary aneurysms, if they are not treated effectively.[1-4] Therefore, a prompt and accurate diagnosis and timely treatment of KD is necessary.[3] However, since there is no definitive diagnostic laboratory test for KD, the diagnosis and treatment is sometimes delayed.[3] Therefore, various candidate biomarkers for suspicion of KD have been investigated.[3] A characteristic laboratory feature of the subacute phases of KD is thrombocytosis, with platelet counts over than 500,000/mm^3.[3] In contrast, thrombocytopenia in the acute stage is a risk factor for earlier coronary aneurysm development.[3,5] Not only are platelets dynamic blood particles whose primary function is hemostasis or the prevention of bleeding, but those are also immune cells that initiate and accelerate many vascular inflammatory conditions.[6] Platelet activity can be evaluated with platelet indices (PI) including, mean platelet volume (MPV), platelet distribution width (PDW) and plateletcrit (PCT).[7] PI is are included in routine blood counts, which may be a more sensitive index than platelet number as a marker in various inflammatory and infectious disease.[7,8] There are only few studies on the changes of PI in KD.[8-10] Hu et al.[9] found MPV to be significantly lower in the 23 KD patients than 33 febrile illness controls. Liu et al.[10] demonstrated that the 309 patients with KD had significantly lower MPV and PDW values than 160 healthy control subjects. However, they enrolled a small number of patients compared with healthy control. Furthermore, they investigated PI only at the

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acute phase. In this study, therefore, we evaluated PI including MPV, PDW and PCT in patients with KD or simple febrile illness as to whether these indexes might support a diagnosis of KD. And we also delineate the changes in PI from the acute to convalescent phases.

MATERIALS AND METHODS

1. Patient selection

We enrolled patients with KD who were admitted to Chonnam National University Hospital between December 2007 and March 2016. Patients with KD were diagnosed on the basis of classic clinical criteria according to the guidelines.[3] The diagnosis was complete Kawasaki disease (cKD) if more than four clinical diagnostic criteria were fulfilled. Patients were categorized as incomplete KD (iKD) when they had persistent fever that lasted five days or longer but with fewer than four of the other features, and if other possible causes of fever had been excluded.[3] We also enrolled 71 age-matched children who visited our hospital for an evaluation of acute febrile diseases. Patients with known inherited or acquired disorders of platelet function were excluded from the study.

2. Peripheral venous blood examination

Serum samples were obtained to measure serum PI, including MPV, PDW, and PCT levels on day 0 (D0), which was when intravenous immunoglobulin (IVIG) was initiated in patients with cKD and iKD, and the day of admission in the simple febrile illness group. Blood samples for the determination of complete blood cell counts (CBC) were collected in tubes containing ethylenediaminetetraacetic acid (EDTA). All measurements, including PI, were performed within 2 h after blood sampling because of the known effect of EDTA on platelet volume.[11] These samples were analyzed on a UniCel DxH 800 (Beckman Coulter, Brea, CA) or Advia 2010i Hematology System (Siemens Healthcare Diagnostics, Eschborn, Germany), under strict daily quality control.

C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), aspartate aminotransferase (AST), alanine aminotransferase (ALT), total bilirubin, total protein, albumin, lactate dehydrogenase (LDH), blood urea nitrogen (BUN), creatinine, creatine kinase (CK), CK-myoglobin (CK-MB), amylase, and N-terminal pro-brain natriuretic peptide (NT-proBNP) levels were obtained from both patients with KD and controls. We serially measured serum PI, WBC, CRP, and ESR four times for each patient with KD from the acute to convalescent phase: on D0 (day of IVIG treatment) and repeated on days 2 (D2), 14 (D14), and 56 (D56) after IVIG therapy. Data from the control group were collected only during the acute stage of the disease (D0). We compared the D0 values of cKD, iKD, and control groups and those of patients with cKD versus iKD at later time points.

3. Statistical analysis

The unpaired two-tailed t-test or chi-square test was used to assess the statistical significance of differences in the values of independent variables. Analysis of variance (ANOVA) was used to compare data among more than three groups, followed by Tukey's honest significant difference post-hoc test. When homogeneity of variance was not present according to Levene's test, Dunnett's T3 test was used as the post-hoc test. When a normal distribution was not observed, as assessed by the Shapiro-Wilk test, the Kruskal-Wallis test was used, followed by the Bonferroni correction. The cutoff values for diagnosing KD were obtained from the receiver operating characteristic (ROC) curve analysis. Continuous variables were expressed as mean±standard deviation. All values were considered statistically significant at $p<0.05$. The SPSS software package (version 20.0; SPSS, IBM Inc., Chicago, IL, USA) was used for all data analyses.

