

BMJ Open Usefulness of natriuretic peptide for the diagnosis of Kawasaki disease: a systematic review and meta-analysis

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ABSTRACT

Objective: To examine the diagnostic value of serum B-type natriuretic peptide (BNP) in acute Kawasaki disease (KD).

Design: Systematic review and meta-analysis.

Data sources: A systematic literature search strategy was designed and carried out using MEDLINE, EMBASE and the Cochrane Library from inception to December 2013. We also performed manual screening of the bibliographies of primary studies and review articles, and contacted authors for additional data.

Study eligibility criteria: We included all BNP and NT-pro (N-terminal prohormone) BNP assay studies that compared paediatric patients with KD to patients with febrile illness unrelated to KD. We excluded case reports, case series, review articles, editorials, congress abstracts, clinical guidelines and all studies that compared healthy controls.

Primary and secondary outcome measures: The performance characteristics of BNP were summarised using forest plots, hierarchical summary receiver operating characteristic (ROC) curves and bivariate random effects models.

Results: We found six eligible studies including 279 cases of patients with KD and 203 febrile controls. Six studies examined NT-proBNP and one examined BNP. In general, NT-proBNP is a specific and moderately sensitive test for identifying KD. The pooled sensitivity was 0.89 (95% CI 0.78 to 0.95) and the pooled specificity was 0.72 (95% CI 0.58 to 0.82). The area under the summary ROC curve was 0.87 (95% CI 0.83 to 0.89). The positive likelihood ratio (LR₊ 3.20, 95% CI 2.10 to 4.80) was sufficiently high to be qualified as a rule-in diagnostic tool in the context of high pre-test probability and compatible clinical symptoms. A high degree of heterogeneity was found using the Cochran Q statistic.

Conclusions: Current evidence suggests that NT-proBNP may be used as a diagnostic tool for KD. NT-proBNP has high diagnostic value for identifying KD in patients with protracted undifferentiated febrile illness. Prospective large cohort studies are needed to help determine best cut-off values and further clarify the role of NT-proBNP in the diagnosis process of KD.

Strengths and limitations of this study

- Currently, diagnosis of Kawasaki disease (KD) in the early course of disease remains challenging, and our review suggests that N-terminal prohormone serum B-type natriuretic peptide (NT-proBNP) may represent a valuable diagnostic tool for KD.
- A bivariate random effect model was used to account for the inherent negative correlation arising from different cut-off values reported by different studies.
- Summary likelihood ratios were used to measure predictive accuracy.
- Considerable heterogeneity was found in the pooled estimates and, unfortunately, the small number of studies does not allow for further exploration of the source of heterogeneity by sensitivity analysis or meta-regression.
- There are limited data available for analysis of KD diagnostic accuracy at different cut-off values, so we cannot conclusively suggest the best cut-off value.

INTRODUCTION

Kawasaki disease (KD) is a potentially fatal acute childhood vasculitis. It is the most common cause of acquired heart disease in children in developed countries.¹ The morbidity and mortality associated with KD is primarily caused by coronary artery aneurysms, which may occur in 20–25% of untreated patients.^{1 2} Early treatment with intravenous immunoglobulin and, recently, with the addition of prednisolone, has been shown to reduce the incidence of coronary aneurysms. On the contrary, if the treatment is delayed, the incidence of coronary artery aneurysms may dramatically increase.²

Timely diagnosis of KD is sometimes a challenging task for clinicians. There is no specific test or pathognomonic clinical features for definitive diagnosis of KD. The

epidemiological case definition includes fever and at least four of five clinical criteria: changes in the extremities, polymorphous exanthema, bilateral conjunctival injection, changes in the lips and oral cavity, and cervical adenopathy.^{1–3} Sometimes, patients have some major clinical features but do not fulfil the complete diagnostic criteria. These patients are diagnosed as having ‘incomplete’ or ‘atypical’ KD. They are more commonly young infants and carry the same risk for coronary artery aneurysms as those with complete presentations.⁴ Failure to diagnose these patients is associated with increased coronary morbidity. Echocardiography usually plays a key role in early diagnosis of children with incomplete KD, but it requires a specialised technique and is not widely available for frontline physicians. A biomarker that can indicate early on the possibility of cardiac involvement in patients with protracted fever may help select appropriate patients for further confirmatory cardiac sonography.

