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Letter to the editor

Value of the N-terminal of prohormone brain natriuretic peptide in diagnosis of Kawasaki disease

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Kawasaki disease (KD) is an acute, self-limiting, agnogenic vasculitis that occurs frequently in children below 5 years of age and mainly involves the coronary artery [1]. It is a common condition resulting in acquired heart disease in children. KD may lead to coronary artery aneurysm or expansion, ischemic heart disease, and sudden death [2], and in some patients, it can greatly affect quality of life even in adulthood [3]. Guidelines on KD state that typical KD should be diagnosed when the patient presents fever persisting for ≥5 d and more than four main clinical features [4]. However, since these clinical features may not be manifested simultaneously, especially in the case of incomplete KD (IKD), which lacks sufficient typical clinical features, the clinical diagnosis of KD is extremely difficult. Further, the serum cytokine level, the N-terminal of prohormone brain natriuretic peptide (NT-proBNP) and C-reactive protein (CRP) levels, and erythrocyte sedimentation rate (ESR) do not differ significantly between typical KD and IKD (Fig. 1). Additionally, in this study we found that KD patients with coronary artery disease usually receive intravenous immunoglobin (IVIG) treatment later than those KD patients without coronary artery disease (median days after illness onset of initial IVIG treatment: 7.2 vs. 5.1, $P = 0.000$) and their fever lasts longer (median fever duration: 11.5 vs. 7.3 days, $P = 0.000$). This finding suggests that early diagnosis and treatment of KD are crucial for preventing the coronary artery lesions caused by KD. Therefore, the present study aimed to evaluate the value of certain laboratory indexes in the diagnosis of KD.

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This prospective study enrolled 658 KD patients, 300 age-matched KD-like febrile children, and 300 age-matched healthy children as controls. After thorough clinical examination, patients who met the following criteria were included: (1) age <18 years and (2) diagnosis of typical KD or IKD. Diagnosis followed the 2004 guidelines of the American Heart Association (AHA) [4]. The exclusion criteria were any heart-related diseases. Informed consent was obtained from all patients, and the study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki and was approved by the institution's human research committee. We certify that we have complied with the Principles of Ethical Publishing in the International Journal of Cardiology.

Cytokines were measured by flow cytometry, as described previously [5,6]. The serum NT-proBNP concentration was measured with a Cobas e601 analyzer (Roche Diagnostics; Germany). CRP levels were measured using QuikRead Go (Finland) with the QuikRead Go CRP kits. ESR was determined using a Vital Diagnostics automatic blood sedimentation analyzer (Italy). Statistical analyses were performed using SPSS Statistics 20.0 software.

Since the pathogenesis of KD is generally considered to be related to bacterial or viral infection [7,8] and it usually involves the heart [9], we tried to determine the value of the levels of cytokines, CRP, and NT-proBNP as well as ESR in KD diagnosis. The results showed that NT-proBNP had the highest diagnostic efficiency for KD (area under the receiver operating characteristic curve = 0.929). When the NT-proBNP level exceeded 209.5 ng/dL, its diagnosis sensitivity and specificity for KD were 89.1% and 80.1%, respectively. Sato et al. also found that NT-proBNP is a reliable marker for KD diagnosis [10]. Further, the laboratory indexes CRP and ESR recommended by the AHA are known to aid in KD diagnosis. Our research, however, showed that although CRP and ESR show high efficiency in KD diagnosis, they are less efficient than NT-proBNP (Table 1).

At present, a single injection of 2 g/kg IVIG together with aspirin taken orally is widely used clinically to treat KD, and the incidence of coronary artery damage has been found to decrease to 3%–5% with this treatment from 20% to 25% without this treatment [4]. However, some patients do not respond to IVIG treatment. Recent statistical data have shown that 20%–30% of KD patients do not respond to IVIG treatment which is quite higher than the 3%–5% counted a decade ago. The proportion of patients who did not respond to the first round of IVIG in the present study was 19.1%, and it increased year on year during follow-up. Moreover, non-responders had a longer total duration of fever and a higher incidence of coronary artery lesions than responders.