4. Ethics statement

This study was approved by the Institutional Review Board of Chonnam National University Hospital (Protocol no.I-2009-09-103). All data were confidentially treated.

RESULTS

1. Patient characteristics

Table 1 shows the demographic characteristics of the 335 patients with KD and 71 control patients. A total of 335 patients were diagnosed with KD, and these patients provided blood samples for PI measurement. Of these, 225 (67.2%) and 110 (32.8%) had cKD and iKD, respectively. In the cKD group, the male-to-female ratio was 1.7 (141/84), and the mean age at diagnosis was 2.9±1.8 years (2 months to 10.5 years). In iKD group, the male-to-female ratio was 1.5 (66/44) and the mean age was 2.2±1.8 years (1 month to 8.3 years). The mean age at diagnosis of patients with iKD was significantly lower than that of patients with cKD ($p=0.002$). All patients with KD were treated with IVIG (2 g/kg) in a single infusion continuously for 12 hours, and high-dose aspirin (30-50 mg/kg) was given during the acute phase. Among the 335 patients, 49 (14.6%, 41 with cKD and 8 with iKD) failed to respond to the initial IVIG therapy and received another dose. Among these 41 patients with cKD, two patients did not respond to the second dose of IVIG and were then administered a third dose of IVIG accompanied with high-dose methylprednisolone. This therapy was initiated as soon as possible after the diagnosis. After the child had been afebrile for 48 to 72 h following the management of IVIG with high-dose aspirin, the aspirin dose was lowered (3-5 mg/kg per day). A total of 71 patients with simple febrile illness were enrolled as controls during the same period, with a male-to-female ratio of 2.2 (49/22) and mean age of 2.9±2.3 years (2 months to 9.1 years). Age and duration of fever at diagnosis did not differ significantly among the three groups (Table 1). The clinical diagnoses of the controls were as follows: pneumonia (n=26), acute tonsillitis (n=10), acute upper respiratory infection (n=4), viral meningitis (n=4), fever of unknown origin (n=4), cervical lym-

TABLE 1. Demographic characteristics and laboratory findings at diagnosis in patients with complete Kawasaki disease (KD), incomplete KD, and simple febrile illness (Control)

	Complete KD		Incomplete KD		Control	
	n	Value	n	Value	n	Value
Age (years)	225	2.9±1.8	110	2.2±1.8 †	71	2.9±2.3
Sex (boy/girl)	225	141/84	110	66/44	71	49/22
Duration of fever prior to admission (days)	225	4.2±2.0	110	4.5±2.4	71	4.3±4.2
Total fever duration (days)	225	6.0±1.8	110	6.4±2.5	71	6.0±5.0
White blood cell (count/mm3)	222	14,382±4,641	110	14,305±5,339	71	11,740±6,273 †,‡
Neutrophil (%)	221	66.9±15.7	110	59.0±16.4 †	71	58.0±19.1 †
Eosinophil (%)	222	3.1±12.8	110	2.8±2.7	71	0.9±1.3 †,‡
Hemoglobin (g/dL)	222	11.4±1.1	110	11.1±1.2	71	11.5±1.3 ¶
Platelet ($\times 10^3/mm^3$)	222	341±103	110	374±135	71	290±128 †,‡
Mean platelet volume (fl)	222	8.4±1.1	110	8.5±0.9	70	8.6±1.3
Platelet distribution width (%)	222	16.5±13.0	110	15.0±11.5	70	15.6±13.1
Plateletcrit (%)	222	0.284±0.085	110	0.313±0.109	70	0.246±0.108 †,‡
C-reactive protein (mg/dL)	219	8.3±5.2	107	7.9±5.9	69	4.2±4.6 †,‡
Erythrocyte sedimentation rate (mm/hr)	93	66±26	38	75±28	19	40±34 †,‡
Aspartate aminotransferase (U/L)	222	96±144	109	70±111*	71	98±265
Alanine aminotransferase (U/L)	222	113±171	109	75±120*	71	45±94 †,¶
Total bilirubin (mg/dL)	148	1.1±1.4	63	0.7±0.9*	28	0.7±1.2
Total protein (g/dL)	206	6.4±0.8	98	6.5±0.7	67	6.6±0.6
Albumin (g/dL)	211	3.6±0.6	102	3.7±0.5	69	3.9±0.5 †,‡
Lactate dehydrogenase (U/L)	88	620±190	43	627±271	24	1,258±1,623*,‡
Blood urea nitrogen (mg/dL)	218	8.7±4.7	107	7.8±4.6	70	9.7±4.7 †
Creatinine (mg/dL)	217	0.3±0.5	106	0.3±0.1	69	0.3±0.1
Creatine kinase (IU/L)	186	187±468	95	106±248	35	753±2565 †,‡
Amylase (U/L)	53	58.6±57.2	20	51.0±60.5	14	39.7±13.4
N-terminal prohormone of Brain Natriuretic Peptide (pg/mL)	217	1,931±3,630	109	1,445±2,312	54	924±2,141 †,‡

