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Original Article

# Value of amino-terminal pro B-natriuretic peptide in diagnosing Kawasaki disease

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**Abstract**

***Background***: The aim of the present study was to investigate the diagnostic value of the N-terminal B-type natriuretic peptide (NT-proBNP) in acute Kawasaki disease (KD) given that the clinical criteria and the current basic laboratory tests lack the necessary specificity for accurate diagnosis.

***Methods***: Basic biological tests and serum NT-proBNP levels obtained from acute KD patients were compared to that of febrile controls. NT-proBNP was considered abnormal based on the following definitions: above a cut-off determined on receiver operator characteristic (ROC) analysis, above the upper limit for age, or above 2 SD calculated from healthy children. Analyses were also performed for KD cases with complete or incomplete criteria combined and separately.

***Results***: There were 81 patients and 49 controls aged 3.60 ± 2.77 versus 4.25 ± 3.88 years ($P = 0.69$). ROC analysis yielded significant area under the curve for NT-proBNP. The sensitivity, specificity, positive and negative predictive values were 70.4–88.9%, 69.4–91.8%, 82.8–93.4%, and 65.2–79.1%. The odds ratios based on NT-proBNP definitions varied between 18.13 (95% confidence interval [CI]: 7.21–45.57), 20.82 (95%CI: 8.18–53.0), and 26.71 (95%CI: 8.64–82.57; $P < 0.001$). Results were reproducible for cases with complete or incomplete criteria separately.

***Conclusion***: NT-proBNP is a reliable marker for the diagnosis of KD. Prospective clinical studies with emphasis on NT-proBNP in a diagnostic algorithm are needed.

**Key words** echocardiography, incomplete criteria, incomplete Kawasaki disease, mucocutaneous lymph node syndrome, NT-proBNP.

The principal complications of Kawasaki disease (KD) are related to coronary artery (CA) aneurysms.[1] This led the American Heart Association (AHA) to recognize KD among the primary childhood risk factors for CA disease.[2] Establishing the diagnosis of KD early in the course of the illness facilitates the use of i.v. immunoglobulin (IVIG) in the appropriate therapeutic window of 10 days.[3] It is therefore essential to enhance the diagnostic certainty of a disease that lacks a gold standard and a reliable laboratory test. In this regard, we initially sought to assess the clinical utility of the natriuretic activity by measuring the amino-terminal pro B-type natriuretic peptide (NT-proBNP) and the metabolically active moiety of the molecule (BNP) at the onset of KD as an adjunctive test in supporting the diagnosis of KD. PreproBNP, the precursor of BNP and NT-proBNP, is a 134-amino-acid peptide that is synthesized and secreted by ventricular cardiomyocytes undergoing shear stress. It is cleaved in the liver during a first pass into a signal peptide and proBNP. ProBNP is then cleaved by a circulating endoprotease into BNP, an active moiety metabolized by the kidney and the vascular tree, and a metabolically inactive NT-proBNP fragment.[4] The clearances for those two moieties are different, BNP having the short half-life of 20–30 min, while NT-proBNP circulates unchanged in the serum for 60–120 min before being cleared primarily by the kidney.[5,6] A precursor to the present study demonstrated that NT-proBNP was a better marker than BNP in acute KD; this was especially true in cases of incomplete KD.[7] Our first study also suggested that a cut-off for NT-proBNP might enable the clinician to distinguish KD cases from other common febrile illnesses. The caveat is that the serum level of NT-proBNP varies with age, because of higher concentrations in infancy and preschool children.[8] The goal of the present work was to study the diagnostic value of NT-proBNP serum levels in KD based on different case definitions: the receiver operating characteristic

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(ROC) cut-off; the upper limit for age; and the age-related Z-value based on healthy children.