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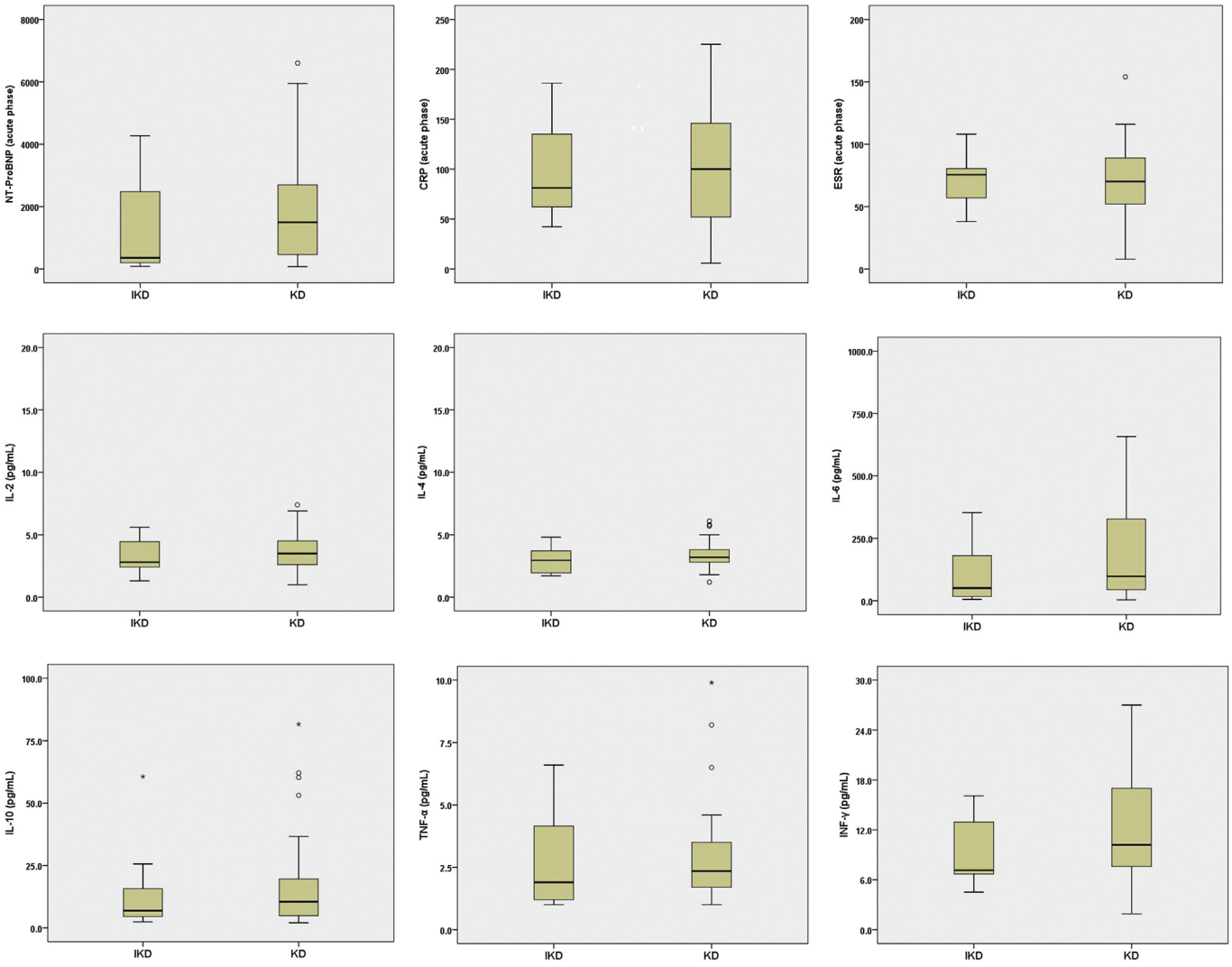

Fig. 1. Comparison of NT-pro BNP, CRP, ESR and cytokine levels between typical Kawasaki disease and incomplete Kawasaki disease. KD represents typical Kawasaki disease.