IVIg: intravenous immunoglobulin administration, KD: Kawasaki disease. Data are shown as mean±SD. *p<0.05, † p<0.01 vs. complete KD, ¶p<0.05, ‡p<0.01 vs. incomplete KD.

phadenitis (n=3), acute bronchiolitis (n=3), acute gastroenteritis (n=3), acute obstructive laryngitis (n=3), bacteremia (n=2), acute myocarditis (n= 2), urinary tract infection (n=1), bacterial keratoconjunctivitis (n=1), acute otitis media (n=1), acute pericarditis (n= 1), herpes viral infection (n=1), infectious mononucleosis (n=1), and acute sinusitis (n=1).

2. Clinical presentations in patients with Kawasaki disease

Among the 225 patients with cKD, 71 patients (31.6%) met the five diagnostic clinical criteria of KD, and the remaining 154 patients (68.4%) met only four criteria. Of the total sample, 221 (98.2%) had bilateral bulbar conjunctival injections, 215 (95.6%) had changes in the oral mucosa, 208 (92.4%) had polymorphous rashes, 164 (72.8%) had changes in the peripheral extremities, and 163 (72.4%) had cervical adenopathy with enlarged lymph nodes greater than 1.5 cm in diameter. Among the 110 patients with iKD, 73 (66.3%) met 3 criteria, 29 (26.4%) met 2 criteria, and the remaining 8 (7.3%) met only one criteria of KD. Ninety (81.8%) had bilateral bulbar conjunctival injections, 78 (70.9%) had changes in the oral mucosa, 55 (50.0%) had polymorphous rashes, 24 (21.8%) had changes in the peripheral extremities, and 38 (34.5%) had cervical adenopathy. All clinical criteria for diagnosing KD were significantly more prevalent in patients with cKD than in those with iKD (p<0.001).

3. Laboratory findings at the time of diagnosis and changes over time

Laboratory findings of the cKD, iKD, and febrile illness control groups at D0 are shown in Fig. 1 and Table 1. At the time of diagnosis, WBC count, percentage of eosinophils, CRP, and ESR levels in cKD and iKD patients were significantly higher than those in the controls. Serum albumin, ALT, LDH, CK, and NT-proBNP levels in cKD and iKD patients were significantly lower than the controls. The percentage of neutrophils in patients with cKD was significantly higher than in patients with iKD (p<0.001) and febrile illness controls (p=0.003). ALT levels in patients with cKD were also significantly higher than patients with iKD (p=0.018).

