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Diagnostic and Prognostic Value of Cardiac Biomarkers in Children with Kawasaki Disease: A State-of-the-Art Review

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Abstract

Kawasaki disease (KD) is characterized as the leading cause of acquired cardiac disease in children. Accurate and timely diagnosis of KD is of high importance for preventing its cardiac complications. However, diagnosis merely based on clinical findings has a number of challenges and, limitations. Therefore, researchers are investigating to find more objective and accurate diagnostic modalities. Cardiac biomarkers, particularly N-terminal pro b-type natriuretic peptide (NT-proBNP), are the most acknowledged diagnostic biomarkers in this regard. Accordingly, this paper reviewed some recent and related studies to evaluate the advantages and disadvantages of each cardiac biomarker.

Key Words: Children, Diagnosis, Mucocutaneous Lymph Node Syndrome, N-terminal pro b-type natriuretic peptide.

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1- INTRODUCTION

Kawasaki disease (KD) is characterized as an acute multisystem vasculitis that predominantly affects children aged six months to five years old (1-5). The incidence of KD in North America, Australia, and Europe is 4 to 25 per 100,000 in children under 5 years (6). However, in Asian countries, particularly in Japan, Korea, and Taiwan, the incidence rate is over 50 per 100,000 children, that has been increasing rapidly over the last decades (6). Although the majority of patients recover completely after the acute phase of KD, it can bring about severe cardiovascular complications that render KD the primary cause of acquired cardiac disease in children (4). A systemic vascular inflammation in different parts of the body can occur in KD; however, the involvement of coronary arteries (including the dilatation, aneurysm, and fistulae of coronary arteries) is the main concern since it can lead to some serious consequences such as myocardial infarction and death (7, 8). Coronary artery aneurysm (CAA) is reported to occur in 10–15% of KD patients over the acute phase of the disease (9, 10). Notably, the delayed diagnosis of KD is associated with a higher risk of CAA development (11). Therefore, an accurate and timely diagnosis of this disease is crucial. However, clinical examination and history taking are not completely reliable in the diagnosis of KD due to the time-sensitive nature of the disease and its symptoms (7).

Many studies have been conducted to find an appropriate biomarker with the highest sensitivity and specificity to diagnose KD. Several types of biomarkers have been suggested in this regard, including inflammatory, immunological, cardiovascular, genetic, etc. In a recent study, Chaudhary et al. reviewed the applicability of different types of biomarkers in the diagnosis of KD (12). It has been indicated that the inflammatory markers are mostly non-specific and cannot distinguish KD from many other inflammatory and infectious diseases (12-15). Moreover, studies on the immunological biomarkers have investigated small sample sizes and the clinical relevance of these biomarkers in the diagnosis and prognosis of KD patients is not well established yet (12, 16, 18). However, the cardiac biomarkers in particular N-terminal pro b-type natriuretic peptide (NT-proBNP) are the most acknowledged biomarkers in this area (12, 19-21). Considering what was mentioned, this study attempted to comprehensively review the published literature on the clinical usefulness of cardiac biomarkers for diagnosis and for predicting the clinical course of KD patients. Therefore, the aim of this study was to evaluate the diagnostic and prognostic value of cardiac biomarkers in children with KD.

2- MATERIALS AND METHODS

An expert librarian and the author meticulously searched the online databases: Medline (via PubMed), Scopus, EMBASE, and proQuest for articles published in English between 01/01/2005 and 12/20/2019. All related articles with the appropriate design were reviewed including preclinical and laboratory studies evaluating the pathophysiology of cardiac biomarkers in KD, case-control, retrospective or prospective observational studies evaluating the diagnostic or prognostic roles of cardiac biomarkers in KD, and interventional studies for therapeutic roles of cardiac biomarkers in patients or models of KD. The search strategy and keywords, as well as the number of obtained citations in the PubMed database, were completely described in the supplementary **Table.1**. We also search the bibliography of the obtained studies, and included their results in our review. The reviewer tried to include all recently published related studies with the most accurate

methodology. The focus of the majority of the studies was on NT-proBNP; however, we detected some positive results advocating the applicability of other cardiac biomarkers among the obtained studies.

3- RESULTS

The present study was conducted on 80 hospitalized children with demographic data presented in (**Table.1**). Age, gender and among children were not significant different in the intervention and control groups (P>0.05) (**Table.1**). The mean and standard deviation of the score of behavioral responses to pain in the control and intervention group were 7.95 ± 1.084 and 2.65 ± 1.577, respectively (**Table.2**). There was a significant difference between the two groups in terms of pain (P<0.001). In addition, 70% of children in the control group experienced severe pain, but most children in the intervention group (77.5%) had a little pain. There was a significant difference found by Chi-square test in terms of pain intensity in both groups (P<0.001) (**Table.3**).

