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Brain natriuretic peptide as a clinical screening tool for the diagnosis of Kawasaki disease

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Abstract

N-terminal pro-brain natriuretic peptide (NT-proBNP) has been studied as a diagnostic screening tool for Kawasaki disease (KD). However, brain natriuretic peptide (BNP) has been less studied while has less variability among age groups. We aimed to find out if BNP can be used as a diagnostic screening tool for KD in Korea. This was a retrospective cohort study performed in a single pediatric emergency department. Patients younger than 19 years of age who presented with fever and underwent BNP examination for suspected KD was included. The primary outcome was the diagnostic performance of BNP for KD, and the secondary outcome was the diagnostic performance of BNP for coronary artery aneurysm (CAA). We also derived a scoring system for predicting KD and CAA. Of the 778 patients who were finally included, 400 were not diagnosed with KD and 378 were diagnosed with KD. The odds ratio of BNP at the cutoff of 30 pg/mL for KD was 7.80 (95% CI, 5.67–10.73) in the univariate analysis and 3.62 (95% CI, 2.33–5.88) in the multivariable analysis. The odds ratio of BNP at the cutoff of 270 pg/mL for CAA was 3.67 (95% CI, 2.18–6.19) in the univariate analysis and 2.37 (95% CI, 1.16–8.74) in the multivariable analysis. The AUC of KD and CAA were 0.884 and 0.726, respectively, which was the highest AUCs among all variables. Additionally, we proposed a scoring system for KD and CAA. It is important to clinically suspect KD and CAA in children with high BNP levels.

Abbreviations: ALT = alanine transferase, AUC = area under the curve, BNP = brain natriuretic peptide, CAA = coronary artery aneurysm, CI = confidence interval, Cr = creatinine, CRP = C-reactive protein, ESR = erythrocyte sedimentation rate, IVIG = intravenous immunoglobulin, KD = Kawasaki disease, NT-proBNP = N-terminal pro-brain natriuretic peptide, PED = pediatric emergency department, ROC = receiver operating characteristics.

Keywords: brain natriuretic peptide, emergency department, Kawasaki disease

1. Introduction

Kawasaki disease (KD) is an acute, systemic vasculitis that mainly affects children younger than 5 years of age. Its incidence in children aged under 5 years in Korea was 194.7 per 100,000 in 2017, with 1.7% of cases demonstrating a coronary artery aneurysm (CAA).[1] However, clear diagnostic values or laboratory tests are not available for KD, and it has long been diagnosed by characteristic clinical features. The diagnostic criteria for KD are "fever persisting at least 5 days" and the presence of at least 4 symptoms of the following 5 principal features:[2] changes in extremities, polymorphous exanthema, bilateral, painless bulbar conjunctival injection without exudate, changes in lips and oral cavity, and cervical lymphadenopathy.

Accordingly, diagnostic tests that can screen KD early on have been continuously studied. There have been many attempts to use biomarkers such as C-reactive protein, ferritin, erythrocyte sedimentation rate, and platelet cou9-10nt, but brain natriuretic peptide (BNP) and N-terminal pro-brain natriuretic peptide (NT pro-BNP) have been investigated recently because of their possible association with cardiac manifestations and relatively good predictive performance.[3–5] NT-pro BNP has become increasingly studied because it has a longer half-life than BNP, and its association with congestive heart failure and left ventricle dysfunction is well known, but the normal range of NT pro-BNP changes with age, and some hospitals use BNP for pediatric patients suspected of having KD.[6–8]

BNP is synthesized as a prehormone (proBNP) comprising 108 amino acids. Upon its release into circulation, it is cleaved in equal proportions into the biologically active 32 amino acid BNP, representing the C-terminal fragment, and the biologically inactive 76 amino acid N-terminal fragment (NT-proBNP).[9]

The authors have no funding and conflicts of interest to disclose.

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

This study was approved by the institutional review board (IRB no. 2007-118-1142). Informed consent was waived since this was a retrospective study with minimal risk to the patients.

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Although there have been many previous studies on the relationship between NT-proBNP and KD, to the best of our knowledge, there have been relatively few studies on BNP, and there has been no study on its value as a diagnostic screening tool for KD in Korea.[7,10] Accordingly, this study aimed to determine whether BNP can be used as a diagnostic screening tool for KD in Korea.