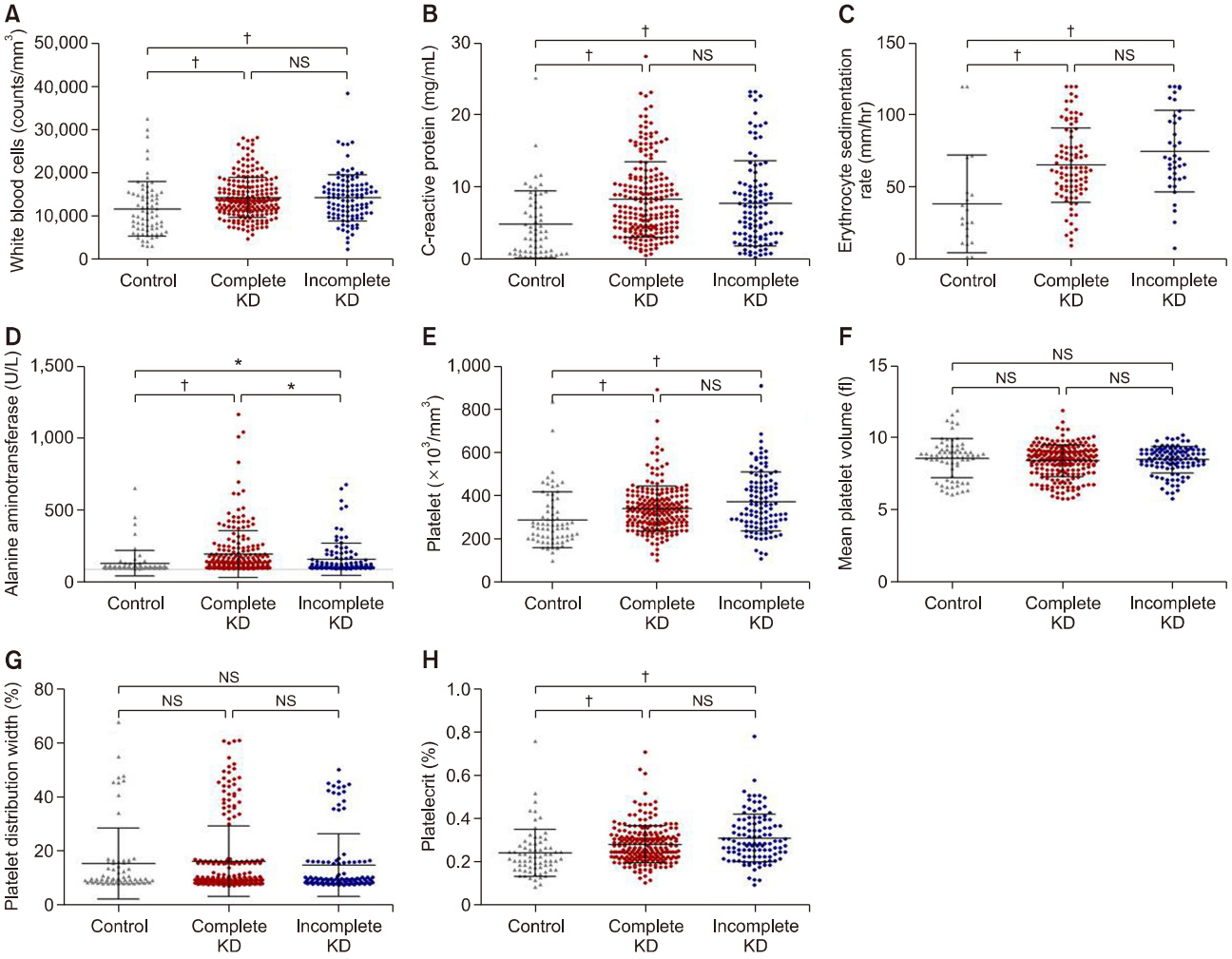

Fig. 1. Dot plots of white blood cells (A), C-reactive protein level (B), erythrocyte sedimentation rate (C), alanine aminotransferase (D), platelet count (E), mean platelet volume (F), platelet distribution width (G), and plateletcrit (H) in patients with febrile illness (control), complete Kawasaki disease (KD), and incomplete KD at diagnosis. *p<0.05, †p<0.01, NS: not significant.

4. Laboratory changes in cKD and iKD after IVIG treatment

As shown in Table 2, WBC counts in both the cKD and iKD group on D2 and D14 were lower than in the control group. The WBC counts in both cKD and iKD group at D2, D14, and D56 were also lower than those at D0. The ESR in both the cKD and iKD groups at D0 and D2 was higher than that in the control group. The increased ESR on D0 and D2 gradually decreased on D14 and D56. In both the cKD and iKD groups, the increased CRP on D0 gradually decreased on D2, D14, and D56.

5. Platelet index levels at the time of diagnosis and changes over time

The platelet counts in the cKD and iKD groups were consistently higher than those in the control group. The platelet counts in the cKD group at D2 and D14 were higher than those at D0 and D56 (Table 1, Fig. 1E and 2A). The platelet count in iKD group at D2 was higher than that at D0 and D56 (Table 1, Fig. 1E and 2B).

At the time of diagnosis, the MPV in patients with cKD (8.4±1.1 fL) and iKD (8.5±0.9 fL) did not differ from those in the control (8.6±1.3 fL). However, the MPV in the cKD group at D2 (7.7±1.2, p<0.001), D14 (7.2±0.8, p<0.001), and D56 (7.4±0.8, p<0.001) were lower than those in the control group. The MPV on D2 was lower than that on D0 (p<0.001). The MPV on D14 and D56 was lower than that on D2 (p<0.001 and, p=0.020, respectively) (Fig. 1F and 2C). The MPV in the iKD group at D2 (7.7±1.0, p<0.001), D14 (7.3±0.8, p<0.001), and D56 (7.4±0.7, p<0.001) were lower than those in the control group, and were also lower than that on D0 (p<0.001) (Fig. 1F and 2D).