## Methods

### *Inclusion parameters*

In this prospective multicenter study, serum concentration of NT-proBNP was measured in patients newly diagnosed with KD at the time of the initiation of therapy. The diagnosis was based on the assessment of the admitting pediatricians, who were unaware of the result of NT-proBNP serum level. In order to compare patients with incomplete criteria and the related natriuretic peptide release, patients were classified based on the classical clinical criteria for KD.[3] Children who presented with fever (≥38.8°C) unrelated to KD lasting between 4 and 14 days served as febrile controls. Exclusion criteria included myocarditis, uncorrected significant structural heart anomalies, dilated or hypertrophic cardiomyopathy, septicemia or septic shock, hypovolemic shock, renal failure, prolonged relapsing fever of unknown etiology (>21 days), systemic autoimmune disease presenting with pericarditis, and history of chemotherapy involving cardiotoxic drugs. Medical charts were reviewed at the analysis phase to verify whether the diagnosis of KD was maintained or rejected following the enrollment phase, and to confirm the final diagnosis of febrile controls.

### *Biochemical testing*

Blood was collected in 2 mL lithium-heparinazed Vacutainers™ (Becton-Dickinson, Mississauga, ON, Canada), without gel then centrifuged, and plasma was stored at −20°C. Samples were analyzed on electrochemiluminescence immunoassay using the Elecsys analyzer (Roche Diagnostics, Indianapolis, IN, USA) with biotinylated polyclonal capture antibodies and polyclonal ruthenium-complexed detection antibodies.[7] The respective institutional review boards of human research approved the study, and informed consent was obtained from the patients or their guardians.

### *Definitions of elevated NT-proBNP*

The ROC analysis was performed on NT-proBNP, white blood cell count, platelet count, C-reactive protein (CRP), erythrocyte sedimentation rate, albuminemia, alanine aminotransferase, and aspartate aminotransferase. ROC analysis was repeated for KD with complete and incomplete diagnostic criteria separately. NT-proBNP levels were converted into categorical classification, normal versus high concentration, according to three different criteria: the cut-off based on the ROC analysis; the upper limit for age (95th percentile: 646 ng/L for infants between 1 month and 1 year old, 413 ng/L for children between 1 and 2 years old, 289 ng/L for those between 2 and 6 years old, and 157 ng/L for those >6 years old);[8] and Z > 2.0 computed from the raw data of a previously reported cohort consisting of 356 healthy children between 4 months and 18 years old.[8] The data distribution was clearly log-normal ($P = 0.11$), that is, assuming linear correlation between the natural logarithm of NT-proBNP and age. Therefore, the following equation was used to derive the expected value for age: Expected Ln(NT-proBNP) = 4.6117 − (0.0639 × age in years), with the following standard error of the estimate (SEE) = 0.8575. The Z-value of a particular patient is therefore (Ln [measured NT-proBNP] – expected Ln value for age)/SEE.

### *Diagnostic role of coronary dilatation*

Because there is an emphasis in current practice on the importance of identifying CA dilatation to support the diagnosis of KD, we sought to calculate the prevalence of such an index upon admission, before initiating IVIG therapy, that is, when the admitting physician is compelled to decide on a diagnosis. CA Z-value was computed based on the recently published equations from the initiating institution of this study.[9] A CA was considered dilated when the Z-value was >2.5 according to current recommendations.[3]

### *Statistical analysis*

Statistical analysis was performed using SPSS-17 software (SPSS, Chicago, IL, USA). Data are expressed as mean ± SD (median; interquartile limits). Student's T-test was used for comparison between normally distributed continuous data. Nonparametric analysis using the Mann–Whitney *U*-test was utilized for continuous data that did not follow a normal distribution. The odds ratios and the 95% confidence intervals (95%CI) were calculated and compared using the Mantel–Haenszel test. The Fisher exact test and the chi-squared test with Yates correction for continuity were used for comparison of categorical data.