B-type natriuretic peptide (BNP) or its inactive cleavage product N-terminal pro-BNP (NT-proBNP) is synthesised and released by ventricular cardiomyocytes in response to myocardial wall stress and ischaemia.⁵ Elevated levels of BNP and NT pro-BNP have been shown to be associated with adverse outcomes in a number of settings, including acute coronary syndrome, congestive heart failure and patients undergoing major cardiac surgery.⁶ Myocardial involvement in KD is widely recognised. The cardiac pathology associated with KD includes coronary artery aneurysms, myocarditis, endocarditis, mild valvular regurgitation and pericardial effusion.^{7–9}

Recently, a number of studies have examined the predictive value of BNP or NT-proBNP for differentiating KD from other febrile illnesses.^{3 10–17} The accuracy estimates of individual studies, however, vary widely among studies. We therefore carried out a systemic review and meta-analysis to summarise evidence on the usefulness of this biomarker in the assessment of patients in whom KD was suspected.

METHODS

We followed the PRISMA guidelines for meta-analysis of diagnostic studies in our data extraction, analysis and reporting.¹⁸

Study selection

We searched three electronic databases (PubMed, EMBASE and the Cochrane Library), through December 2013, for records of studies that evaluated the diagnostic performance of serum or plasma BNP for diagnosis of KD. We used broad search terms to avoid missing studies. The search terms used were “natriuretic peptide or b-type natriuretic peptide or n-terminal pro-b type natriuretic peptide or BNP or NT-proBNP” crossed with ‘Kawasaki disease or mucocutaneous lymph node syndrome’. The same strategy with EMTREE tools was used to search the EMBASE database without setting any time

or language restrictions. We also performed manual screening of the bibliographies of primary studies and review articles and contacted authors for additional data. Initial eligibility was determined independently by two reviewers. Disagreements between the reviewers were resolved by additional reviewers in a consensus meeting.

We included studies comparing patients with KD and patients with febrile illness unrelated to KD. For inclusion, studies were required to have a study population of paediatric patients. Studies that compared healthy controls were not eligible for inclusion, because they tend to overestimate the sensitivity and specificity. BNP assays from any manufacturer were eligible. We excluded case reports, case series, review articles, editorials, congress abstracts and clinical guidelines. The study inclusion and exclusion process is summarised in [figure 1](#).

Data extraction

From each of the included studies, we extracted information about the publication (title, authors and journal), study population, comparison group, study design (case-control or cohort), assay used for BNP or NT-proBNP measurement, cut-off value, criteria used for the diagnosis of KD and data for 2×2 contingency tables. We also extracted patient data regarding the sensitivity and specificity with the BNP or NT-proBNP assay. If multiple cut-offs were reported in one study, we consistently used the cut-off that optimised the Youden index.