On D0, the PDW in patients with cKD (16.5±13.0%) and iKD (15.0±11.5%) also did not differ from those in controls (15.6±13.1%). However, the PDW in the cKD group at D2 (21.1±13.3%, p<0.001), D14 (21.4±11.2%, p<0.001), and D56 (22.4±12.0%, p<0.001) were higher than those in the control group, which were also higher than those at D0 (p<0.001) (Fig. 1G and 2E). The PDW in the iKD group at D2 (22.5±14.9%, p<0.001), D14 (20.9±11.6%, p<0.001), and

TABLE 2. Laboratory findings of patients with complete and incomplete Kawasaki disease (KD) on day of diagnosis and 2, 14, and 56 days after intravenous immunoglobulin treatment and simple febrile illness (Control) at diagnosis

	Complete KD		Incomplete KD		Control	
	n	Value	n	Value	n	Value
Platelet ($\times 10^3/mm^3$)						
At diagnosis	222	341±103	110	374±135	71	290±128†,‡
2 days after treatment	220	417±139	106	460±177*		
14 days after treatment	213	404±132	103	413±154		
56 days after treatment	186	348±84	89	349±86		
Mean platelet volume (fl)						
At diagnosis	222	8.4±1.1	110	8.5±0.9	70	8.6±1.3
2 days after treatment	219	7.7±1.2	106	7.7±1.0		
14 days after treatment	213	7.2±0.8	103	7.3±0.8		
56 days after treatment	186	7.4±0.8	89	7.4±0.7		
Platelet distribution width (%)						
At diagnosis	222	16.5±13.0	110	15.0±11.5	70	15.6±13.1
2 days after treatment	219	21.1±13.3	106	22.5±14.9		
14 days after treatment	213	21.4±11.2	103	20.9±11.6		
56 days after treatment	186	22.4±12.0	89	22.1±11.6		
Plateletcrit (%)						
At diagnosis	222	0.284±0.085	110	0.313±0.109	70	0.246±0.108†,‡
2 days after treatment	219	0.318±0.101	106	0.349±0.132		
14 days after treatment	213	0.291±0.095	103	0.301±0.110		
56 days after treatment	186	0.255±0.061	89	0.255±0.060		
White blood cell ($count/mm^3$)						
At diagnosis	222	14,382±4,641	110	14,305±5,339	71	11,740±6,273†,‡
2 days after treatment	218	8,903±4,647	106	8,608±3,762		
14 days after treatment	213	8,487±2,463	103	8,870±3,122		
56 days after treatment	186	8,993±2,072	89	8,738±2,317		
Erythrocyte sedimentation rate (mm/hr)						
At diagnosis	93	66±26	38	75±28	19	40±34†,‡
2 days after treatment	158	75±27	77	76±27		
14 days after treatment	208	42±26	101	38±25		
56 days after treatment	181	11±11	86	11±15		
C-reactive protein (mg/dL)						
At diagnosis	219	8.3±5.2	107	7.9±5.9	69	4.2±4.6†,‡
2 days after treatment	217	4.7±4.1	106	3.6±3.3†		
14 days after treatment	210	0.3±1.0	103	0.2±0.4		
56 days after treatment	185	0.1±0.3	89	0.1±0.3		

KD: Kawasaki disease. Data are shown as mean±SD. *$p<0.05$, †$p<0.01$ vs. complete KD, ‡$p<0.01$ vs. incomplete KD.

D56 (22.1±11.6%, $p<0.001$) were higher than those in the control group, and were also higher than those at D0 ($p<0.001$) (Fig. 1G and 2F).

PCT in the cKD group at D0 (0.284 ± 0.085%, $p<0.001$), D2 (0.318±0.101%, $p<0.001$), and D14 (0.291±0.095%, $p<0.001$) were higher than those in the control group (0.246±0.108%). PCT increased at D2 compared to D0, and then gradually decreased at D14 and D56 (0.255±0.061%) (Fig. 1H and 2G). The PCT in the iKD group at D0 (0.313± 0.109%, $p<0.001$), D2 (0.349±0.132%, $p<0.001$), and D14 (0.301±0.110%, $p<0.001$) were higher than those in the control group. PCT decreased at D14 and D56 (0.255±0.060%) compared to that at D2 (Fig. 1H and 2H).