## Results

There were 81 KD patients and 49 febrile controls who met the study criteria between November 2005 and September 2010. The male : female distribution was 43/38 and 26/23 in KD and controls ($P = 0.570$). Age at enrollment was 3.60 ± 2.77 years (2.80 years; 1.71–5.07 years) versus 4.25 ± 3.88 years (3.00 years; 1.35–6.80 years; $P = 0.695$), with 14 (17.3%) and 11 infants (22.4%) ≤12 months old in the respective groups ($P = 0.497$). The duration of fever at enrolment was 6.58 ± 2.82 days (6 days; 5–8 days) versus 8.35 ± 6.34 days (7 days; 4–10 days; $P = 0.378$). Finally, 46/81 (56.8%) had complete KD criteria in the KD group versus 3/49 (6.1%) in the febrile control group ($P < 0.001$), with a median of five criteria (range, 2–6) in KD and of three (range, 1–6) in febrile controls. Among the various diagnoses of the febrile controls (Fig. 1) two patients with bacterial otitis media and one with tonsillitis who were responders to antibiotic therapy had 5–6 clinical criteria that might have simulated KD. NT-proBNP was significantly increased in KD (1287.7 ± 2090.3 ng/L; 662 ng/L, 318–1471 ng/L) compared to controls (199.5 ± 274.3 ng/L; 122 ng/L, 64–229 ng/L; $P < 0.001$). Among the remaining laboratory tests, KD patients had lower hematocrit, serum albumin, and serum sodium, and higher CRP compared to controls (Table 1). The ROC results for NT-proBNP and the biological tests are summarized in Figure 2. In short, NT-proBNP yielded an area under the curve (AUC) that significantly deviated from the identity line (AUC, 0.881 ± 0.031; $P < 0.0001$), followed by albumin then CRP. The statistical significance for NT-proBNP AUC remained strong when cases with complete or incomplete diagnostic criteria were analyzed separately (Fig. 2).

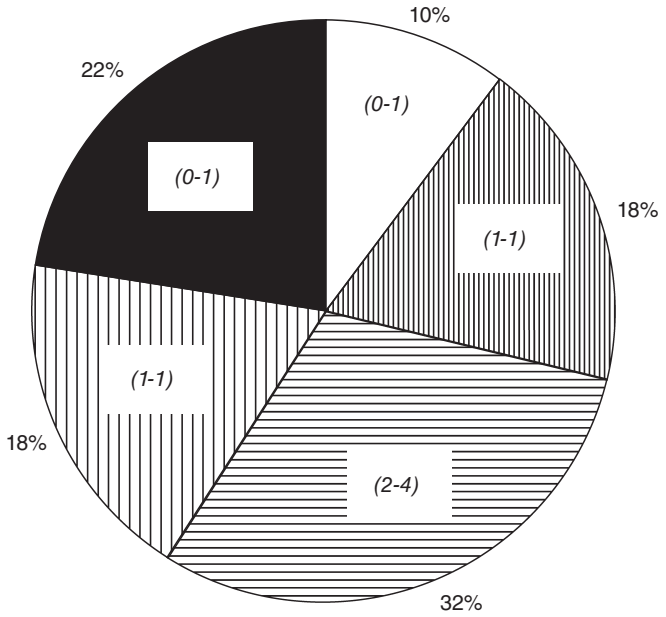


**Fig. 1** Diagnoses of febrile controls. (□) Autoimmune arthritis; (▥) viral (specific); (▤) viral (presumed); (▥) bacterial (specific); (■) bacterial (other). (x–x), no. subjects with elevated N-terminal B-type natriuretic peptide according to upper limit for age and Z-score categorization, respectively. Autoimmune arthritis: juvenile rheumatoid arthritis, reactive arthritis and sinuvitis, systemic lupus erythematosus; viral (specific): mononucleosis, Epstein–Barr, adenovirus, herpangina; viral (presumed): non-immune non-bacterial self resolving fever; bacterial (specific): cervical adenitis, retropharyngeal abscess, scarlatin; bacterial (other): otitis sinusitis, osteomyelitis/cellulitis, bacteremia, meningitis, urinary tract infection.

