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Cardiac Biomarkers for Early Detection of Cardiac Involvement in Children with Kawasaki Disease: A Cross-Sectional Study

Akbar Molaei[1], Mahnaz Sadeghi-Shabestari[2], Azizollah Khomahani[2], Shamsi Ghaffari[1], *Seyyed-Reza Sadat-Ebrahimi[1]

[1]Cardiovascular Research Center, Shahid Madani Heart Center, Tabriz University of Medical Sciences, Tabriz, Iran.
[2]Pediatric Health Research Center, Tabriz Children Hospital, Tabriz University of Medical Sciences, Tabriz, Iran.

Abstract

Background: Kawasaki disease (KD) is one of the most prevalent vasculitis diseases in children and can bring about serious cardiovascular complications. Early detection of cardiac involvement in KD can play an essential role in managing and preventing the cardiac sequels. We aimed to evaluate the applicability and diagnostic accuracy of cardiac biomarkers including cardiac troponin I (cTnI), and N-terminal pro-brain natriuretic (NT-proBNP) for early detection of cardiac involvement in children with KD.

Materials and Methods

In this cross sectional study, 32 children with KD who were admitted to the Children's Hospital of Tabriz University of Medical Sciences, Tabriz, Iran, in a three-year period, were consecutively included. Transthoracic echocardiography was performed to evaluate cardiac involvement. Also, the serum levels of NT-proBNP and cTnI were measured to evaluate their diagnostic accuracy. ROC curve analysis was conducted to evaluate the discriminatory power of NT-ProBNP for the diagnosis of cardiac involvement in KD and to determine the best cut-off point at which the sensitivity and specificity were optimal.

Results: Of 32 enrolled patients, 4 (12.5%) had cardiac involvement including 3 patients with perivascular brightness of coronary arteries and one patient with small aneurysm of the coronary arteries. In all study patients, the cTnI levels were lower than 0.35 ng/ml and the NT-proBNP measurement revealed an average of 678.5 pg/ml. Children with cardiac involvement had significantly higher NT-proBNP (p= 0.001). Both sensitivity and specificity of NT-proBNP at the optimum cut-off point of 1354 pg/ml were 100 percent (AUC=1.000, p=0.001).

Conclusion: Unlike the cTnI, our results support the applicability of NT-proBNP as an excellent objective test for early detection of cardiac involvement in children with KD.

Key Words: Cardiac Biomarkers, Children, Kawasaki disease.

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Corresponding Author:

Seyyed-Reza Sadat-Ebrahimi, Cardiovascular Research Center, Shahid Madani Heart Center, Tabriz University of Medical Sciences, Tabriz, Iran; +989144717151.

Authors 1 and 2, contributed equally.

Email: Sadatr@tbzmed.ac.ir

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1- INTRODUCTION

Although Kawasaki Disease (KD) is the second most prevalent vasculitis disease in children after Immunoglobulin A vasculitis (IgAV, Henoch–Schönlein purpura), it is known as the main cause of acquired cardiac disease in pediatrics (1-3). KD is typically a self-limiting disease and the majority of patients show a complete recovery after the acute phase, but in some cases they disclose serious cardiovascular involvement both in acute and chronic stages (4). KD is more common among the Asian children under 5 years of age (1), and approximately 15-25 percent of children with untreated KD will develop coronary aneurysms. Although the coronary aneurysms in those children could be reduced by intravenous immunoglobulin (IVIG), five percent of those treated still develop coronary aneurysms (4). Moreover, histopathological findings have reported diffuse myocardial inflammation (5, 6). Also, some studies have reported diastolic dysfunction in KD patients (7, 8).