6. Cutoff value of platelet count and PCT levels for diagnosing KD

We used ROC curves to obtain the cutoff values of platelet count and PCT in patients with cKD, iKD, and all KD patients compared with the simple febrile illness control group (Table 3, Fig. 3). The cut-off value of platelet count in the cKD patient group was $280\times10^3/mm^3$, with a sensitivity of 71.6% and a specificity of 63.4% (area under the curve [AUC]=0.677, $p<0.001$), and the cutoff value of PCT was 0.245%, with a sensitivity of 65.3% and specificity of 60.0% ([AUC]=0.666, $p<0.001$) (Table 3, Fig. 3A). For the iKD patient group, the cutoff value of platelet count was $280\times10^3/mm^3$, with a sensitivity of 74.5% and specificity of 63.4% (area under the curve [AUC]=0.708, $p<0.001$), and the cutoff value of PCT was 0.255%, with a sensitivity of

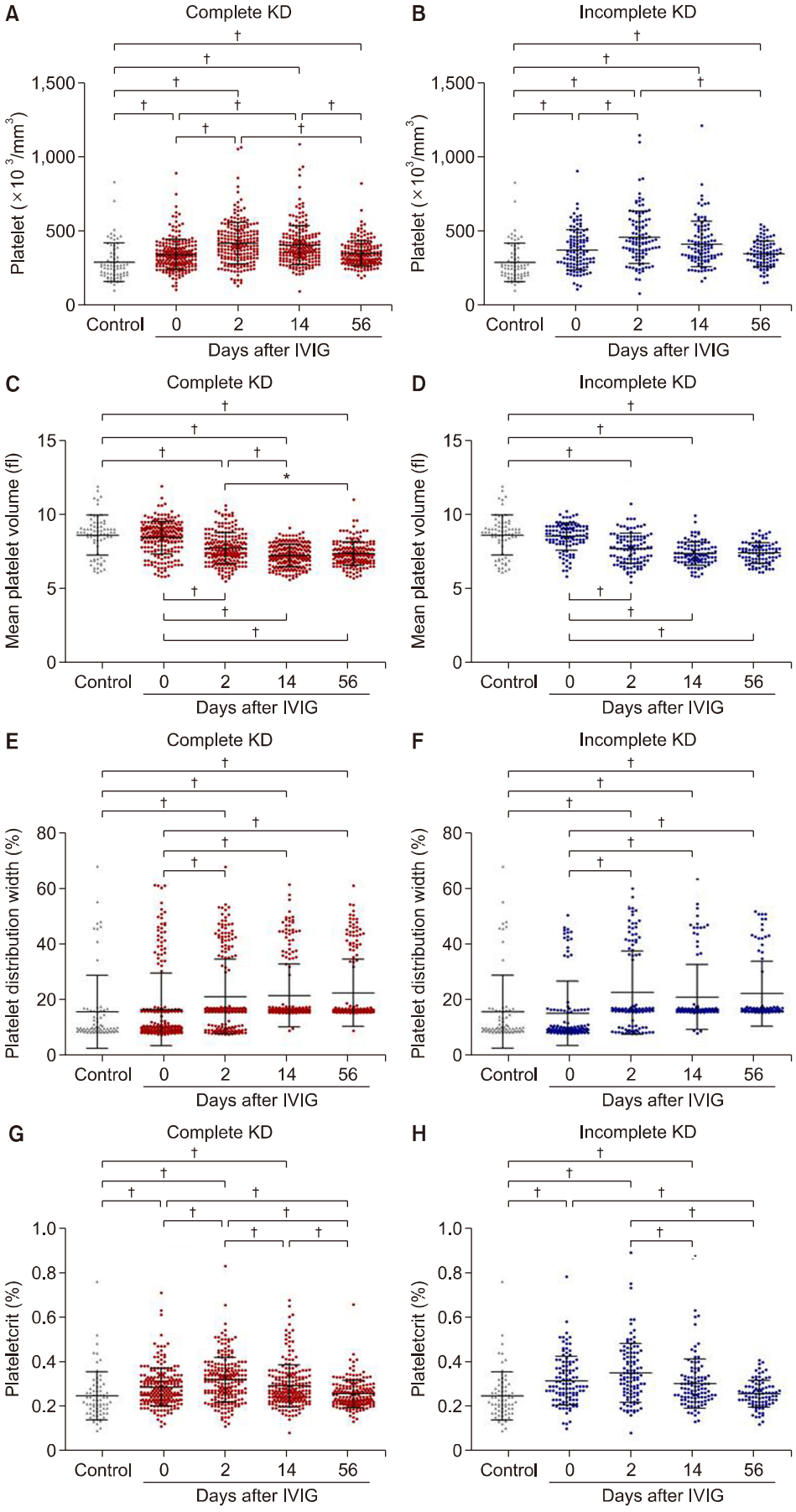

FIG. 2. Dot plots of platelet count (A, B), mean platelet volume (C, D), platelet distribution width (E, F), and plateletcrit (G, H) in patients with febrile illness (control), complete Kawasaki disease (KD), and incomplete KD at diagnosis and 2, 14, and 56 days after intravenous immunoglobulin (IVIG) treatment. *p<0.05, †p<0.01.