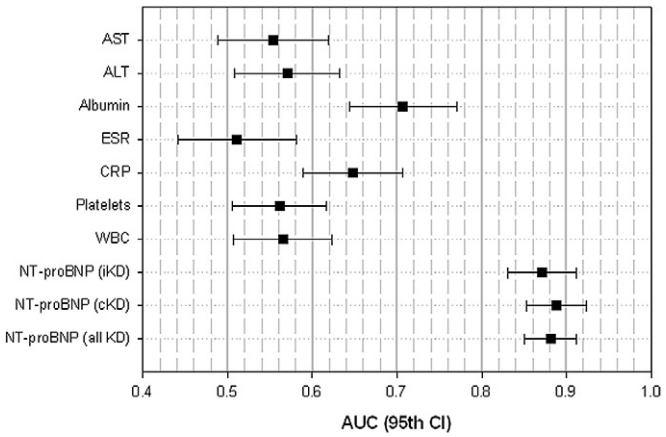


**Fig. 2** Receiver operator characteristic (ROC) analysis yielded significant area under the curve (AUC) of 0.881 ± 0.031 for N-terminal B-type natriuretic peptide (NT-proBNP; $P < 0.0001$), albumin ($P = 0.004$) and C-reactive protein (CRP; $P = 0.017$), but no distinctive value for the remaining tests ($P = 0.05$–$0.60$). Only NT-proBNP maintained significance for incomplete (iKD) or complete (cKD) criteria ($P = 0.001$ and 0.024, respectively), vs the remaining tests ($P = 0.11$–$0.28$). ALT, alanine aminotransferase; AST, aspartate aminotransferase; CI, confidence interval; ESR, erythrocyte sedimentation rate; WBC, white blood cell count.

The albumin and CRP AUC became statistically non-significant when cases with complete or incomplete diagnostic criteria of KD were analyzed separately ($P = 0.11$–$0.28$). Based on ROC analysis the cut-off of 190 ng/L maintained sensitivity >88% and was identified for further dichotomous classification. The categorical distribution of NT-proBNP was based separately on the three working definitions of a positive or negative test (Tables 2,3). Accordingly, 10.2% of controls had elevated NT-proBNP while 26.5% fell in the gray zone (between the cut-off and the upper limit for age), and 80.2% of KD patients had high NT-proBNP, with 8.6% falling in the gray zone (Table 2). With the Z-value calculation of NT-proBNP, 8.2% of febrile controls had high serum NT-proBNP (Table 3). The individual data are plotted against the three working definitions

**Table 1** Basic laboratory tests

| | Kawasaki disease<br>Mean ± SD<br>Median [interquartile range] | Febrile controls<br>Mean ± SD<br>Median [interquartile range] | *P* |
|---|---|---|---|
| White blood cells ($10^9$/L) | 14.4 ± 6.8<br>13.0 [9.6–16.4] | 12.7 ± 5.9<br>11.1 [8.0–17.2] | 0.248 |
| Hematocrit (%) | 31.7 ± 3.8<br>32.4 [29.5–34.0] | 33.3 ± 3.7<br>33.2 [31.0–35.0] | 0.028 |
| Platelet count ($10^9$/L) | 357.2 ± 159.0<br>347 [252–438] | 329.0 ± 155.2<br>288 [242–419] | 0.279 |
| Albumin (g/L) | 29.5 ± 7.2<br>29 [23.5–33] | 35.5 ± 7.7<br>33 [29–42] | 0.002 |
| C-reactive protein (mg/L) | 115.1 ± 94.8<br>95.3 [34.6–156.0] | 73.3 ± 79.7<br>41.2 [18.6–97.0] | 0.017 |
| Sedimentation rate (mm/h) | 50.1 ± 18.8<br>52 [41–58] | 48.6 ± 24.8<br>53 [33–60] | 0.877 |
| Alanine aminotransferase (U/L) | 50.9 ± 67.4<br>21 [15–55] | 48.4 ± 75.4<br>18 [12–36] | 0.254 |
| Aspartate aminotransferase (U/L) | 46.0 ± 41.3<br>36 [27–49] | 56.7 ± 62.4<br>30 [22–50] | 0.379 |
| Natremia (mEq/L) | 134.3 ± 2.9<br>135 [133–136] | 136.3 ± 2.4<br>136 [134–138] | <0.001 |