Quality assessment of the included studies

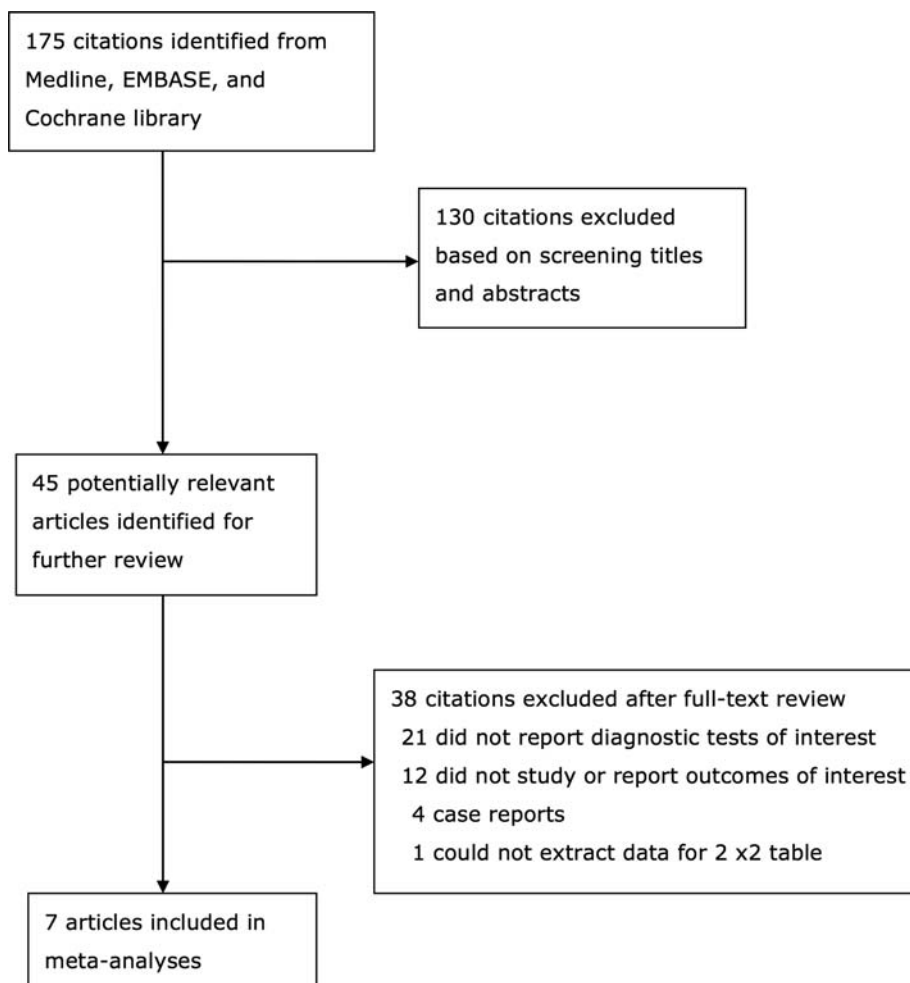
Methodological quality was assessed using the quality assessment for studies of diagnostic accuracy (QUADAS) tool.¹⁹ We used the international diagnostic criteria for KD as a reference standard. The spectrum of patients included in a study was considered to be representative of the target population if the patients had clinical manifestation suspected of KD. We considered partial and differential verification bias if all the paediatric patients were not assessed with the same reference standard. In addition, we considered there was no incorporation bias if the diagnosis of KD was established strictly based on the KD diagnostic criteria, regardless of the value of serum BNP or NT-proBNP levels.

Data analysis

To evaluate the diagnostic performance of BNP testing for KD, we performed a comparison evaluating the performance of BNP assays for case patients with proven KD compared with control febrile patients without KD. Data were extracted to construct 2×2 tables, which were used to calculate sensitivity and specificity.

The sensitivity and specificity estimates were pooled by using bivariate random effects regression models based on the recommendation of the Cochrane Diagnostic Test Accuracy Working Group. The bivariate model takes into consideration the potential negative correlation between sensitivity and specificity by explicitly incorporating this correlation factor as well as between-study

Figure 1 Flow chart describing systematic literature search and study selection process.