Table-1: Suggested biomarkers for diagnosis of KD.

Cardiac marker	Study	Number of KD patients	Control	Outcome	Suggested/ Optimal cut-off point	Sensitivity	Specificity	Additional findings/ comment	Ref.
NT-proBNP	Rodriguez-Gonzalez et al., 2019	19 iKD	51 febrile controls	AUC=0.90	-	84	95		(90)
NT-proBNP	Choi et al., 2018a	123	40 adenoviral pharyngoconjunctival febrile controls	AUC=0.89	265 pg/mL	85	75.6		(40)
	Satoh et al., 2018	24 cKD	61 patients with respiratory syncytial virus and 50 with UTI	AUC=0.869	1555 pg/mL	80	85		(91)
	Lee et al., 2017	214 cKD 129 iKD	62 febrile controls	AUC=0.774	289 pg/mL	71.7	71.9	762 and 762 pg/mL for complete and incomplete KD (<6 months), 310 and 310 pg/mL (6–12 months), 326 and 326 pg/mL (12–24 months), and 208 and 137 pg/mL (>24 months)	(41)
	Reddy et al., 2016	25	25 age- and sex-matched febrile controls	AUC=0.954	1025 pg/mL	88	96		(42)
	Kwon et al., 2016	231	111 febrile controls	AUC=0.763	244.7 pg/mL	68.6	70.3		(42)
	Ye et al., 2015	658 cKD	300 age-matched febrile and 300 healthy children	AUC= 0.929	2095 pg/mL[#]	89.1	80.1	Although CRP and ESR show high efficiency in KD diagnosis, NTproBNP had the highest diagnostic efficiency for KD	(39)
	Lee et al., 2015b	138	50 febrile viral respiratory infections	Significantly higher NTproBNP in KD patients p<0.05	-	-	-		(92)
	Wu et al., 2015	291 cKD and 74 iKD	401 cases of unclear infectious diseases	AUC= 0.906	225.5 pg/mL	86	95		(93)
	Ye et al., 2015a	330	330 age-matched febrile and 330 healthy children	AUC= 0.923	209 pg/mL	87	80		(94)
					387 pg/mL	78	90		(94)
	Bae et al.,	24[@]	20	AUC= 0.900	1,488	84	100	Sensitivity and specificity of 88%	(95)

	2014				pg/mL			and 85%; at 1,264 pg/mL	
	Sato et al., 2013	55	54 febrile controls and 50 healthy children	Significantly higher NTproBNP in KD patients p<0.0001	-	-	-		(63)
	Shiraishi et al., 2013	149	506 control patients with acute infectious disease	AUC=0.85	Z-score >2.0	47.0	97.8	The cut- off for NTproBNP were 1,000 pg/ml for 1–11 months of age, 900 pg/ml for 1 year of age, 800 pg/ml for 2 years, 700 pg/ml for 3 years, 600 pg/ml for 4 and 5 years of age, 500 pg/ml for 6 and 7 years of age, 400 pg/ml for 8 and 9 years of age, and 300 pg/ml for 10–15 years of age.	(46)
	McNeal-Davidson et al., 2012	81 cKD	49 febrile controls and 356 healthy children	AUC= 0.881	190 pg/mL	70.4–88.9	69.4–91.8	The statistical significance for NT-proBNP AUC remained strong when cases with complete or incomplete KD were analyzed separately	(96)
	Cho et al., 2011	59	59 febrile controls	AUC= 0.78	235.2 pg/mL	66	77		(97)
	Dahdah et al., 2009	43	19 febrile controls	AUC=0.813	170 pg/mL	78	63		(36)
BNP	Kishimoto et al., 2011	54	18 age- matched controls	*p < 0.01	-	-	-		(37)
	Dahdah et al., 2009	43	19 febrile controls	BNP did not differ significantly from the diagonal reference line p = 0.11	-	-	-		(36)
	Takeuchi et al., 2007	42	62 healthy children and 38 febrile controls	*p<0.05	-	-	-	Plasma BNP level in acute KD patients was significantly higher (65±9 pg/ml) than in controls (13±2 pg/ml).	(57)
Soluble ST2	Sato et al., 2013	55	54 febrile controls, and 50 healthy controls	*p≤0.002	-	-	-	It is negatively correlated with deceleration time and illness day.	(63)
	Hoshino et al., 2019	93	88 age-matched healthy controls	Comparable between KD patients and healthy control group (p>0.05)	-	-	-		(66)
CTNI	Sato et al., 2013	55	54 febrile controls, and 50 healthy controls	Comparable between KD patients and febrile control group but significantly higher than healthy control group (p<0.05)	-	-	-	The levels of cTnI were elevated in the convalescent as compared to the acute stage of KD (p=0.0003, n=30) and normalized in all 17 subjects with late convalescent samples.	(63)
GGT	Ogata, et al., 2013	20	10 febrile controls	*p =0.006	-	-	-		(71)
	Sato et al., 2013	55	54 febrile controls, and 50 healthy controls	*p<0.0001	-	-	-		(63)
Clusterin	Yu et al., 2009	30	30 age-matched febrile controls	*p < 0.001	-	-	-		(82)