It has been postulated that early diagnosis and management of KD can prevent further serious complications (9). According to the American Heart Association's guidelines (3), the diagnosis of classic KD is based on clinical manifestations including a prolonged fever that lasts more than five or four days along with four of five of the principal characteristics including the changes in extremities (erythema of palms and soles or edema of hands and feet in acute phase; periungual peeling of fingers and toes in sub-acute phase), polymorphous exanthema, bilateral bulbar conjunctival injection without exudate, erythema and cracking of lips, strawberry tongue, and/or erythema of oral and pharyngeal mucosa, unilateral cervical lymphadenopathy with diameter greater than 1.5 cm (3, 9). In the atypical or incomplete form of KD, patients have prolonged fever with less than four of five principal clinical signs (9). Furthermore, some laboratory findings such as elevated erythrocyte sedimentation rate, C-reactive protein level, hyponatremia and hypoalbuminemia could be helpful in diagnosis of suspected KD patients. Recently, several biomarkers have been suggested for diagnosis of KD including serum T-helper 1 and T-helper 2 cytokines (interleukin 6 and 20, tumor necrosis factor alpha [TNF-α], and interferon gamma [IFN-γ]), and serum N-terminal (NT)-pro hormone BNP (NT-proBNP) (10-12).

Early detection of cardiac involvement of KD is also important in managing and preventing the cardiac sequels in KD patients (13). Transthoracic echocardiography (TTE) is a diagnostic imaging modality of choice for examining the coronary aneurysms; however, more objective diagnostic tools are required for early detection of cardiac involvement in KD patients (3). It is for more than a decade that elevated cardiac troponin I (cTnI) has been considered as a reliable marker of cardiac disorders (14), since it is the most sensitive and specific laboratory test for diagnosing myocardial infarction (14). It has been demonstrated that NT-proBNP is a proper marker of congestive heart failure and it is elevated in acute myocardial injuries, as well (15, 16).

Also, it has been indicated that NT-proBNP has a high diagnostic value for cardiac involvement in some diseases such as amyloidosis and Marfan syndrome (MFS) (17). Both cTnI and NT-proBNP have been suggested by some studies as the predictors of cardiac involvement in KD. Although, Kim et al., demonstrated that cTnI level significantly increases in KD patients especially in those with symptomatic myocarditis (18), Checchia et al. did not show any of the significant findings through the cTnI elevation in KD patients (19). Also, Kaneko et al., revealed that NT-proBNP

level significantly increases in patients who have developed coronary artery lesion; their findings were lately confirmed by the study of Adjagba et al., and Jung et al. (20-22). In contrast, a study by Iwashima et al., did not present any significant differences in levels of NT-proBNP between KD patients with and without coronary artery lesions, however, those patients who developed mitral regurgitation showed significant higher levels of NT-proBNP (23). To date, none of cTnI and NT-proBNP biomarkers have been adequately evaluated for their clinical applicability in early diagnosis of cardiac involvement in KD patients. Thus, this study aimed to evaluate the applicability and diagnostic accuracy of cardiac biomarkers including cTnI and NT-proBNP for early detection of cardiac involvement in children with KD.

2- MATERIALS AND METHODS

2-1. Study design and population

In this cross-sectional study, children with KD who were admitted to the children teaching hospital of Tabriz University of Medical Sciences, Tabriz, Iran, between April 2015 and April 2018, were consecutively included. This hospital is a tertiary-level referral center in North-West of Iran.

2-2. Inclusion and exclusion criteria

The inclusion criteria was the diagnosis of KD by two attending pediatricians. Diagnosis of KD was made based on the American Heart Association's criteria for classic KD in children (3). The patients with a previous history of congenital heart disease, uncorrected structural heart abnormality, dilated or hypertrophic cardiomyopathies, a previous episode of KD or carditis, the ones who were recently treated with IVIG, and those undergoing or had undergone chemotherapy involving cardio-toxic drugs were excluded from the study. Also, the patients with a final diagnosis of incomplete KD due to its ambiguity were excluded as well.

2-3. Methods

Sample size was calculated based on the method used by previous similar studies (19, 21). The sizes were based on the required sample number to perform the analysis. Alpha was considered as 0.05 with the power of 80 percent. Baseline characteristics and KD information were recorded for each child. The onset of KD was defined as the onset of fever in the children. Blood specimens (3 mL from each patient from a venues access from left forearm) were obtained at time of admission by experienced laboratory staff before any treatment intervention.