heterogeneity in the analysis.¹⁹ The model was also used to construct a hierarchical summary receiver operating characteristic (HSROC) curve and to calculate the area under the curve (AUC). Confidence regions for the summary points and the prediction regions of 95% of future studies were plotted in the HSROC. To deal with values of zero in 2×2 contingency tables, continuity correction was performed by adding half to each cell. This correction also helped to reduce the small study bias. Heterogeneity between studies was tested using the Cochran Q statistic ($p < 0.05$) and quantified with the I^2 statistic. The value of the I^2 statistic describes the variation of effect size that is attributable to heterogeneity across studies.²⁰ Statistically significant heterogeneity was considered present if I^2 was greater than 50%. Subgroup analyses were performed on studies using the NT-proBNP or BNP assays. We tested the publication bias by Egger's test for the asymmetry of funnel plots by regression methods. Skewed and asymmetrical funnel plots indicate the presence of publication bias.²¹ All statistical analyses were conducted using the STATA software V.11.0 (Stata Corp, College Station, Texas, USA). All statistical tests were two tailed, and statistical significance was defined as a p value less than 0.05.

RESULTS

In total, 175 studies (excluding duplicates) were identified using the search strategy outlined above (figure 1). After the first round of screening of title and abstracts, 131 ineligible studies, case reports, or reviews were excluded. Forty-four potentially relevant studies were retrieved for full text evaluation, of which 38 studies were further excluded for varying reasons, leaving 6 that met the inclusion criteria.

The seven eligible studies included 428 patients of confirmed KD and 709 control febrile patients without KD. Table 1 presents a summary of the characteristics of the seven included studies and patients. The number of patients with KD in each study ranged from 6 to 149, and their mean/median ages ranged from 19 to 52 months. All studies used the appropriate prospective case-control designs and the outcome is verified by the classical clinical diagnostic criteria for KD, which requires the presence of 5 days and four of the five principal clinical features.² Six studies measured the NT-proBNP at the acute stage of KD, while only one study measured BNP. The cut-off values of NT-proBNP ranged from 98 to 260 pg/mL. Table 2 summarised the characteristics of the test kit, characteristics of control

Table 1 Characteristics of patients for included studies

Author, country, year	Case/controls (N)	Mean age (months)	Biomarkers tested	Cut-off	Sensitivity, specificity
Kawamura T, Japan, 2000	32/26 (58)	21	BNP	16.8 pg/mL	0.97, 0.86
Lee H, Korea, 2006	58/34 (92)	33.6	NT-proBNP	260 ng/L	0.93, 0.88
Zhang QY, China, 2006	6/16 (22)	19	NT-proBNP	103.6 ng/L	1, 1
Dahdah N, Canada, 2009	43/19 (62)	47.1	NT-proBNP	170 ng/L	0.78, 0.63
Cho SY, Korea, 2011	59/59 (108)	33.2	NT-proBNP	235.2 ng/L	0.66, 0.77
McNeal-Davidson A, Canada, 2012	81/49 (130)	42	NT-proBNP	190 ng/L	0.89, 0.69
Shiraishi M, Japan, 2013	149/506 (655)	33	NT-proBNP	98 pg/mL	0.98, 0.47

BNP, B-type natriuretic peptide; NT-proBNP, N-terminal prohormone serum BNP.

patients and mean serum levels of NT-proBNP or BNP in case or control patients. All studies used age matched patients with febrile illness unrelated to KD as the controls. Six studies reported NT-proBNP levels, and three studies reported BNP levels. Mean serum levels of NT-proBNP were between 750 and 1511 pg/mL in patients with KD, in contrast to 47 and 199 pg/mL in the control group. Mean serum levels of BNP were between 52 and 142 pg/mL in patients with KD, in contrast to 4 and 60 pg/mL in the control group.

We used the QUADAS tool for study quality assessment. [Figure 2](#) provides an overall impression of the methodological quality of the studies. All blood drawn was taken in proximity to the confirmation diagnosis. All patients were verified by the same reference standards in all studies. None of the included studies explained the withdrawals or uninterested results. Only two of six studies reported the physicians were blinded to the index test while verifying outcomes by reference standards. We could not exclude the possibility of incorporation bias.