* Significantly higher biomarker level in KD patients vs control @ younger than 3 months of age # converted from ng/dL to pg/ml for better comparison; AUC, area under the curve; UTI, urinary tract infection; RSV, Respiratory syncytial virus; KD, Kawasaki disease; iKD, incomplete Kawasaki disease; cKD, complete Kawasaki disease; GGT, gamma glutamyl transpeptidase.

3-1. Pathophysiology KD in relation with cardiac biomarkers

Both innate and adaptive immune systems are engaged in the pathophysiology of KD. Some immune system mediators are indicated to play essential roles in arterial wall destruction in KD, including immune-related cells (such as neutrophils, $CD8^+$ T

cells, dendritic cells, and monocyte/macrophages), and some cytokines (such as interleukin (IL)-1, IL-6, IL-12, and transforming growth factor-beta (TGFb)) (22-26). The inflammatory process of KD leads to internal elastic lamina destruction, the smooth muscle cells necrosis, myointimal proliferation, and subsequently, CAA (9, 10, 27). Also, some studies suggest the role of imbalances of matrix metalloproteinases (MMPs) or MMP/tissue inhibitor of MMP in the pathophysiology of the development of CAA in KD (10). Both the arterial wall and the myocardium are affected by the inflammatory process of KD (28). The involvement of cardiac components in this disease induces secretion of cardiac-related substances, which can be detected in body fluids to serve as biomarkers. The secretion of cardiac biomarkers does not necessarily occur in KD patients with coronary artery involvement and they can even be detected in those without any evident clinical signs or para-clinical findings of CAA (21). Myocarditis is the most primitive feature of KD and occurs in nearly all KD patients in the early days of the disease. Harada et al. performed cardiac biopsies in over 200 patients after the diagnosis of KD and demonstrated that there were varying degrees of cellular infiltration, fibrosis, and abnormal myocardial structure in all KD patients regardless of coronary arteries involvement (29). Therefore, one of the possible explanations of increase in cardiac biomarkers in KD patients is through myocarditis. The specific mechanism of increase in the level of each cardiac biomarker is discussed separately within the following sections.

3-2. NT-proBNP and BNP

3-2-1. NT-proBNP and BNP in KD diagnosis: BNP and NT-proBNP are established biomarkers of acute and chronic heart failure and become elevated in acute myocardial injuries (30, 31). Also, they can serve as the diagnostic markers of cardiac involvement in some conditions, such as amyloidosis and Marfan syndrome (32). ProBNP (prohormone) is cleaved by the atrial natriuretic peptide-converting enzyme into BNP and NT-proBNP which are its physiologically active and inactive fragments, respectively. BNP has some physiological roles such as diuresis, vasodilation, renin-angiotensin-aldosterone secretion inhibition, reduced sympathetic tone, antifibrotic and anti-inflammatory activities, etc. (33). Although NT-proBNP has no particular physiological role, it is proposed to be more appropriate for the diagnosis of KD due to its longer half-life (34-36). Since Dahdah et al. demonstrated higher applicability of NT-proBNP for diagnosis of KD as compared to BNP, the majority of investigations have focused on NT-proBNP and only a few studies have been conducted using BNP (19, 35-38). Although the majority of studies have reported a significant diagnostic value of NT-proBNP for KD, there is little consensus regarding the optimal cut-off point, sensitivity, and specificity of measuring it (**Table.2**). The optimal cut-off point has been reported in the range of 170 to 2095 pg/ml (36, 39). These suggested cut-off points yielded a sensitivity of 47.0 up to 89.1 percent and specificity of 63 up to 100 percent. One of the possible reasons for this discrepancy is that the studies have compared the NT-proBNP level of KD patients with different control groups. For instance, Choi et al. included 40 febrile patients with adenoviral pharyngoconjunctivitis as control group reporting a cut-off point of 265 pg/mL (area under the curve [AUC]=0.89, sensitivity and specificity of 85% and 75.6%, respectively) (40). Satoh et al. compared the NT-proBNP level in 24 KD cases with 61 patients with respiratory syncytial virus and 50 patients suffering from urinary tract infection; they reported a considerably higher cut-off point of 1555 pg/mL (AUC=0.869, sensitivity, and