**Table 2** NT-proBNP concentration vs two cut-offs

| | <CV-190 and <UL-age *n* (%) | >CV-190 and <UL-age *n* (%) | <CV-190 and >UL-age *n* (%) | >CV-190 and >UL-age *n* (%) |
|---|---|---|---|---|
| Controls | 31 (63.3) | 10 (20.4) | 3 (6.1) | 5 (10.2) |
| Kawasaki disease | 9 (11.1) | 7 (8.6) | 0 (0.0) | 65 (80.2) |

$\chi^2 = 62.99$, d.f. = 3, $P < 0.001$, statistical power 1.0.
CV-190, cut-off 190 ng/L; NT-proBNP, N-terminal B-type natriuretic peptide; UL-age, upper limit for age.

(Fig. 3). The sensitivity, specificity, positive and negative predictive values are summarized in Table 4. Accordingly, the odds ratios of abnormal NT-proBNP in KD versus controls varied between 18.13 (95%CI: 7.21–45.57), 20.82 (95%CI: 8.18–53.0), and 26.71 (95%CI: 8.64–82.57), for the 190 ng/L cut-off, the upper limit for age, and the Z-value >2.0, respectively ($P < 0.001$).

**Table 3** NT-proBNP concentration vs Z according to age

| | Z ≤ 2.0 *n* (%) | Z > 2.0 *n* (%) |
|---|---|---|
| Controls | 45 (91.8) | 4 (8.2) |
| Kawasaki disease | 24 (29.6) | 57 (70.4) |

$\chi^2 = 47.43$, d.f. = 1, $P < 0.001$, statistical power 1.0.
NT-proBNP, N-terminal B-type natriuretic peptide; Z, SD for NT-proBNP serum level according to age.

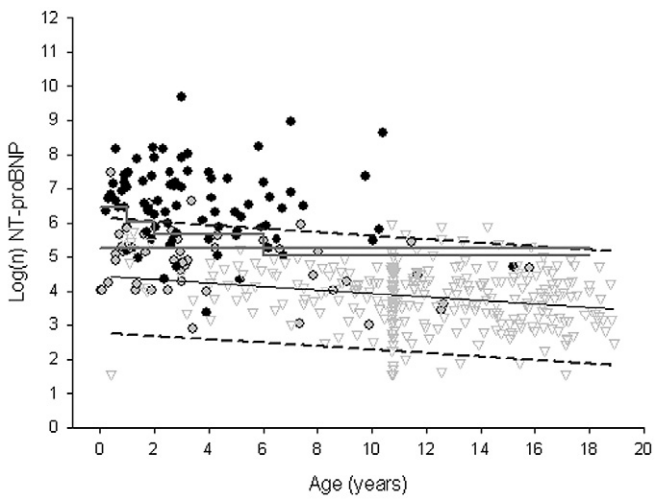


**Fig. 3** Scatter plot comparison of the three working definitions of N-terminal B-type natriuretic peptide (NT-proBNP: (red line) upper limit for age; (green line) cut-off 190 ng/L; and (upper blue dashed line) 2 SD. To aid comparison, all data are represented by their natural logarithmic transformation. (●), Febrile controls; (●), Kawasaki disease; (▽), healthy subjects.