Diagnostic accuracy indices

Results of the meta-analysis indicated that PCT testing has an acceptable accuracy regarding differentiating KD from other causes of prolonged febrile illness ([table 3](#)). The pooled sensitivity and specificity estimates were 0.89 (95% CI 0.79 to 0.95) and 0.77 (95% CI 0.62 to 0.88), respectively. When the analysis was restricted to six studies measuring NT-proBNP, there is no change in sensitivity (0.89, 95% CI 0.78 to 0.95) but a slight decrease in specificity (0.72, 95% CI 0.58 to 0.82). The positive likelihood ratio (LR+, 3.20, 95% CI 2.10 to 4.80) of NT-proBNP is not sufficient for a standalone rule-in test. The negative likelihood ratio (LR-, 0.15, 95% CI 0.07 to 0.31), in the context of low pretest probability (<10%), could reduce the post-test probability to such a level that KD could be safely excluded. To take within and between study variation into account, we constructed HSROC and forest plot for NT-proBNP, which derived an area under the curve (AUC) of 0.87 (95% CI 0.83 to 0.89) and a summary OR of 21.6 (95% CI 8.33 to 55.97), respectively ([figures 3](#) and [4](#)). According to Hosmer and Lemeshow, our AUC of between 0.80 and 0.90 can be regarded as

‘good’.²² High statistical heterogeneity was also noted, but the Galbraith plots did not indicate a major outlier, which, for the most part, could account for the observed heterogeneity.²³ Results of Eggers tests are presented in [table 3](#), but the small number of studies may prevent a meaningful exam of publication bias.

DISCUSSION

We present a systematic review assessing the diagnostic accuracy of serum BNP or NT-proBNP measurement in the clinical setting of KD. We found that NT-proBNP can be a useful marker for the diagnosis of KD. The plasma NT-proBNP level was elevated in patients with KD in the acute phase, whereas it was only mildly elevated in febrile control patients. Unfortunately, according to the rules of thumb by Jaeschke in interpreting sizes of likelihood ratios, our positive likelihood ratio for NT-proBNP provides only weak evidence for KD diagnosis.²⁴ Even though NT-proBNP is not sufficient for a standalone rule-in test, the widely available blood test may help clinicians decide whether there is a need to arrange confirmatory cardiac sonographic examination for suspected patients. Cardiac sonographic examination is rarely available in front-end settings such as emergency departments or in ambulatory clinics. In addition, the current standard for diagnosis of KD is largely based on empirical clinical criteria, and it will be interesting for others to find out whether incorporating NT-proBNP test results would further enhance the accuracy of current criteria in diagnosing atypical KD.

In addition, we calculated the post-test probability to make our results more informative to clinicians. In a group of patients with a 20% pretest probability of KD, a positive NT-proBNP test with a LR+ of 3.20 would increase the post-test probability to 44%, and a negative NT-proBNP test with a LR- of 0.15 would reduce the post-test probability to 4%.²⁵ Therefore, NT-proBNP measurements had a moderate rule-in value and a good rule-out value for the diagnosis of KD among febrile patients. We cannot draw any conclusions on the comparative diagnostic value between BNP and NT-proBNP tests because only one study reported data on BNP.

Currently, diagnosis of KD in the early course of disease remains challenging. Classical clinical diagnostic