specificity of 80% and 85%, respectively) (46). Moreover, the control group of other studies comprised febrile patients due to a variety of known or unknown causes (39, 41-43). Another challenge is the age-dependent pattern of the physiologic serum levels of NT-proBNP (44). NT-proBNP is considerably high in newborns, drops a few days after birth, and continues to further decrease with lower rate thereafter throughout early childhood (44, 45). Hence, in a few studies, the investigators tried to find age-based cut-off points and z values (41, 46). In this regard, Lee et al. evaluated the level of 214 KD patients fulfilling complete criteria (complete KD), and 129 patients with incomplete KD and compared it with 62 febrile patients. They reported an overall NT-proBNP cut-off point of 289 pg/mL (AUC=0.774). Furthermore, they suggested age-dependent NT-proBNP cut-off points of 762 and 762 pg/mL for complete and incomplete KD, respectively in under six months of age, 310 and 310 pg/mL in 6–12 months, 326 and 326 pg/mL in 12–24 months, and 208 and 137 pg/mL in more than 24 months (41). Another study by Shiraishi et al. indicated relatively higher age-based cut-off points for NTproBNP, including 1,000 pg/ml for 1–11 months of age, 900 pg/ml for 1 year, 800 pg/ml for 2 years, 700 pg/ml for 3 years, 600 pg/ml for 4 and 5 years, 500 pg/ml for 6 and 7 years, 400 pg/ml for 8 and 9 years, and 300 pg/ml for 10–15 years of age (46). Two meta-analyses tried to perform an inclusive assessment of the applicability of NTproBNP in the diagnosis of KD through the evaluation of studies conducted before 2016 (47, 48). Lin et al. reported a pooled sensitivity, specificity, and area under the summary ROC curve of 0.89 (95% CI 0.78 to 0.95), 0.72 (95% CI 0.58 to 0.82), and 0.87 (95% CI 0.83 to 0.89). Accordingly, Yu et al. reported similar overall sensitivity, specificity, and area under the summary ROC curve. Moreover, it was notable that across those five studies which adopted the threshold of approximately 200 ng/L, the overall sensitivity and specificity were 0.85 (95% CI: 0.78 - 0.90) and 0.76 (95% CI: 0.69 - 0.82), respectively. After these studies, two other studies also detected a cut-off point of approximately 200 ng/L, in which both sensitivity and specificity were close to that reported by Yu et al. (40, 41). Therefore, despite some significant limitations of available studies, such as the considerable heterogeneity among studies, small sample size, suboptimal study design, ambiguity of the reported data about the important factors that could alter the level of NT-proBNP, the most successful cut-off point until now has been approximately 200 ng/L. However, future well-crafted studies with larger sample sizes and inclusive control groups are needed to confirm it. Furthermore, as indicated by Albers et al., the results of studies about NT-proBNP using different assays may not be comparable considering that different assay methods such as Roche NT-proBNP assay and the Biomedical NT-proBNP assay bring about diverse results (49). Therefore, future studies need to use matched and standard measurement modalities.

3-2-2. Specific pathophysiology of increase in NT-proBNP in KD: NT-proBNP is synthesized and secreted from both myocardium in response to myocyte stretch and the intima of coronary arteries (50). Some proposed mechanisms of increase of NT-proBNP in KD patients are as follows: local areas of ischemia can affect the pericardium, myocardium, endocardium, and coronary arteries during the acute phase of KD leading to secretion of NT-proBNP. Moreover, local myocardial inflammation with subsequent production of cytokines can also result in the stimulation of NT-proBNP secretion (34, 51). It is denoted that TNF-α in the acute phase of KD can lead to NT-proBNP elevation (52). Moreover, the increase of

NT-proBNP in KD patients with CAA could be due to the micro-damage to the intima of coronary arteries caused by the turbulent bloodstream in dilated coronary arteries (53).