We hypothesized that, similar to NT-proBNP, BNP can also be used as a diagnostic screening tool for KD. We also derived scoring systems for the diagnosis of KD and prediction of CAA.

2. Method

2.1. Study design

This was a retrospective cohort study performed in a pediatric emergency department (PED) in an urban tertiary, teaching hospital, with annual visits of approximately 18,000 children. A resident emergency physician with a pediatric emergency specialist treated all patients. When a child is suspected of KD due to prolonged fever and presence of 3 or more above-mentioned KD clinical manifestations, the emergency physician examines him/her, and electrocardiogram and laboratory tests, including BNP testing, are performed. Subsequently, on-duty cardiologists are consulted for possible echocardiography, intravenous immunoglobulin (IVIG) therapy, or hospitalization.

2.2. Participants

We included patients younger than 19 years of age who presented with fever to the Seoul National University Hospital (SNUH) PED between January 1, 2010, and December 31, 2019, and underwent BNP examination for suspected KD. We excluded patients who had underlying cardiac disease (congenital heart disease, previous history of cardiac operation, or past history of KD) or underlying renal failure, received cardiotoxic chemotherapy, or whose final diagnosis was unknown because of transfer or discharge against medical advice (AMA). We divided patients who presented with fever into 2 groups for analysis: the KD group and non-KD group, which comprised children diagnosed with other febrile diseases. The KD group was defined based on the final discharge diagnosis, consisting of children diagnosed with Kawasaki disease, while the non-KD group included children diagnosed with other febrile diseases.

2.3. Data collection

The list of eligible patients and variables was extracted from the Clinical Data Warehouse of SNUH. We collected and analyzed several demographic information, including age at PED visit; sex; and clinical information, including fever duration, clinical manifestations associated with the abovementioned KD diagnosis criteria; final diagnosis; length of hospitalization; and underlying diseases. Moreover, we collected diagnostic and treatment variables, including laboratory tests for complete blood count, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), alanine transferase (ALT), aspartate transferase, blood urea nitrogen, creatinine (Cr), albumin, and total bilirubin, data on echocardiography on admission and at 4 to 8 weeks of follow-up, if possible, and data on IVIG administration. Coronary artery z scores were calculated using the Boston formula, and CAA was defined as a z-score ≥ 2.5 of any coronary artery on echocardiography.

2.4. Outcomes

The primary outcome was the diagnostic performance of BNP for KD, and the secondary outcome was the diagnostic performance of BNP for CAA. We also derived a scoring system for predicting KD and CAA.

2.5. Statistical analysis

For continuous variables, we compared children diagnosed with KD (patient group) and those who were not (control group) using the *t* test or Mann–Whitney *U* test, including BNP testing, after assessing normality using the Shapiro–Wilk test. For categorical variables, we used the chi-squared test. After the odd ratios were calculated from a logistic regression analysis, and the receiver operating characteristic (ROC) curves for KD and CAA were obtained, univariate and multivariate logistic regression analyses with a stepwise selection for variables were performed after multicollinearity identification using a variance inflation factor.

Moreover, based on the logistic regression model, we proposed scoring systems for KD and CAA. When building the scoring systems, numerical variables were converted into factor variables according to a cutoff point determined by a locally weighted scatterplot smoothing smoother. Subsequently, risk points are derived from the coefficients in logistic regressions, and each value is assigned to a variable. Finally, the total score was calculated for each child to predict outcome event probability.

Categorical variables are presented as numbers and percentages, and continuous variables are presented as medians and range. A $P < .05$ was considered statistically significant. All statistical analyses were performed using R software version 4.0.3 (R Foundation for Statistical Computing, Vienna, Austria).

3. Results

A total of 1443 patients were screened; 411 patients were excluded because of cardiac disease, 7 were excluded because of renal disease, 30 were excluded because of sepsis/septic shock, 18 were excluded because of malignancy, 14 were excluded because their final diagnosis was unknown (transfer or AMA discharge), and 181 were excluded because of missing variables. Accordingly, 778 patients were finally included (Fig. 1).