In all included KD patients, at the time of admission, the coronary artery involvement was evaluated by a pediatric cardiologist using a ransthoracic echocardiography (TTE) (Vivid- 3, General Electric Co., USA), coronary arteries were evaluated and the Z-values were calculated with a similar method described by Miura et al. (24). Cardiac involvement was defined as the intra-luminal diameter of Z-score of ≥2.5 (coronary artery aneurysm) or perivascular brightness of coronary arteries (25). Also, we classified the coronary artery abnormalities as small if the Z-score was ≥ 2.5 to <5, large if the Z-score was ≥ 5 to < 10, and giant if the Z-score was ≥ 10 (26).

2-4. Laboratory measurements

The obtained blood specimens were immediately transferred to the laboratory of the hospital under standard condition for evaluation of the serum level of NT-proBNP and cTnI. Serum levels of NT-proBNP were analyzed using an electrochemiluminescence immunoassay using ECLusys 2010 analyzer (Roche Diagnostics, Indianapolis, IN); the manufacturer recommended the 125 pg/ml as cut-off point for NT-proBNP level (27); cTnI levels were assessed using the Stratus

fluorometric enzyme immunoassay (Dade Pharmaceuticals, USA). The manufacturer recommended 1.5 ng/ml as the cut-off point for cTnI level in diagnosing the myocardial disorder (28). The lower bond of detection by the applied immunoassay was 0.35 ng/ml.

2-5. Ethical consideration

Ethics approval and consent to participate: Ethical clearance was sought from medical ethics committee of Tabriz University of Medical Sciences, Tabriz, Iran (IR.TBZMED.REC.1394.142). Written informed consent was obtained from a parent or guardian of the participants.

2-6. Data Analyses

Data were analyzed using SPSS software version 22.0. Normal numerical data were reported as mean ± standard deviation (SD), and non-normal ones were reported as median (minimum-maximum). Categorical data was reported as frequency (percentage). Statistical comparisons between the two groups (with or without cardiac involvement) were performed by a two-tailed Student's t-test or Mann-Whitney U test for numerical data (for normal and non-normal distribution respectively) and a Fisher's exact test for categorical data. The power of predicting cardiac involvement was evaluated based on the serum levels of NT-proBNP using the receiver operating characteristic curve (ROC). Also, their areas under the curve (AUCs), and specificity and sensitivity were calculated. A p-value of less than 0.05 was considered as significant.

3- RESULTS

Among 54,124 patients admitted during the study period, 41 patients were diagnosed as KD. However, 9 patients were excluded due to the following reasons: 5 patients had a previous history of congenital heart disease, 4 patients had a previous episode of carditis. Of 32 included patients, 24 (75%) were male, and mean age of participants was 3.38±1.96 years old. The past medical history of all patients was negative except for one patient who had cystic fibrosis.

Echocardiographic imaging showed 4 (12.5%) patients had cardiac involvement including 3 patients with perivascular brightness of coronary arteries and one patient with small aneurysm of the coronary arteries. One of the patients with perivascular brightness of coronary arteries had also developed tricuspid valve regurgitation (TR). In all study patients, the cTnI levels were in the normal range (all of them were lower than 0.35 ng/ml), and the NT-proBNP levels were all higher than the normal range (all of them were over than 125 pg/ml). The NT-proBNP measurements revealed a median of 678.5 (min-max, 220-5735) pg/ml.

Also, the highest level of NT-proBNP belonged to the patient who had perivascular brightness of coronary arteries (5735 pg/ml). The other two patients with perivascular brightness of coronary arteries had NT-proBNP levels of 2427 and 5276 pg/ml. The level of NT-proBNP in the patient with small aneurysm of coronary arteries was 1427 pg/ml. The mean ages of the patients with and without cardiac involvement were 2.0 ± 1.0 and 4.0 ± 2.0 years, respectively, which had no statistical difference (p=0.209, **Table.1**).