Table 2 Mean serum levels of BNP in patients with KD and control patients

Author, country, year	Biomarkers tested	Diagnostic kit	Controls	Mean NP levels in patients with KD (SD)	Mean NP levels in controls (SD)
Kawamura T, Japan, 2000	BNP	Enzyme immunoassay (SRL Co, Tokyo, Japan)	Children with febrile viral illness, including adenovirus, influenza, measles and herpes group virus infections	55.0±39.5 pg/mL	6.8±7.3 pg/mL
Lee H, Korea, 2006	NT-proBNP	Elecsys (Roche Diagnostics, Mannheim, Germany)	Febrile children with skin rashes such as scarlet fever, exanthem subitum, urticaria and erythema multiform	1510.6±2173.2 pg/mL	139.0±88 pg/mL
Zhang QY, China, 2006	NT-proBNP	Elecsys (Roche Diagnostics, Mannheim, Germany)	Febrile children without KD or other chronic heart diseases	691±86 pg/mL	47±10 pg/mL
Dahdah N, Canada, 2009	NT-proBNP	Elecsys (Roche Diagnostics, Indianapolis, IN)	Children with a febrile illness unrelated to KD from 3 to 20 days	923±1362.7 pg/mL	186±198.0 pg/mL
Dahdah N, Canada, 2009	BNP	AxSYM (Abbott; Abbott Park, IL)	Children with a febrile illness unrelated to KD from 3 to 20 days	141.9±227.5 pg/mL	59.9±72.4 pg/mL
Sun YP, China, 2010	BNP	AxSYM (Abbott; Abbott Park, IL)	Febrile children without KD or other chronic heart diseases	51.7±21.3 pg/mL	3.76±7.6 pg/mL
Cho SY, Korea, 2011	NT-proBNP	Elecsys (Roche Diagnostics, Mannheim, Germany)	Age matched children with febrile illnesses, mostly respiratory tract infections	749.66±997.11 pg/mL	174.41±144.30 pg/mL
McNeal-Davidson A, Canada, 2012	NT-proBNP	Elecsys (Roche Diagnostics, Indianapolis, IN)	Children with fever unrelated to KD lasting between 4 and 14 days	1287.7±2090.3 pg/mL	199.5±274.3 pg/mL
Shiraishi M, Japan, 2013	NT-proBNP	Elecsys (Roche Diagnostics, Tokyo, Japan)	Children with other acute infectious disease	NA	NA

BNP, B-type natriuretic peptide; KD, Kawasaki disease; NA, not applicable; NT-proBNP, N-terminal pro-hormone serum BNP.