Of the 778 patients, 400 were not diagnosed with KD, and 378 patients were diagnosed with KD. 226 patients (56.5%) were male in the non-KD group, and 232 patients (61.4%) were male in the KD group ($P = .19$). The mean age was 35.26 (95% confidence interval, 17.98–59.52) months in the non-KD group, and 26.73 (95% CI, 12.90–43.76) months in the KD group ($P < .05$). Mean BNP was 15.50 (95% CI, 10.00–30.00) pg/mL in the non-KD group and 59.00 (95% CI, 28.00–146.50) pg/mL in the KD group. Other baseline characteristics are shown in Table 1. Moreover, among 778 patients,

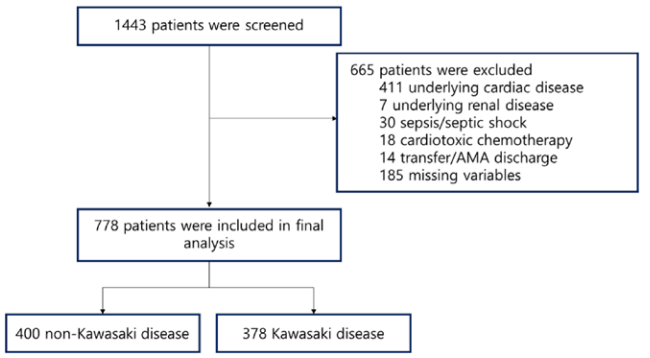

Figure 1. Study flowchart.

Table 1

Demographic and clinical characteristics of the Kawasaki disease and non-Kawasaki disease groups.

	Non-KD	KD	*P*
n	400	378	
Sex (male)	226 (56.5)	232 (61.4)	.191
Age (mo)	36.26 [17.98, 59.52]	26.73 [12.90, 43.78]	<.001
BNP (pg/mL)	15.50 [10.00, 30.00]	59.50 [28.00, 146.50]	<.001
CRP (mg/dL)	2.32 [0.76, 5.48]	6.50 [3.83, 10.43]	<.001
WBC (10^3/μL)	9.65 [7.08, 13.64]	13.18 [10.41, 16.70]	<.001
ESR (mm/h)	27.00 [12.00, 47.00]	54.50 [38.25, 73.75]	<.001
PLT (10^3/μL)	267.50 [203.00, 341.25]	342.00 [278.25, 411.00]	<.001
ANC (/μL)	4934.00 [2768.75, 7722.75]	8020.00 [5799.25, 11009.50]	<.001
BUN (mg/dL)	9.00 [7.00, 11.00]	8.00 [6.00, 10.00]	<.001
Cr (mg/dL)	0.36 [0.28, 0.44]	0.32 [0.26, 0.39]	<.001
Fever duration (h)	111.00 [81.00, 145.00]	108.00 [82.00, 139.75]	.491
AST (U/L)	34.00 [27.00, 47.25]	36.00 [27.00, 74.75]	.01
ALT (U/L)	17.00 [12.00, 25.00]	37.50 [17.00, 118.75]	<.001
Albumin (g/dL)	4.00 [3.80, 4.20]	3.80 [3.60, 4.10]	<.001
Na (mmol/L)	137.50 [136.00, 139.00]	136.00 [135.00, 138.00]	<.001
T. bil (mg/dL)	0.40 [0.30, 0.50]	0.50 [0.30, 0.70]	<.001
Seg (%)	53.40 [38.88, 64.50]	62.30 [51.78, 73.30]	<.001

ALT = alanine transferase, ANC = absolute neutrophil count, AST = aspartate transferase, BNP = brain natriuretic peptide, BUN = blood urea nitrogen, Cr = creatinine, CRP = C-reactive protein, ESR = erythrocyte sedimentation rate, PLT = platelet count, Seg = segmented white cell count, T = bil, total bilirubin, WBC = white blood cell count.

Table 2

Demographic and clinical characteristics of study participants, grouped by coronary artery aneurysm.