69.1% and specificity of 65.7% ([AUC]=0.710, p<0.001) (Table 3, Fig. 3B).

The cutoff value of platelet count in the total (complete and incomplete) KD patient group was 280×10^3/mm^3, with a sensitivity of 72.6% and specificity of 63.4% (area under the curve [AUC]=0.688, p<0.001), and the cutoff value of PCT was 0.250%, with a sensitivity of 67.5% and specificity of 60.0% ([AUC]=0.681, p<0.001) (Table 3, Fig. 3C).

DISCUSSION

In this study, we found that patients with KD had significantly higher platelet counts and PCT levels than simple febrile control subjects at the time of diagnosis. There were no statistically significant differences in the MPV and PDW between the KD and control groups.

Although the laboratory findings in KD are not specific for diagnosis, a characteristic laboratory feature of the subacute phases of KD is thrombocytosis.[3] In contrast, thrombocytopenia at KD presentation is known to be a risk factor for earlier coronary aneurysm development and may be a sign of disseminated intravascular coagulation.[3,6,7] In our study, platelet count was higher in both the cKD and iKD groups than in controls. When the cut-off value of platelet count was determined as 280×10^3/mm^3, the diagnosis of KD was supported by a sensitivity of 72.6% and specificity of 63.4%. The platelet count increased at 2 and 14 days after IVIG treatment in patients with cKD and iKD, respectively, and decreased 56 days after IVIG treatment.

Platelet volume is correlated with platelet function, and PI may be a more sensitive index than platelet number as a marker of clinical interest in various disorders.[7] Although clinical utility and validity of PI have not been established yet, PI has been demonstrated as a marker of pro-inflammatory and pro-thrombotic state in cardiovascular diseases.[12] In our study, we found that there was no significant difference in MPV between KD groups and febrile illness controls. However, MPV gradually decreased until 14 days after IVIG treatment in patients with KD. Hu et al.[9] and Liu et al.[10] demonstrated that patients with KD had significantly lower MPV values than febrile and healthy control subjects, respectively. Recently, Roy et al.[8] proposed that at MPV ≤10.0 fl, KD can be diagnosed with 75% sensitivity and 80% specificity from 28 KD children and 50 febrile illness children. Although the reason for reduced MPV in KD remains unclear, the mechanism for decreased MPV may be because of the consumption or sequestration of the enlarged platelets in the vasculature, or the regulation defect of thrombopoiesis.[10] Furthermore, inflammatory mediators stimulate the bone marrow to produce smaller platelets by shortening their maturation time, therefore smaller platelets enter the blood stream and active platelets are destroyed at the site of inflammation; hence, MPV is decreased.[13]

PDW is another indicator of platelet volume directly measured by flow cytometry, which reflects the consistency of the size and distribution of platelets.[13,14] An increase in PDW indicates a deterioration in the size consistency of platelet volume, which means that megakaryocyte hyperplasia is responsible for PDW increase. In contrast, a decrease in PDW correlates with increased consistency. Under normal bone marrow function, MPV is positively associated with PDW.[14] PDW has an inverse relationship with the severity of inflammatory disease.[13,15,16] Liu et al.[10] demonstrated that the 309 patients with KD had significantly lower PDW values than 160 healthy control

TABLE 3. Diagnostic cut-off values of platelet count and plateletcrit in patients with complete, incomplete, and total (complete and incomplete) Kawasaki disease (KD) compared to patients with simple febrile illness

	Cut off value	Sensitivity (%)	Specificity (%)
Complete KD			
Platelet (×10^3/mm^3)	280	71.6	63.4
Plateletcrit (%)	0.245	65.3	60.0
Incomplete KD			
Platelet (×10^3/mm^3)	280	74.5	63.4
Plateletcrit (%)	0.255	69.1	65.7
Total KD			
Platelet (×10^3/mm^3)	280	72.6	63.4
Plateletcrit (%)	0.250	67.5	60.0