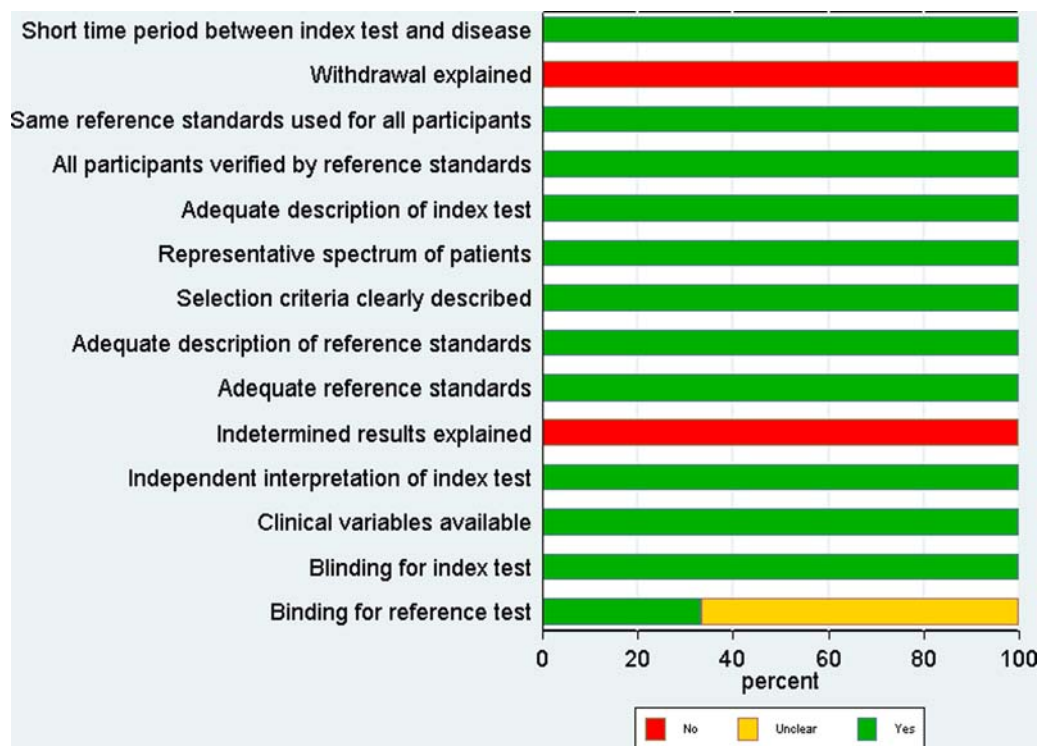


Figure 2 Quality of included studies.

criteria are sufficient to exclude KD. Some laboratory findings have shown their usefulness in identifying KD: the presence of raised C reactive protein (CRP), a raised white cell count, urine analysis showing white cell counts under microscopy, and raised transaminases or bilirubin.²⁶ However, these tests are neither pathognomonic nor diagnostic. Without a valid biomarker for predicting CA aneurysms in patients with KD, Harada *et al* and Beiser *et al* developed instruments that incorporate age, gender, leucocyte count, fever duration, haemoglobin levels and CRP levels, to predict CA aneurysms.²⁷ The accuracy of these instruments was not consistently high in several validation studies. For patients with incomplete clinical manifestations, transthoracic echocardiography is usually required. This diagnostic procedure is expensive and has limited availability at different settings. Therefore, until now, diagnosis and the time-sensitive immunoglobulin therapy are usually delayed until a fever has persisted for at least 5 days. Our study showed NT-proBNP measurement may represent a major advance in the diagnostic pathways in patients with suspected KD.

Serum BNP is elevated due to ventricular wall stress imposed by volume or pressure overload. In addition to the haemodynamic stress, inflammation of the myocardial tissue may also induce the production of BNP.²⁸ Immunohistochemical analysis of endomyocardial biopsy specimens from patients with myocarditis showed immunoreactivity for BNP and histological change such as myocyte necrosis, inflammatory infiltrates and fibrosis were more prominent in immunohistochemically

positive biopsy specimens.²⁸ It has been shown that the cardiac pathology, including endocardium, myocardium and pericardium can be found in nearly all patients with KD.^{7,9} The vasculitis and myocarditis associated with KD may thus be an important cause of BNP elevation, even in the absence of functional haemodynamic change. Limited by the studies available for BNP testing, we cannot draw any conclusion regarding the accuracy of BNP in comparison with NT-proBNP. In adult reports, BNP and NT-proBNP are equally accurate in diagnosing acute heart failure. For clinical use, NT-proBNP may have some advantages over BNP. NT-proBNP has a longer half-life (60–120 min) than BNP (20–30 min) and the interpretation of serum levels of NT-proBNP is less affected by kidney functions.⁵ Another advantage of NT-proBNP is its stability at room temperature.

The interpretation of the NT-proBNP levels in paediatric patients is complicated because children have the physiological secretion of BNP in early life. According to previous work, the upper limit for age (95th centile) is 646 ng/L for infants between 1 month and 1 year, 413 ng/L for children between 1 and 2 years, 289 ng/L for those between 2 and 6 years, and 157 ng/L for those >6 years.²⁹ We do not recommend these cut-off levels for differentiating between KD and other febrile illness. The mean age of patients for the included studies ranged from 19 to 47 months, and the best cut-off values recommended by each study varied between 103 and 260 ng/L, depending on the characteristics of febrile illness in the comparison group. Based on the two studies with the largest sample sizes, a cut-off value

Table 3 Summary of subgroup analysis of the included studies by different study characteristics