	No CAA	CAA	*P*
n	613	165	
Sex (male)	362 (59.1)	96 (58.2)	.91
Age (mo)	34.13 [17.13, 56.03]	25.45 [12.03, 41.10]	<.001
BNP (pg/mL)	22.00 [11.00, 54.00]	61.00 [29.00, 190.00]	<.001
CRP (mg/dL)	3.75 [1.26, 7.50]	6.60 [4.01, 10.20]	<.001
WBC (10^3/μL)	11.12 [7.95, 15.00]	12.59 [10.32, 16.45]	<.001
ESR (mm/h)	38.00 [19.00, 60.00]	53.00 [37.00, 71.00]	<.001
PLT (10^3/μL)	298.00 [224.00, 375.00]	331.00 [275.00, 411.00]	<.001
ANC (/μL)	6089.00 [3572.00, 9727.00]	7607.00 [5372.00, 10878.00]	<.001
BUN (mg/dL)	9.00 [7.00, 11.00]	8.00 [6.00, 10.00]	.001
Cr (mg/dL)	0.35 [0.28, 0.43]	0.30 [0.25, 0.38]	<.001
Fever duration (h)	109.00 [82.00, 141.00]	108.00 [81.00, 151.00]	.722
AST (U/L)	34.00 [27.00, 53.00]	36.00 [28.00, 66.00]	.277
ALT (U/L)	19.00 [13.00, 43.00]	41.00 [19.00, 125.00]	<.001
Albumin (g/dL)	4.00 [3.70, 4.20]	3.80 [3.60, 4.00]	<.001
Na (mmol/L)	137.00 [135.00, 139.00]	136.00 [135.00, 138.00]	.021
T. bil (mg/dL)	0.40 [0.30, 0.60]	0.50 [0.40, 0.70]	<.001
Seg (%)	57.00 [42.90, 69.00]	61.00 [51.40, 72.00]	.002

ALT = alanine transferase, ANC = absolute neutrophil count, AST = aspartate transferase, BNP = brain natriuretic peptide; CRP1, C-reactive protein 1, BUN = blood urea nitrogen, Cr = creatinine, ESR = erythrocyte sedimentation rate, PLT = platelet count, Seg = segmented white cell count, T = bil, total bilirubin, WBC = white blood cell count.

613 did not have CAA, and 165 had CAA on echocardiography. Demographic and clinical characteristics are shown in Table 2.

Figure 2A shows the ROC curves for each variable, and Table 3 shows area under the curve (AUC) with 95% CI of each ROC curve for predicting KD. BNP had the highest AUC (0.813; 95% CI, 0.783–0.843), followed by ESR (0.756; 95% CI, 0.722–0.790) and CRP (0.752; 95% CI, 0.718–0.786). Figure 2B and Table 3 show the ROC curve and AUC with 95% CI of each ROC curve for predicting CAA, respectively. BNP had the highest AUC (0.755; 95% CI, 0.719–0.792), followed by CRP (0.703; 95% CI, 0.665–0.741), ALT (0.687; 95% CI, 0.645–0.741), and ESR (0.683; 95% CI, 0.645–0.729). When predicting KD and CAA, fever duration had the lowest AUC (0.514; 95% CI, 0.474–0.555 for KD; and 0.488; 95% CI, 0.443–0.534 for CAA) among all explored variables.

The results of the logistic regression are shown in Tables 4 and 5. After a logistic regression analysis, the odds ratio (OR) of BNP for KD was 7.80 (95% CI, 5.67–10.73) in the univariate analysis and 3.62 (95% CI, 2.33–5.88) in the multivariable analysis. The OR of CRP was 8.27 (95% CI, 5.85–11.70) in the univariate analysis and 2.83 (95% CI, 1.80–4.46) in the multivariable analysis. The OR of ESR was 6.55 (95% CI, 4.75–9.05) in the univariate analysis and 3.73 (95% CI, 2.42–5.73) in the multivariable analysis. The odds ratio of BNP for CAA was 3.67 (95% CI, 2.18–6.19) in the univariate analysis and 2.37 (95% CI, 1.37–4.10) in the multivariate analysis. The odds ratio of CRP was 4.83 (95% CI, 3.02–7.71) in the univariate analysis and 3.62 (95% CI, 2.20–5.98) in the multivariate analysis. The odds ratio of ESR was 2.63 (95% CI, 1.85–3.74) in the univariate analysis and 1.76 (95% CI, 1.20–2.58) in the multivariate analysis.