Of those without cardiac involvement, 21 (72.4%) children were male and 8 (27.6%) were female; however, all children with cardiac involvement were male (p=0.001, **Table.1**). Patients with cardiac involvement had significantly higher levels of NT-proBNP (p=0.001; **Table.2**, **Figure.1**). ROC analysis for power of the NT-proBNP in predicting the cardiac involvement in children with KD, revealed an excellent power for NT-proBNP (Area under the curve [AUC]: 1.000, p=0.001, **Figure.2**). Both sensitivity and specificity of NT-proBNP at the optimum cut-off point of 1,354 pg/ml were 100 percent.

Table-1: Characteristics of KD patients with or without cardiac involvement (n=32).

Variables		Cardiac involvement	Normal echocardiography	P-value
Age, year (mean ± SD)		2.0 ± 1.0	4.0 ± 1.0	0.209
Gender	Male (n, %)	21 (72.4)	4 (100)	0.001#
	Female (n, %)	8 (27.6)	0	
Time duration from onset of KD till referring to hospital (day, mean ± SD)		8.25 ± 1.71	7.75 ± 2.22	0.491*

KD: Kawasaki Disease; cTnI: Cardiac troponin I; NT-proBNP: Serum N-terminal pro-brain natriuretic peptide; SD: Standard deviation; *Mann-Whitney U test, #Fisher's Exact test.

Table-2: Laboratory results of cardiac biomarkers in KD patients with or without cardiac involvement (n=32).

Parameters	Cardiac involvement	Normal echocardiography	P-value
cTnI (ng/ml)	Less than 0.35	Less than 0.35	1.000
NT-proBNP (pg/ml, mean ± SD)	3716.3±2114.3	835.8 ±352.8	0.001

KD: Kawasaki Disease; cTnI: Cardiac troponin I; NT-proBNP: Serum N-terminal pro-brain natriuretic peptide; SD: Standard deviation. *Mann-Whitney U test.