3-2-3. Prediction and diagnosis of cardiac involvement: Recently, we demonstrated that NT-proBNP can serve as an excellent predictor of cardiac involvement in KD patients (21). It is significantly elevated in the serum of KD patients with early stages of cardiac involvement (21). Although some studies have noted that NT-proBNP failed to propose a further diagnostic value for cardiac involvement in KD, the majority of the studies have confirmed its applicability in this regard (**Table.2**). A recent study with a considerably large sample size of 5,151 KD patients, including 524 (9.8%) KD patients with cardiac involvement demonstrated that NT-proBNP was significantly higher in KD patients with cardiac involvement; however, it had poor value in the prediction of cardiac involvement (AUC=0.530), and no significant association with risk of coronary artery lesion in the multivariate logistic regression analyses (20). One of the possible reasons for this discrepancy in reported data of the studies is the limitations of echocardiography as the current standard strategy for evaluation of cardiac involvement in KD patients. Detection of cardiac involvement in KD patients by this method is largely operator-dependent. Trained pediatric cardiologists should perform the examination of coronary artery abnormalities in small children; however, they may not always be available, particularly in developing countries and those studies with larger sample sizes, and adult cardiologists possibly performed it (20, 54, 55). However, due to lack of expertise and experience on children, they cannot meticulously examine the coronary arteries to detect the KD-related pathologies. Moreover, these abnormalities are subtle and hard to detect in the majority of cases. As a result, there is a high possibility for some pathologies to be missed in these circumstances (56). It is noted that this issue is prevalent even over the examination of gross coronary artery abnormalities (56). Moreover, consensus about the reporting of echocardiography findings in children with KD is still lacking in developing countries (56). This challenge further highlights the importance of finding novel objective tests for the evaluation of these patients. A few studies have also assessed the applicability of BNP for the diagnosis of cardiac involvement in KD patients (**Table.2**). Hashimoto et al. reported that left ventricular dysfunction was significantly correlated with BNP (38). Correspondingly, Takeuchi et al. reported a significant negative correlation between week 1 peak systolic velocity and plasma BNP level (57). Another study demonstrated that serum BNP level was significantly higher in KD patients with diastolic abnormalities (35). Despite the promising results of these studies, the need for a comprehensive evaluation of BNP utility for proper detection of cardiac involvement in the early stages still exists.

3-2-4. Prediction of intravenous immunoglobulin (IVIG) resistance: IVIG is the major part of standard treatment for KD. However, 10 to 20% of KD patients do not properly respond to IVIG treatment (58). Timely prediction of this phenomenon can be helpful in dose adjustment of IVIG treatment. Many studies have reported successful prediction of IVIG resistance by measurement of NT-proBNP with relatively high sensitivity and specificity (**Table.3**). However, there are still similar limitations to those, which existed in the diagnosis of KD. Of note, there is a wide discrepancy in reported cut-off points ranging from 360 pg/ml to 3755 pg/ml. The two largest studies

investigating this issue are the studies conducted by Kim et al., and Ye et al., which included 5151 KD patients with 524 IVIG-resistant cases and 658 KD patients with 125 IVIG-resistant cases, respectively (20, 39). Although they both demonstrated a significantly higher serum level of NT-proBNP in IVIG-resistant cases, considerably divergent cut-off points are proposed by these studies. Recently, Shao et al. reported optimal age-based cut-off points of 3710, 2800, and 2480 pg/ml for those aged 2–6 years, 1–2 years, and <1 year, respectively (59). The overall cut-off point for all KD patients was 3755 pg/ml with 44 and 84.1 percent sensitivity and specificity, respectively. Providing these age-based cut-off points improved the sensitivity considerably as compared with the overall cut-off point but moderately reduced the specificity (59).

Table-2: Biomarkers in prediction/diagnosis of cardiac involvement in KD patients.

Cardiac marker	Study	Number of KD patients	Number of KD patients with CA sequelae	Outcome	Suggested/ Optimal cut-off point	Sensitivity	Specificity	Comment	Ref.
NT-proBNP	Molaei et al., 2019	32	4 (12.5%)	*AUC=1.000	1354 pg/ml	100	100		(21)
	Jung et al., 2019	109	23 (21.1%)	*AUC= 0.749	515.4 pg/ml	78.26	61.63		(98)
	Satoh et al., 2018	41	5 (21%)	No significant difference between KD patients with or without CA sequelae	-	-	-		(91)
	Kim et al., 2018	5,151	524 (9.8%)	*AUC=0.530	709 pg/mL	41.2	70.5	The multivariate logistic regression analyses showed only CRP was associated with risk for CAL, not NT-proBNP	(20)
	Xie et al., 2017	560	153 (27.32%)	No significant difference between KD patients with or without CA sequelae: p =0.069 for cKD and p =0.869 for iKD	-	-	-		(99)
	Reddy et al., 2016	25	8 (32%)	*p = 0.013	-	-	-		(42)
	Jun et al., 2016	131	17 (12.9%)	*p=0.001	-	-	-		(100)
	Kang et al., 2015	20 infantile KD patients	16 infantile febrile patients	*AUC= 0.889	700 pg/ mL	78	88		(101)
	Ye et al., 2015a	303	65 (19.7)	No significant difference between KD patients with or without CA sequelae	-	-	-		(94)
	Adjagba et al., 2015	109	18 (16.7%)	High NT-proBNP level was associated with coronary artery dilatation at onset in 22.2 versus 5.6% for normal NT-proBNP (odds ratio 4.8 [95% CI: 1.05–22.4]; p=0.031).	0.716 ± 0.059 pg/mL	Z-score-related specificity and sensitivity levels of 0.889–0.772	0.378–0.589		(102)
	Iwashima and Ishikawa, 2013	54	17 (31.4%)	No significant difference between KD patients with or without CA sequelae	-	-	-		(103)
	Yoshimura et al., 2013	80	19 (23.7%)	*AUC=0.932	1300 pg/mL	95	85		(104)
	Kaneko et al., 2011	43	6 (13.9%)	*AUC=0.788	1,000 pg/mL	68	83		(105)
BNP	Hashimoto et al., 2015	50	-	Mitral annular plane systolic excursion (marker of left ventricular dysfunction) had a significant negative correlation with Log-BNP ($r = -0.45$, $p < 0.0039$).	-	-	-		(38)