Figure S1, Supplemental Digital Content, http://links.lww.com/MD/J269 shows the ROC curve for KD and CAA, respectively. For logistic regression models, the AUC was 0.884 for KD and 0.726 for CAA. From the locally weighted scatterplot smoothing smoother, appropriate cutoff values for each variable were determined, and scores for each variable were derived from the coefficients of the multivariate logistic regression. For the KD scoring system, age, BNP, CRP, ESR, PLT, Cr, ALT, and T. bil were selected and assigned 1 point each, totaling 8 points. The optimal cutoff was 3 points, with a sensitivity of 63.5%, specificity of 80.2%, positive likelihood ratio of 3.2, and negative likelihood ratio of 0.46. For the CAA scoring system, age, BNP, CRP, ESR, PLT, and Cr were selected and assigned 1 point each, totaling 6 points. The optimal cutoff was made in 3 points, with a sensitivity of 51.6%, specificity of 64.6%, positive likelihood ratio of 1.46, and negative likelihood ratio of 0.75 (Table 6). Figure S1, Supplemental Digital Content, http://links.lww.com/MD/J269 also compared the ROC curve plots of the logistic regression model with full variables and scoring system for KD and CAA, respectively.

4. Discussion

In this study, we investigated the efficacy of BNP in discriminating KD from other febrile illness. The odds ratio of BNP at the cutoff of 30 mg/dL for KD was 7.80 (95% CI, 5.67–10.73) in the univariate analysis and 3.62 (95% CI, 2.33–5.88) in the multivariable analysis. The odds ratio of BNP at the cutoff of 270 pg/mL for CAA was 3.67 (95% CI, 2.18–6.19) in the univariate analysis and 2.37 (95% CI, 1.16–8.74) in the multivariable analysis. The AUC of KD and CAA were 0.884 and 0.726, respectively, which was the highest AUCs among all variables. In a previous study on the discrimination ability of NT-proBNP regarding KD, the AUC of NT-proBNP was 0.78 (95% CI, 0.69–0.85), which was lower than the BNP value reported herein.[11] Since it is known that the normal value of NT-proBNP varies among different age groups,[12] the use of the z-score of NT-proBNP rather than the value itself would be recommended. In another study regarding the z-score of NT-proBNP,[13] the AUC for diagnosing KD with a z-score of NT-proBNP > 2.0 was 0.85, which was similar to our study. While NT-proBNP has a longer half-life, it may be troublesome to calculate the z-score for every child.

Other acute inflammatory markers, such as ESR and CRP, also had high AUC for both KD and CAA, while some previously studied risk factors for IVIG resistance or CAA, including fever duration, AST, T. bil, and Na, had lower AUC for