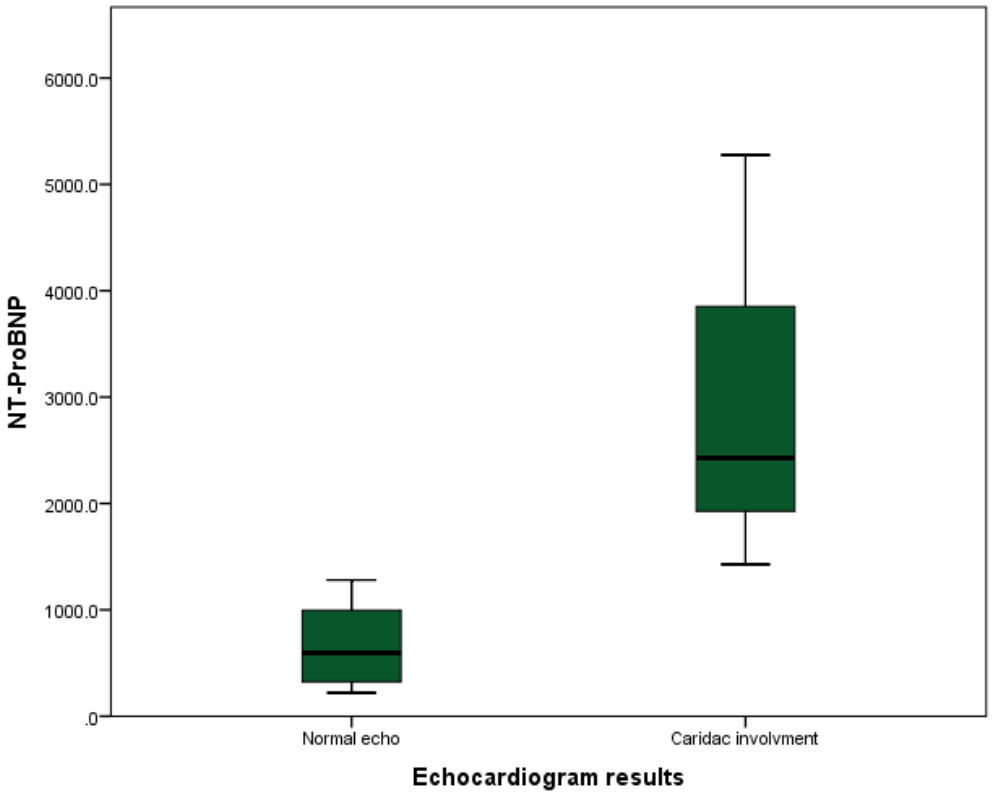

Fig.1: Boxplots of NT-proBNP levels in KD patients based on cardiac involvement (n=32). NT-proBNP: Serum N-terminal pro-brain natriuretic peptide.

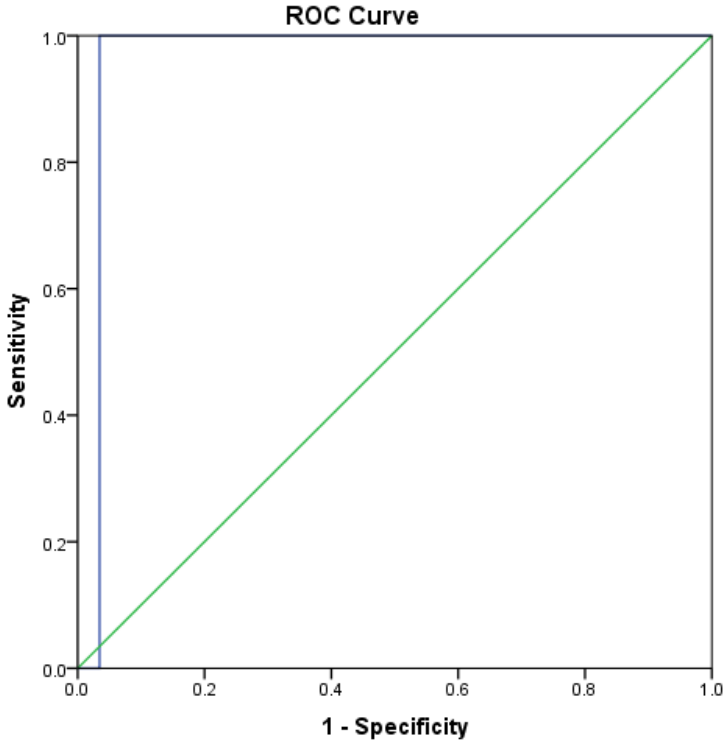

Fig.2: ROC analysis for power of the NT-proBNP in predicting the cardiac involvement in KD patients (n=32). NT-proBNP: Serum N-terminal pro-brain natriuretic peptide.

4- DISCUSSION

The current study investigated the applicability of NT-proBNP and cTnI levels in diagnosing the cardiac involvement in children with KD. Our results demonstrated that NT-proBNP was elevated in KD patients particularly in those with cardiac involvement including perivascular brightness of coronary arteries or coronary artery aneurysm; however, cTnI was in the normal range in all patients regardless of cardiac involvement. NT-proBNP showed an excellent power in predicting the presence of cardiac involvement in KD patients. There were no significant differences between the KD patients with and without cardiac involvement in age and the average days between onset of KD and referring to hospital. The majority of patients without cardiac involvement and all patients with cardiac involvement were males. It has been indicated that males are at a higher risk of developing coronary artery aneurysm than females (29). Our results were in agreement with the previous findings in value of NT-proBNP in predicting the presence of cardiac involvement (20, 21, 23). However, they had limited the definition of cardiac involvement to the development of coronary artery aneurysm but we also assessed the presence of perivascular brightness of coronary arteries as a preceding factor of developing of coronary artery aneurysm or subsequent coronary ectasia (30, 31). Though detecting this abnormality in echocardiography is qualitative and its evaluation depends on the experience of individual echocardiographers. Therefore, an objective test like serum NT-proBNP could be a useful substitute in this regard. Although Iwashima et al., found no significant difference in levels of the NT-proBNP between those patients with and without coronary artery lesions, they