	Takeuchi et al., 2007	42	-	There was a significant negative correlation between week 1 peak systolic velocity and plasma BNP level (r=–0.55, p=0.0001).	-	-	-		(57)
	Kurotobi et al., 2005	25	6 (24%)	Significantly higher in KD with diastolic abnormalities (p < 0.01)	-	-	-		(35)
CTNI	Molaei et al., 2019	32	4 (12.5%)	CTNI was not elevated in KD patients with or without CAA					(21)
Clusterin	Yu et al., 2010	47	14 (29.7%)	-	11.9 mg/l	69.7	64.3	Relative risk of CAA in clusterin≥12 = 4.53 (95% CI 1.060-19.347%, P = 0.014)	(83)

* Biomarker was significantly higher in those with CA sequelae; AUC, area under the curve; KD, Kawasaki disease; iKD, incomplete Kawasaki disease; cKD, complete Kawasaki disease; CAA, coronary artery aneurysm; CA, coronary arteries; BNP, brain natriuretic peptide.

Table-3: Biomarkers in prediction/diagnosis of IVIG resistance in KD patients.

Cardiac marker	Study	Number of KD patients	Number of KD patients with IVIG resistance	Outcome	Suggested/ Optimal cut-off point	Sensitivity	Specificity	Comment	Ref.
NT-proBNP	Shao et al., 2019	393	54 (13.7%)	-	3755 pg/ml	44	84.1	Optimal age-based cut-off points of 3710, 2800, 2480 pg/ml for those aged 2–6 years, 1–2 years and < 1 year, respectively	(59)
	Kim et al., 2018	5151	524 (10.2%)	*p<0.001	503 pg/mL	51.9	61.7	The multivariate logistic regression analyses showed that the PMN, AST, ALT, CRP, and NT-proBNP levels were significantly higher in the IVIG-resistant group compared with the IVIG-responsive group in patients with KD	(20)
	Xie et al., 2017	410 cKD	30(7.32%)	*p=0.000	1300 pg/ml	73.91	76.43		(99)
		150 iKD	26(17.33%)	*p=0.022	360 pg/ml	78.57	56.67		(99)
	Reddy et al., 2016	25	3	Comparable between IVIG-resistant and IVIG-responsive patients p = 0.425	-	-	-		(42)
	Jun et al., 2016	131	28 (21.4%)	Comparable between IVIG-resistant and IVIG-responsive patients p = 0.051	-	-	-		(100)
	Ye et al., 2015a	330	60 (18.1%)	*AUC= 0.73	1573 pg/ml	70	61		(94)
	Ye et al., 2015b	658	125 (19.1%)	*p=0.015	3100.1 pg/dL	53	85.7		(39)
	Lee et al., 2014	91	11 (12%)	*P=0.001	-	-	-		(58)
	Cho and Kang, 2014	75 cKD	8 (10.6%)	NT-proBNP Z-score was comparable between IVIG-resistant and IVIG-responsive patients p = 0.190	-	-	-		(106)
		77 iKD	9 (11.6%)	NT-proBNP Z-score was comparable between IVIG-resistant and IVIG-responsive patients p = 0.118	-	-	-		(106)
	Kim et al., 2013	135	22 (16.2%)	*p < 0.05	1093 pg/mL	70	76.5		(107)
	Yoshimura et al., 2013	80	17 (21.2%)	*AUC= 0.724	800 pg/mL	71	62		(104)
	Park et al., 2013	309	30 (9.7%)	*p = 0.017	-	-	-		(108)