In KD infants ≤12 months of age only two had normal NT-proBNP according to the upper limit for age criteria, and only one of these two according to the Z-value criteria ($P = 0.055$ and 0.72, respectively). The rate of abnormal NT-proBNP level was comparable between KD patients with complete criteria and those with incomplete diagnostic criteria, regardless which definition of elevated NT-proBNP was used (Table 5). There was a trend towards higher prevalence for CA dilatation in patients with incomplete criteria, who also appear less likely to be resistant to IVIG, both observations were statistically non-significant (Table 5). From this perspective, NT-proBNP Z-score was comparable between IVIG-resistant and IVIG-responsive patients (2.81 ± 1.24 vs 2.43 ± 1.31 respectively; $P = 0.294$). The overall prevalence of CA dilatation at initial echocardiography was 16.0% among KD patients and 2.0% among controls, with an estimated odds ratio of 9.17 (1.16–72.52; $P = 0.017$).

## Discussion

The diagnosis of KD is based on clinical criteria and supportive laboratory data that lack specificity. Unfortunately there is no diagnostic test that could facilitate the early identification and treatment of children with KD with certainty. The present study demonstrates that NT-proBNP is elevated in the acute phase of KD compared to febrile controls. It yields the best available predictive values, unlike the currently used laboratory tests. To date, this is the first report on a clinically available blood test with diagnostic value for KD. In contrast, the finding of dilated CA would support the diagnosis of KD in a relatively small proportion.

### *Diagnostic impact of coronary dilatation*

Kawasaki disease remains a self-limited clinical syndrome that requires a high index of suspicion from practitioners because it can mimic other common childhood febrile illnesses and, above all, could also be highly associated with documented infections

**Table 4** Predictive power of NT-proBNP for the diagnosis of KD vs definition of increased level

| Definition | PPV (%) | NPV (%) | Sensitivity (%) | Specificity (%) |
|---|---|---|---|---|
| CV-190 | 82.8 | 79.1 | 88.9 | 69.4 |
| UL-age | 89.0 | 71.9 | 80.2 | 83.7 |
| Z > 2.0 | 93.4 | 65.2 | 70.4 | 91.8 |

CV-190, cut-off of 190 ng/L; KD, Kawasaki disease; NPV, negative predictive value; NT-proBNP, N-terminal B-type natriuretic peptide; PPV, positive predictive value; UL-age, upper limit for age; Z, SD for NT-proBNP serum level according to age.

**Table 5** Patient characteristics vs completeness of KD diagnostic criteria

| | Kawasaki disease | | | Febrile controls | | |
|---|---|---|---|---|---|---|
| | Complete | Incomplete | *P* | Complete | Incomplete | *P* |
| *n* | 46 | 35 | | 3 | 46 | |
| M/F | 25/21 | 18/17 | 0.82 | 3/0 | 23/23 | 0.24 |
| Age (years), mean ± SD | 3.63 ± 2.31 | 3.57 ± 3.32 | 0.92 | 2.47 ± 1.46 | 4.36 ± 3.97 | 0.42 |
| Duration of fever (days) | 5.93 ± 2.54 | 7.43 ± 2.97 | 0.018 | 6.67 ± 2.31 | 8.49 ± 6.55 | 0.387 |
| Resistance to IVIG, *n* (%) | 10 (21.7) | 6 (17.1) | 0.78 | NA | NA | NA |
| NT-proBNP >UL-age, *n* (%) | 38 (82.6) | 27 (77.1) | 0.58 | 1 (33.3) | 7 (15.2) | 0.42 |
| NT-proBNP >CV-190, *n* (%) | 41 (89.1) | 31 (88.6) | 1.0 | 1 (33.3) | 14 (30.4) | 1.0 |
| NT-proBNP >2 Z-value, *n* (%) | 32 (69.6) | 25 (71.4) | 1.0 | 0 (0.0) | 4 (8.7) | 1.0 |
| Initial CA dilatation, *n* (%) | 5 (10.9) | 8 (22.9) | 0.22 | 0 (0) | 1 (2.2) | 1.0 |

CA, coronary artery; CV-190, cut-off of 190 ng/L; IVIG, i.v. immunoglobulin; KD, Kawasaki disease; NT-proBNP, N-terminal B-type natriuretic peptide; UL-age, upper limit for age; Z-value, SD for NT-proBNP serum level according to age.