reported that those patients with valvular dysfunction had significantly higher levels of NT-proBNP (23). Also, in this study, the highest level of NT-proBNP belonged to a patient with TR. It is postulated that TR in KD patients could be a great predictor in their intensive care unit (ICU) admission (32). Therefore, we expected NT-proBNP levels to be higher in those with more severe cardiac damage. However, considering that the NT-proBNP levels in other patients with sole perivascular brightness of coronary arteries (without TR) were more than in the patients with small aneurysm of coronary arteries, we could not conclude a meaningful association between NT-proBNP levels and the severity of cardiac involvement in our study. Although, if we could enroll more KD patients with cardiac involvement, declaring that association could be more accurate.

ProBNP primarily is synthesized and secreted in response to myocyte stretch. Another source of proBNP can be the intima of coronary arteries (33). Therefore, the possible mechanism behind the increase of NT-proBNP in KD patients with coronary aneurysm could be explained by the micro-damage of intima of dilated coronary arteries by turbulent bloodstream that results in releasing proBNP (34). Also, two other mechanisms have been postulated including local myocardial inflammation with subsequent production of cytokines, stimulated BNP secretion and local areas of ischemia which can affect the pericardium, myocardium, endocardium, and coronary arteries during the acute phase of KD (35, 36). Previously the optimum cut-off points for NT-proBNP levels for diagnosing the coronary artery aneurysm in KD patients were indicated to be at 1000 pg/ml with a sensitivity of 83% and a specificity of 68% by Kaneko et al., and to be at 1300 pg/ml with 95% sensitivity and 85% specificity by Yoshimura et al., which were both close to the occupied cut-off point in our study (37). However, a very recent study of Jung et al., found a lower cut-off point of 515.4 pg/ml with a sensitivity of 78.2% and a specificity of 61.6% (21). The high values of sensitivity and specificity of NT-proBNP at the cut-off point of 1354 pg/ml in our study could be due to the evaluation of perivascular brightness of coronary arteries as the preceding factor of developing of coronary artery aneurysm. Also, due to a relatively small number of included patients in the study, we may have missed some overlapping patients. Therefore, we should note some limitations of our study. As far as the appropriate and accessible setting for our study was only the children teaching hospital center, only a limited number of patients with KD, even after extending the study duration, were admitted to the study setting. Also, due to the paucity of patients with cardiac involvement, we could not properly evaluate the association between NT-proBNP levels and severity of cardiac involvement. Since that, numerous studies have failed to establish the applicability of routine serum tests (e.g. weight blood cells count, C - reactive protein, erythrocyte sedimentation rate) for diagnosing the cardiac involvement in KD patients, we did not evaluate those serum tests.

5- CONCLUSION

The result of the current study demonstrated that NT-proBNP was elevated in KD patients particularly in those with cardiac involvement; however, cTnI did not change in the serum of KD patients. Furthermore, NT-proBNP could detect the presence of cardiac involvement with an excellent power and high sensitivity and specificity (both 100 percent).Therefore, our results supports the applicability of using NT-proBNP as an excellent objective test for early detection of cardiac involvement in children with KD.

6- AUTHORS' CONTRIBUTIONS

Conceived the idea: AM. Designed the study methodology: AM, MS, SG. Conducted the study: AK, AM, SRSE. Analyzed the data: SG, SRSE. Interpreted the results: MS, SG, AM. Wrote the draft manuscript: SRSE, AK. Revised and edited the final manuscript: AM, SG. Approved the manuscript: AM, AK, MS, SG, SRSE.

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8- CONFLICT OF INTEREST: None.

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