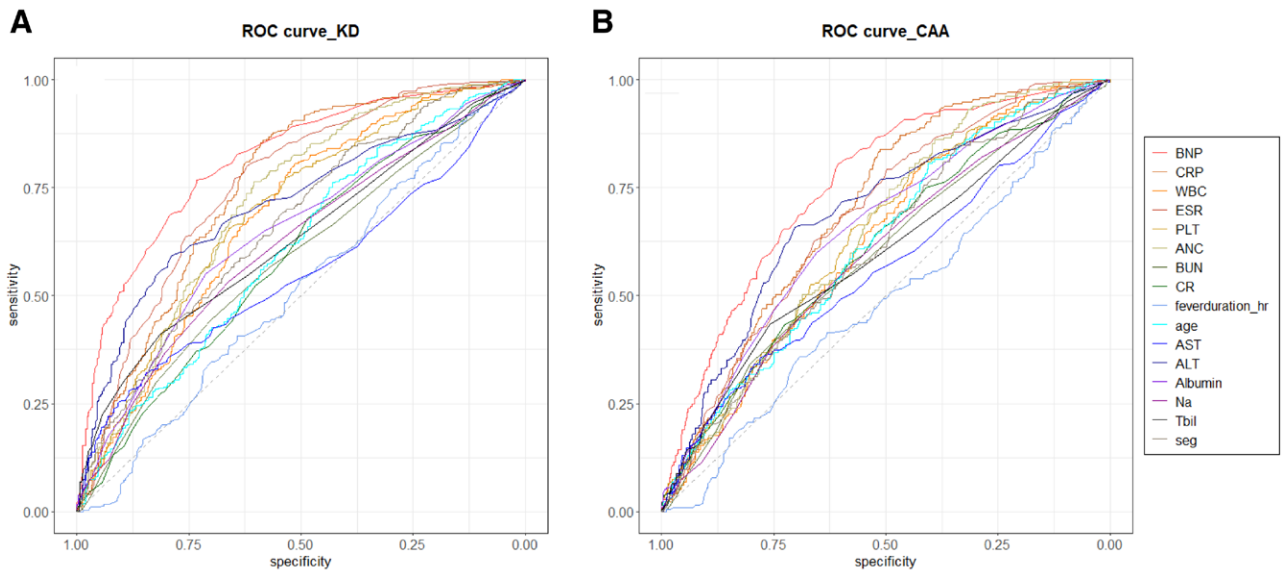

Figure 2. (A) Receiver operating characteristic curve plot of the parameters for predicting Kawasaki disease. (B) Receiver operating characteristic curve plot of parameters for predicting a coronary artery aneurysm. ALT = alanine transferase, ANC = absolute neutrophil count, AST = aspartate transaminase, BNP = brain natriuretic peptide, BUN = blood urea nitrogen, CAA = coronary artery aneurysm, CR = creatinine, CRP = C-reactive protein, ESR = erythrocyte sedimentation rate, KD = Kawasaki disease, PLT = platelets, ROC = receiver operating characteristics, seg = segmented neutrophil, Tbil = total bilirubin, WBC = white blood cells.

Table 3

Area the under curve of the receiver operating characteristics curve plot for each variable for predicting Kawasaki disease and coronary artery aneurysm.

	Kawasaki disease		Coronary artery aneurysm	
Variable	**AUC**	**95% CI**	**AUC**	**95% CI**
BNP	0.813	0.783–0.843	0.755	0.719–0.792
ESR	0.756	0.722–0.790	0.703	0.665–0.741
CRP	0.752	0.718–0.786	0.687	0.645–0.729
ANC	0.713	0.677–0.749	0.683	0.644–0.723
ALT	0.709	0.672–0.746	0.655	0.613–0.697
PLT	0.693	0.657–0.730	0.646	0.606–0.686
WBC	0.683	0.645–0.720	0.642	0.600–0.683
seg	0.665	0.628–0.703	0.629	0.588–0.670
Albumin	0.645	0.607–0.684	0.621	0.579–0.663
T. bil	0.630	0.591–0.668	0.611	0.568–0.654
Na	0.618	0.579–0.657	0.611	0.567–0.654
age	0.609	0.569–0.648	0.594	0.549–0.640
Cr	0.591	0.551–0.631	0.593	0.548–0.637
BUN	0.584	0.545–0.624	0.592	0.548–0.636
AST	0.553	0.512–0.594	0.562	0.516–0.609
FD (hr)	0.514	0.474–0.555	0.488	0.443–0.534

ALT = alanine transferase, ANC = absolute neutrophil count, AST = aspartate transferase, AUC = area under the curve, BNP = brain natriuretic peptide, BUN = blood urea nitrogen, Cr = creatinine, CRP = C-reactive protein, ESR = erythrocyte sedimentation rate, FD (hr) = fever duration (hour), PLT = platelet count, seg = segmented white cell count,T. bil = total bilirubin, WBC = white blood cell count.

both KD and CAA. In previous studies, CRP and ESR, as well as PLT,[5,14–16] were elevated in children with KD, though these factors are only used to evaluate children with prolonged fever.

Several studies attempted to differentiate KD from other febrile illness. Huang et al[15] used acute phase inflammatory markers such as hypoglaucin/apolipoprotein ratio to differentiate KD, showing a sensitivity of 89.7% and specificity of 85.6%.[15] However, these laboratory markers are not routinely tested in PED, making it difficult to apply in daily clinical practice. Moreover, Tsai et al[17] proposed a novel score system of blood tests to differentiate KD from other febrile illness, comprising 8 variables (PLT, eosinophil, ALT, CRP, hemoglobin, MCH, MCHC, and monocyte). However, some of these variables need differential counts, which may not be always available.