	McNeal-Davidson et al., 2012	81	16 (19.7%)	NT-proBNP was comparable between IVIG-resistant and IVIG-responsive patients (p = 0.294)	-	-	-		(96)
	Kim et al., 2011	129	22 (17%)	*p=0.000	479 pg/mL	78.9%	86.0%		(109)
GGT	Xing et al., 2015	20	8 (40%)	GGT level between IVIG-resistant and IVIG-responsive patients was comparable p>0.05	-	-	-		(73)
	Cho et al., 2014	77 iKD	9 (11.6%)	GGT level between IVIG-resistant and IVIG-responsive patients was comparable p=0.225	-	-	-		(75)
		75 cKD	8 (10.6%)	GGT level between IVIG-resistant and IVIG-responsive patients was comparable P=0.089	-	-	-		(75)
	Yi et al., 2014	54	17 (31.4%)	GGT level between IVIG-resistant and IVIG-responsive patients was comparable p=0.365	-	-	-		(74)
	Ogata, 2013	20	10 (50%)	GGT level between IVIG-resistant and IVIG-responsive patients was comparable p>0.05	-	-	-		(71)
	Tremoulet, 2011	380	-	*p=0.006	-	-	-		(14)
	Tremoulet, 2008	362	60 (16.5%)	*p=0.0001	60	-	-		(72)
	Sano et al., 2007	25	10 (40%)	GGT level between IVIG-resistant and IVIG-responsive patients was comparable p=0.076	-	-	-		(76)
Clusterin	Ou-Yang et al., 2013	63	5 (7.6%)	The difference between clusterin level before and after treatment is significantly higher in IVIG resistant patients (p=0.040) and can predict IVIG resistance (AUC=0.78)	8.52 mg/L	80	74.1	The level of clusterin before treatment was comparable between IVIG-resistant and IVIG-responsive patients.	(84)

IVIG, intravenous immunoglobulin, AUC, area under the curve; KD, Kawasaki disease; iKD, incomplete Kawasaki disease; cKD, complete Kawasaki disease, GGT, gamma-glutamyl transpeptidase. *biomarker was significantly higher in IVIG resistant patients.

3-3. Cardiac troponin T and I (CTNI)

Cardiac troponins (cardiac troponin T and I) are predominantly released from injured heart muscle cells and are considered as sensitive and specific markers to diagnose acute coronary syndromes or myocardial damage such as acute myocarditis (60). Dysfunctions of endothelia of the coronary arteries, induced by inflammatory factors in KD, may lead to cardiac-muscle damage and subsequent release of cardiac troponins (61). A few studies have reported elevated cardiac troponin I (CTNI) in KD patients (7, 62). However, Sato et al. using a highly sensitive assay reported that the level of CTNI was significantly higher in acute KD patients than the healthy control group, but it was similar to that in other febrile non-KD patients. Furthermore, it was significantly elevated in the convalescent phase of KD and normalized within two years of disease onset (63). A meta-analysis including the studies on the association between coronary artery lesions in Chinese KD patients and CTNI revealed that CTNI and other nine non-cardiac markers are associated with the development of coronary artery lesions (61). However, we did not find any elevation from the normal range in 32 KD patients with or without coronary artery lesions in our study (21). Qiu et al. evaluated a series of serum markers in KD shock syndrome. CTNI and NT-proBNP were among those markers significantly elevated in patients with KD

shock syndrome as compared to other KD patients (64). Despite the promising results of these studies, comprehensive investigations are needed to confirm the applicability of CTNI as a diagnostic and prognostic test in KD patients.

3-4. Soluble suppression of tumourigenicity-2 (ST2)

ST2 receptor is one of the Toll-like/IL-1 receptor family members. It contributes to stress-induced cardioprotective signaling resulting in some antihypertrophic and antifibrotic effects. It can be detected in both bound and soluble forms (sST2). The sST2 is reported to have valuable diagnostic and prognostic roles in heart failure (65); but limited data is available for its applicability in pediatric patients. Sato et al. evaluated 55 KD patients as compared with a similar number of febrile and healthy control participants and demonstrated significantly higher ST2 levels in KD patients, in particular in the early days after onset of disease (63). However, in a recent study, Hoshino et al. found no significant difference between the serum level of sST2 between KD patients and healthy subjects (66). Therefore, this biomarker warrants more studies in KD patients to establish its value in diagnosis and prognosis.