Therefore, the early recognition and effective treatment of non-responsive KD are significant challenges and research focus. In our study we found significant differences in the NT-proBNP levels between IVIG-responsive KD patients and IVIG non-responsive KD patients ($P = 0.015$). When NT-proBNP ≥3100.1 pg/dL, its sensitivity in diagnosing IVIG non-responsive KD was only 53%, but its specificity was high, at 85.7%. Therefore, adoption of further rescue therapy for non-responsive patients would be an effective measure to shorten the disease course and reduce the incidence of coronary artery lesions.

Clinically, few specific laboratory indexes are available to evaluate the effects of KD therapy; alleviation of clinical symptoms seems to be the main indicator of therapeutic efficacy. In this study we found that ESR does not decline but in fact increases slightly during the recovery phase of KD, and it therefore cannot be used as an index of therapeutic efficacy. However, since CRP and NT-proBNP levels reduce rapidly when patients' conditions improve, these may be useful as indexes of therapeutic efficacy for KD patients.

In conclusion, NT-proBNP is useful for KD diagnosis, prediction of IVIG treatment sensitivity, and evaluation of treatment effects. However, this marker is not a specific index for KD, and its levels may increase significantly in other heart-related diseases. Thus, further investigations are needed to better examine its application.

Table 1
ROC curve for diagnostic value of laboratory indexes for Kawasaki disease.

Diagnostic indicators	Kawasaki disease (n = 658)	Normal control (n = 300)	P value	AUC	95% CI	Associated criterion	Sensitivity (%)	Specificity (%)
NT-ProBNP (pg/dL)	1386.5 (79.0 → 24,078.0)	21.0 (7.0 → 71.0)	0.000	0.929	0.884 to 0.975	≥209.5	89.1%	80.1%
ESR (mm/h)	92.0 (6.0 → 225.0)	3.0 (1.0 → 7.0)	0.000	0.911	0.860 to 0.962	≥40	87.5%	76.8%
CRP (mg/L)	72.0 (8.0 → 154.0)	8.0 (4.0 → 14.0)	0.000	0.839	0.771 to 0.906	≥30	89.1%	68.9%
IL-2 (pg/mL)	3.5 (1.0 → 67.3)	5.8 (2.7 → 7.8)	0.000	0.631	0.539 to 0.723	≥2.75	73.2%	52.2%
IL-4 (pg/mL)	3.2 (1.2 → 75.4)	1.4 (1.0 → 2.1)	0.000	0.656	0.567 to 0.746	≥2.95	63.1%	62.5%
IL-6 (pg/mL)	94 (3.2 → 1919.4)	4.1 (1.2 → 8.5)	0.000	0.700	0.612 to 0.787	≥41.65	74.8%	65.0%
IL-10 (pg/mL)	10.0 (2.0 → 375.6)	2.4 (1.3 → 3.7)	0.000	0.582	0.489 to 0.676	≥6.95	62.8%	54.4%
TNF-α (pg/mL)	2.2 (1.0 → 80.7)	2.3 (1.3 → 3.1)	0.678	0.461	0.367 to 0.555	≥2.15	53.3%	38.3%
INF-γ (pg/mL)	9.8 (1.9 → 193.9)	4.6 (3.3 → 7.8)	0.000	0.625	0.533 to 0.717	≥8.75	62.3%	60.4%

P value of kawasaki disease compared with normal control group. Range and median values are represented for each group.

Conflict of interest

None of the authors has any conflict of interest to declare.

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