This study has limitations. First, this study was a single-centered study conducted in Asian children, making it prone to selection bias and lack of racial diversity to apply to a general population. Therefore, further studies with multiple centers involving various countries are much needed. Moreover, although we included children suspected of KD in this study, we did not review how many of the 5 principal features of KD were present in each individual. As a result, we were unable to distinguish between complete and incomplete KD cases. A previous study proposed a KD scoring metric using both clinical and laboratory parameters,[16] with an AUC of 0.95

Table 4

Univariate and multivariate logistic regression for the prediction of Kawasaki disease.

	Univariate				Multivariate			
Variables	**Odds ratio**	**2.50%**	**97.50%**	***P* value**	**Odds ratio**	**2.50%**	**97.50%**	***P* value**
CRP	8.27	5.85	11.70	<.05	2.83	1.80	4.46	<.05
BNP	7.80	5.67	10.73	<.05	3.62	2.42	5.41	<.05
ESR	6.55	4.75	9.05	<.05	3.73	2.42	5.73	<.05
ALT	5.95	4.21	8.42	<.05	3.70	2.33	5.88	<.05
ANC	4.84	3.53	6.64	<.05	1.49	0.95	2.33	<.05
WBC	3.95	2.89	5.38	<.05	–	–	–	–
AST	3.74	2.37	5.89	<.05	–	–	–	–
PLT	3.72	2.76	5.01	<.05	2.33	1.53	3.55	<.05
T. bil	3.06	2.21	4.24	<.05	1.76	1.11	2.77	<.05
Albumin	2.81	1.76	4.48	<.05	–	–	–	–
seg	2.45	1.83	3.27	<.05	–	–	–	–
CR	2.02	1.43	2.84	<.05	1.86	1.13	3.07	<.05
Age	1.99	1.48	2.67	<.05	1.70	1.10	2.63	<.05
BUN	1.98	1.41	2.77	<.05	–	–	–	–
FD	1.73	1.24	2.43	<.05	1.57	1.00	2.47	.051
Sex (male)	1.22	0.92	1.63	.17	1.52	1.02	2.26	<.05

Cutoffs: age, ≤40 months; ANC, >5400 cells/μL; BNP, >30 pg/mL; CRP, >3 mg/L; ESR, >35 mL/h; fever duration, $42 < \times \leq 165$ h; PLT, >300 k/μL; WBC, $10 < \times < 28$ k/μL; BUN, ≥7 mg/dL; Cr, >0.43 mg/dL; albumin, ≤3.5 g/dL; AST, >88 IU/L; ALT, >40 U/L; Na, $136 < \times \leq 150$ mmol/L; seg, >60%; T. bil, >0.6 mg/dL.

ALT = alanine transferase, ANC = absolute neutrophil count, AST = aspartate transferase, BNP = brain natriuretic peptide, BUN = blood urea nitrogen, Cr = creatinine, CRP = C-reactive protein, ESR = erythrocyte sedimentation rate, FD = fever duration (hour), PLT = platelet count, T.bil = total bilirubin, seg = segmented white cell count, WBC = white blood cell count.

Table 5

Univariate and multivariate logistic regression for prediction of coronary artery aneurysm.

	Univariate				Multivariate			
Variables	**Odds ratio**	**2.50%**	**97.50%**	***P* value**	**Odds ratio**	**2.50%**	**97.50%**	***P* value**
CRP	4.83	3.02	7.71	<.05	3.62	2.20	5.98	<.05
BNP	3.67	2.18	6.19	<.05	2.37	1.37	4.10	<.05
PLT	3.07	1.19	7.91	<.05	3.18	1.16	8.74	<.05
ESR	2.63	1.85	3.74	<.05	1.76	1.20	2.58	<.05
CR	2.59	1.22	5.50	<.05	2.10	0.93	4.73	.073
Albumin	2.35	0.96	5.77	.062	–	–	–	–
ALT	1.99	1.16	3.43	<.05	–	–	–	–
age	1.91	1.31	2.79	<.05	1.95	1.31	2.92	<.05
T.bil	1.60	1.14	2.27	<.05	–	–	–	–
seg	1.45	1.03	2.05	<.05	–	–	–	–
WBC	1.40	0.37	5.34	.622	–	–	–	–
Sex (male)	0.97	0.68	1.37	.840	–	–	–	–