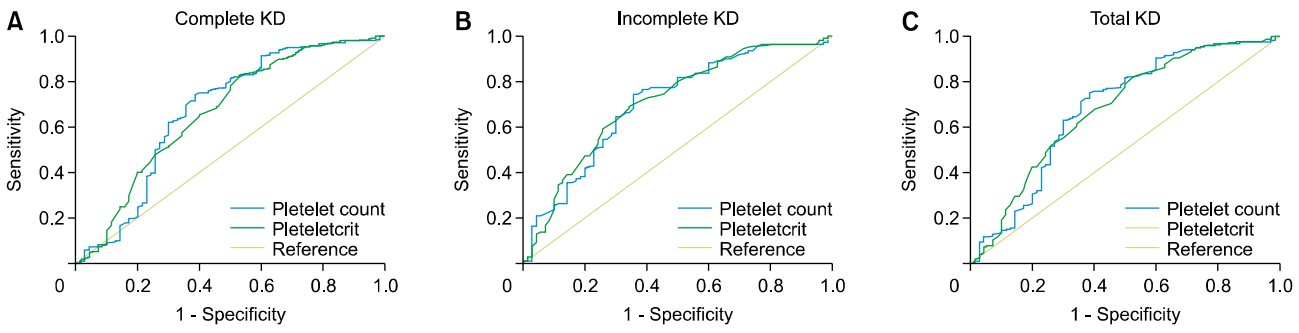

FIG. 3. Receiver operating characteristics (ROC) curves of platelet count and plateletcrit in patients with complete Kawasaki disease (KD) (A), incomplete KD (B) and total KD patients (C) compared with the simple febrile illness control group.

subjects. In the current study, there were no significant differences in PDW between KD and febrile illness controls. However, PDW increased at 2, 14, and 56 days after IVIG treatment in patients with KD. Unlike other PI that are measured directly by a machine, PCT is the volume percentage of platelets in the whole blood volume and is positively associated with platelet count and MPV.[13,14,17] Evaluation of PCT can help determine the severity of the inflammatory process in the follow-up and treatment process, and PCT is higher in the active phase than in the remission period of rheumatoid arthritis.[15] Recently, Ergelen and Uyarel reported high PCT values (>0.237%) as a predictor of long-term cardiovascular mortality in patients with acute coronary syndrome.[18] In our study, we found that patients with complete and incomplete KD had significantly higher PCT levels than control subjects. Therefore, we suggest that the diagnosis of iKD can be supported by a sensitivity of 67.5% and specificity of 60.0% when the cut-off value of PCT is determined to be 0.250%. PCT levels increased 2 days after IVIG treatment in patients with cKD and iKD. The platelet count gradually decreased 14 and 56 days after IVIG treatment.

NT-proBNP, as well as CRP or ESR, have been used as adjuvant diagnostic biomarkers in patients with KD.[3] A meta-analysis study of NT-proBNP showed a sensitivity of 89.0% and specificity of 72.0% (area under the curve [AUC]=0.87).[19] Ko et al.[20], found interleukin (IL)-17F, IL-33, sCD40L, E-selectin, myeloid progenitor inhibitory factor 1, and IFN-γ-inducible protein 10 (IP-10) were increased during the acute phase in patients with KD when compared with that in the controls. They observed a cut-off value of IP-10 in the patient with KD was 1318 pg/mL, with a sensitivity of 100% and a specificity of 77% (area under the curve [AUC]=0.94). Hirono et al.[21] also investigated to validate a myeloid-related protein (MRP)-8/MRP-14 as a marker of KD activity. They found MRP-8/MRP-14 was elevated in 45 patients with IVIG treatment responder KD (3,251±1,981 ng/mL), compared with 33 healthy control patients (220±40 ng/mL).[21] Although our study showed relatively low sensitivity and specificity of the cut-off values, PCT is one of the adjuvant parameters for the early diagnosis of KD from simple febrile illnesses.

Our study has a few limitations. We enrolled a relatively small number of patients with simple febrile illnesses as the control group. The control patients had heterogeneous febrile illnesses, which could have affected the measured PI values owing to different severities or cascades of inflammation. Furthermore, we found relatively low sensitivity and specificity of the cut-off values for platelet count and PCT. Further large prospective investigations are required to select higher cut-off values for platelet count and PCT as diagnostic parameters.

In conclusion, patients with KD have significantly higher platelet counts and PCT levels than simple febrile control subjects at the time of diagnosis. Platelet count and PCT are adjuvant parameters for the differential diagnosis of complete KD and incomplete KD from simple febrile illnesses.

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CONFLICT OF INTEREST STATEMENT

None declared.

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