(33%).[10] Although CA involvement is reported when KD diagnosis is associated with an infection,[10] one should be careful about the accuracy of KD diagnosis in these cases. In the acute phase of KD, the prevalence of CA aneurysm or ectasia is approximately 15–25% in untreated cases, and approximately 5% when adequately treated with IVIG.[3,11] In the last AHA recommendations on the diagnosis and treatment of KD, there were suggested ancillary tests that could aid in the evaluation of suspected cases with incomplete criteria, including laboratory data and echocardiographic findings.[3] The recommendations iterated that incomplete KD should be considered in all children presenting with fever ≥5 days and 2–3 major diagnostic criteria. They also proposed that febrile infants <6 months without an identified cause must have an echocardiogram. Although echocardiography is easily available, the identification of CA dilatation is not as sensitive as one would hope at the time when IVIG is efficient, because most CA lesions do not form before day 10 of illness, and CA ectasia and perivascular brightness are at best subjective findings.[3,12] In addition, it is possible that fever alone unrelated to KD, may cause CA dilatation. In the present series one febrile control with sinovitis had a transitory CA dilatation, a finding previously described in a small series of juvenile idiopathic arthritis.[13] Also, new definitions for CA dilatation continued to emerge until very recently that seem to fall midway between the early underestimation of the rate of CA dilatation by the Japanese Ministry of Health criteria, and the overestimation by subsequent formulas.[9]

### *Myocarditis in Kawasaki disease*

The present study used NT-proBNP as a laboratory marker, due to its superiority in detecting the subtle myocardial involvement in acute KD. The rationale for using this marker is the notion that there is not only a vasculitis in acute KD but also a degree of myocardial inflammation as reported in a large biopsy series, obtained at different stages of the disease.[14] Accordingly, myocarditis, cellular infiltration and fibrosis were present in every KD case, regardless of the presence or absence of major CA involvement. Chronologically, myocarditis is the first documented histopathological injury in the course of the disease, followed by CA arteritis.[15] In addition to echocardiography,[16–19] there are data indicating that electrical anomalies, such as QT dispersion and atrioventricular conduction disturbances, may be present in KD patients without significant CA complications.[20]

From an echocardiographic standpoint, myocardial edema and abnormal myocardial contractility have been demonstrated in the majority of patients with acute KD.[16,17,21,22] An attempt to correlate myocardial systolic and diastolic parameters with the natriuretic peptides was also reported.[18,19,23] In the latter two studies BNP was used with a cut-off of 50 ng/L. It is possible that elevated levels of BNP are detectible in KD patients with measurable myocardial dysfunction, but not in the majority of KD patients, as suggested in our initial report.[7] It was recently suggested that increased BNP in acute KD correlates with CRP and interleukin-6.[23] In this regard, a linear correlation between CRP level and NT-proBNP Z-score was present in the current series (data not shown). One might argue that the lower NT-proBNP level in the present febrile controls may be secondary to lower CRP. Nevertheless, only two febrile controls (4.1%) versus three KD patients (3.7%) had CRP <10 mg/L ($P = 0.717$), in addition, ROC analysis clearly demonstrated a less favorable diagnostic value of CRP not only in comparison with NT-proBNP but to serum albumin as well. From another perspective, the myocarditis in KD is often subclinical, with low incidence of myocardial cell breakdown to cause increased troponin levels.[24] Therefore, a biological marker of the subtle myocardial dysfunction has more potential in terms of clinical screening. In fact, NT-proBNP is the inactive metabolite obtained from cleaving proBNP into BNP and NT-proBNP. It is easier to sample than BNP because its clearance is slower than BNP and therefore sustained for a longer period of time in the circulation.[7,10] In the present study we used a commercially available test for NT-proBNP measurement because of the available literature in children and because of the reported minimal variation between laboratories (3.8–6.5%), as well as intra- and inter-assay variability (0.9–3.0% and 3.6–5.8%, respectively).[8,25] Because different epitopes are targeted by other commercially available methods,[26] the present data do not allow us to extrapolate to those methods until they have been clinically tested in KD, thus determining the related diagnostic values.