3-5. Gamma-glutamyl transpeptidase

Gamma-glutamyl transpeptidase (GGT) is an extracellular glutathione catabolizing enzyme. It is normally found in the serum and on the outer surface of numerous cell types and is active in a variety of organs, including proximal renal tubule, pancreas, and intestine, but primarily in the liver (67, 68). GGT plays an essential role in the pathophysiology of a series of cardiovascular diseases, including coronary artery disease, heart failure, hypertension, etc. (69). A significant correlation between GGT and other cardiac biomarkers is detected in KD patients (63). Moreover, the addition of GGT to a panel of serum markers (absolute neutrophil count, erythrocyte sedimentation rate, concentrations of alpha-1-antitrypsin, C-reactive protein, and fibrinogen, and platelet count) improved the diagnosis of KD and increased AUC from 0.91 to 0.96 (70). Ogata et al. indicated that GGT was significantly higher in KD patients as compared to patients with other febrile illnesses (71). Furthermore, GGT is significantly higher in the serum of KD patients with IVIG resistance (14, 72). A new scoring system including GGT (GGT$\geq$ 60 IU/L [1 point], % bands $\geq$ 20 [2 points], illness day at diagnosis $\leq$ 4 days [1 point], and zHgb $\leq$ 2.0 [1 point]) yielded a sensitivity and specificity of 73.3% and 61.9%, respectively (72). However, several studies failed to demonstrate any significant difference in the serum level of GGT between IVIG-responsive and -resistant patients (71, 73-76). Nevertheless, a meta-analysis confirmed that GGT was significantly higher in IVIG-resistant KD patients (GGT = 0.551, 95 %CI 0.157–0.946, p = 0.006) (77). Wang et al. investigated the biological mechanisms that relate IVIG resistance in KD patients with elevated GGT levels. Finally, they indicated that higher GGT level may intensify IVIG resistance through blocking IVIG-induced neutrophil apoptosis (78). Although these studies have revealed significant elevation in GGT level in IVIG-resistant KD patients, we could not find any study evaluating specifically the diagnostic or prognostic value of GGT in this regard.

3-6. Clusterin

Clusterin is expressed in most tissues and has several functions such as regulation of complement activity, lipid transport, apoptosis, and cell interaction. Recently, it has been demonstrated that clusterin is significantly elevated in the plasma of patients with myocardial infarction and is associated with survival of patients with

heart failure (79-81). Moreover, Yu et al. plasma samples of KD patients as compared to other febrile controls (82). Likewise, in 47 KD patients including 14 with coronary artery lesions, the plasma level of clusterin was significantly associated with the occurrence of coronary artery lesions (83). Additionally, Ou-Yang et al. demonstrated that the difference between before and after treatment in the level of plasma clusterin is significantly higher in IVIG-resistant KD patients and can predict resistance to IVIG (84).

3-7. Other cardiac biomarkers

A few studies reported some promising results using other cardiac biomarkers. Urine filamin C is reported to be a novel candidate molecular marker of KD (85). Galectin-3 is suggested as a marker of myocardial and vascular fibrosis in KD patients with CAA (86, 87). Pre-IVIG D-dimer showed a statistically significant direct correlation with IVIG doses, suggesting possible applicability of this parameter to predict IVIG resistance (88). Lee et al. postulated that creatine kinase-MB was significantly higher in IVIG-resistant patients (58). However, Niu et al. detected a similar level of creatine kinase-MB in KD patients with or without cardiac involvement (89). The findings of these studies may lay the foundation for future investigations in this area. However, it is not recommended to apply them to clinical settings.

4-CONCLUSION

Several cardiac biomarkers have been suggested for diagnosis and prediction of cardiac involvement and resistance to IVIG. Despite a series of major limitations of related studies, NT-proBNP is the most prominent cardiac biomarker, which has been proposed in both diagnosis and prediction of cardiac involvement and resistance to IVIG. However, little consensus exists on the best way to denoted that it is significantly elevated in distinguish cut-off point of NT-proBNP. Therefore, this issue remains to be investigated by future studies. Regarding the other cardiac biomarkers, some studies advocate the applicability of CTNI, sST2, GGT, and in particular Clusterin. However, further studies are warranted to establish their value in the diagnosis and prognosis of KD.

5- ABBREVIATION

AUC: Area under the curve
CAA: Coronary artery aneurysm
CTNI: Cardiac troponin I
GGT: Gamma-glutamyl transpeptidase
IL: Interleukin
IVIG: Intravenous immunoglobulin
KD: Kawasaki Disease
MMPs: Matrix metalloproteinases
NT-proBNP: N-terminal pro b-type Natriuretic Peptide
sST2: Soluble ST2
TGFb: Transforming growth factor-beta.

6- CONFLICT OF INTEREST: None.

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