Cutoffs: age, ≤40 months; BNP, >270 pg/mL; CRP, >3 mg/L; ESR, >50 mL/h; PLT, >600 k/μL; WBC, >28 k/μL; Cr, >0.2 mg/dL; albumin, ≤3.0 g/dL; ALT, $200 < \times \leq 1600$ U/L; Na, >130 mmol/L; seg, >60%; Tbil, >0.5 mg/dL.

ALT = alanine transferase, BNP = brain natriuretic peptide, Cr = creatinine, CRP = C-reactive protein, ESR = erythrocyte sedimentation rate, PLT = platelet count, T.bil = total bilirubin, WBC = white blood cell count.

for a 10-variable score model. Although this model is not yet externally validated, it showed excellent performance, while inexperienced clinicians such as early-year residents may have difficulty judging changes, including polymorphous rashes, conjunctival injections, and changes in extremities, which may make the performance of the model less effective. Additionally, due to the retrospective nature of this study, sequential laboratory testing was not available. Kawamura et al demonstrated elevated BNP levels during the acute phase (within 9 days of illness) of KD, followed by a decrease to the normal range in the convalescent phase, through serial follow-up of BNP in a small number of children.[18] In our study, the median time from fever onset to the emergency department (ED) visit was less than 5 days, indicating that the majority of participants were in the acute phase of the illness. However, further study with sequential laboratory testing will be helpful to identify earlier phase of KD with BNP levels.

Another limitation of this study is the limited availability of echocardiography data in the non-KD group within the study population. This hampers our ability to assess the potential confounding effects of cardiac function in each child. It is important to acknowledge that this limitation is inherent to retrospective studies, and future research with prospective setting to gather more comprehensive data on cardiac function in both KD and non-KD groups. Finally, it would have been more helpful for clinical practice if a scoring system that could predict IVIG response in addition to predict CAA had been developed. When validating existing risk scoring systems in Korean children with KD,[19] the diagnostic performance was poor with all 3 scoring systems (Harada, Kobayashi, and Egami), warranting the development of a risk scoring system more widely applicable to other populations.

5. Conclusion

In this study, we found the role of BNP as a diagnostic screening tool for KD in Korean children and also investigated the association of BNP with CAA, a fatal complication of KD. Our results

Table 6

Scoring system for predicting Kawasaki disease and coronary artery aneurysm.

	Cutoff	Point
Kawasaki disease scoring system		
Age	≤40 mo	1
BNP	>30 pg/mL	1
CRP	>3 mg/dL	1
ESR	>35 mm/h	1
PLT	>300 10^3/μL	1
Cr	>0.43 mg/dL	1
ALT	>40 U/L	1
T. bil	>0.6 mg/dL	1
	Total	8
Sum of points	3	Sensitivity, 63.5%; specifity, 80.2%; PPV, 30.1%; NPV, 24.8%; LR+, 3.2; LR–, 0.46
Coronary artery aneurysm scoring system		
Age	≤40 months	1
BNP	>270 pg/mL	1
CRP	>3 mg/dL	1
ESR	>50 mm/h	1
PLT	>600 10^3/μL	1
Cr	>0.2 mg/dL	1
	Total	6
Sum of points	3	Sensitivity, 51.6%; specifity, 64.6%; PPV, 50.2%; NPV, 33.7%; LR+, 1.46; LR-,0.75

ALT = alanine transferase, BNP = brain natriuretic peptide, Cr = creatinine, CRP = C-reactive protein, ESR = erythrocyte sedimentation rate, PLT = platelet count, T bil = total bilirubin.

suggest that it is important to clinically suspect KD and CAA in children with high BNP. Moreover, we proposed a scoring system for KD and CAA, and it is thought that further research on whether it can be applied in clinical practice is needed.

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