### *Clinical application of NT-proBNP in acute KD*

The clinical utility of NT-proBNP in acute KD depends on which definition of abnormal is used. Although all appeared to have

favorable profiles, the Z-value method maintained the highest specificity and positive predictive value. Typically, the use of a single cut-off, such as the one derived from the ROC analysis, seems attractive. It is nevertheless the least appropriate due to the variation of NT-proBNP with age.[8] We adjusted the variation with age by calculating the correlation of the natural logarithm of NT-proBNP, which was free of heteroskedasticity. A continuous estimate of the upper limit for age with z-values would essentially avoid the assumption that children within a predetermined age bracket have a unique upper limit. Nonetheless, there was little variation between the use of the upper limit for age and that of the Z-value classification method in terms of predictive value, sensitivity and specificity. In the era of increased awareness of KD diagnosis and the practitioners' susceptibility to administer IVIG when KD is suspected but not necessarily confirmed, it is possible that some of the KD patients with normal NT-proBNP were over-diagnosed with KD. Subsequently, prospective testing of the validity of NT-proBNP when the diagnosis of KD is suspected should be coupled with the appropriate short-term and long-term differential diagnoses in those with normal serum NT-proBNP. In our experience this would reduce the complexity of the diagnostic algorithm suggested in the AHA recommendations.[3] A recent retrospective assessment of these recommendations as applied to a series of patients with CA aneurysms concluded that the AHA algorithm improves the rate of IVIG treatment. The caveat is that, in that analysis, five patients who did not adhere to the classical clinical criteria would have been missed by the proposed algorithm, among whom four developed CA aneurysms.[27] The use of NT-proBNP also surpasses the reliance on echocardiography in search of CA dilatations. In the present series the prevalence of CA dilatation on initial echocardiogram was limited to 16.0%, whereas the proportion of KD patients with elevated NT-proBNP varied between 70% and 80%.

It is recognized that the classical criteria for KD are suggestive but not diagnostic for the disease, mainly because children with incomplete criteria are at risk for developing CA complications.[3] In the absence of a gold standard, the response to IVIG consolidates the diagnosis of KD as opposed to the poor immediate response in patients with viral myocarditis.[24,28] We could conclude that the NT-proBNP myocardial release in the present series delineated a KD-related phenomenon rather than viral carditis, given the observed proportion of IVIG resistance among patients with high NT-proBNP in line with the reported figures.[3,11]

### *Study limitations*

A potential limitation of the present study relates to the relatively small number of subjects in the complete versus incomplete criteria subgroups. Notwithstanding, we believe that this is compensated for by the even distribution of these subgroups and the high statistical power of the chi-squared analysis and the maintained statistical significance of the NT-proBNP ROC analysis. Another limitation was the fact that there is no gold standard to confirm the diagnosis of KD. The only option at this stage of the investigation was to rely on the intention to treat and to verify the maintenance of the diagnosis. Another limitation may have been related to the variety in the diagnoses of the febrile controls. Given that some might argue that KD may be triggered by an infectious agent, bacterial and viral alike,[29,30] the inflammatory nature of KD places auto-immune illnesses high in the differential diagnoses of KD.[13] For these reasons, we elected to include bacterial, viral and auto-immune illnesses in the febrile control group, as suggested in the differential diagnosis list of KD.[31]

### *Conclusion*

NT-proBNP is a useful cardiac biomarker in acute KD. It is commercially available, affordable, fast to process, and operator independent. A prospective multicenter study with emphasis on NT-proBNP in a diagnostic algorithm of KD is needed.

## Acknowledgment

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