Variables	Number of studies	Sensitivity (95% CI)	Specificity (95% CI)	Likelihood ratio+	Likelihood ratio-	AUROC (95% CI)	Diagnostic OR (95% CI)	I ² (95% CI)	Publication bias (Egger's test p)
Overall	7	0.89 (0.79 to 0.95)	0.77 (0.62 to 0.88)	4.0 (2.30 to 6.90)	0.14 (0.07 to 0.27)	0.91 (0.88 to 0.93)	26.9 (10.33 to 69.96)	73.7 (43.8 to 87.7)	0.057
NT-pro BNP	6	0.89 (0.78 to 0.95)	0.72 (0.58 to 0.82)	3.20 (2.10 to 4.80)	0.15 (0.07 to 0.31)	0.87 (0.83 to 0.89)	21.6 (8.33 to 55.97)	73.2 (38.5 to 88.3)	0.146

AUROC, area under the receiver operating characteristic curve; BNP, B-type natriuretic peptide; NT-proBNP, N-terminal prohormone serum BNP.

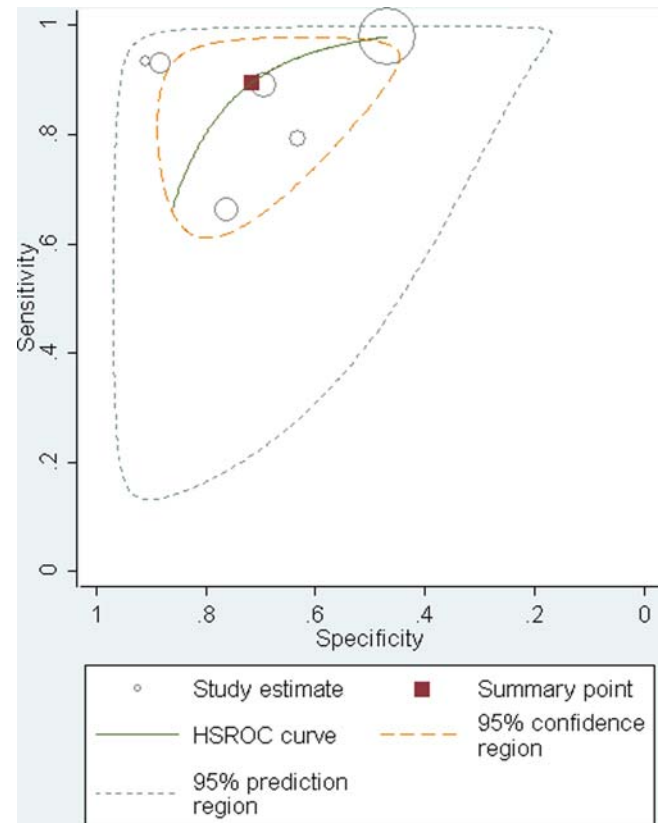


Figure 3 Hierarchical summary receiver-operator curves (HSROC) for NT-proBNP (NT-proBNP, N-terminal prohormone serum B-type natriuretic peptide).

between 190 and 260 ng/L may be a recommended cut-off value for this meta-analysis.

Limitation

The results of this study have to be interpreted in the context of several limitations. First, considerable heterogeneity was found in the pooled estimates. The small number of studies does not allow further exploration of the source of heterogeneity by sensitivity analysis or meta-regression. Some factors that may have contributed to this heterogeneity cannot be assessed or adjusted. For example, duration of fever and symptoms of the case patients and the characteristics and severity of febrile illness in the control group are likely to have an important effect on BNP testing performance. These factors are not reported in detail and their effect cannot be assessed. Second, the case patients enrolled in the studies include patients with KD with several types of cardiac pathologies, including those without CA aneurysms. Results of this study did not provide support for NT-proBNP to be used as an important diagnostic tool for the medical decision of intravenous immunoglobulin (IVIG) therapy. Third, given the limited data available for analysis of KD diagnostic accuracy at different cut-off values, no strong conclusions for the best BNP cut-off value use can be reached without further large cohort studies. The ideal approach for determining the cut-off

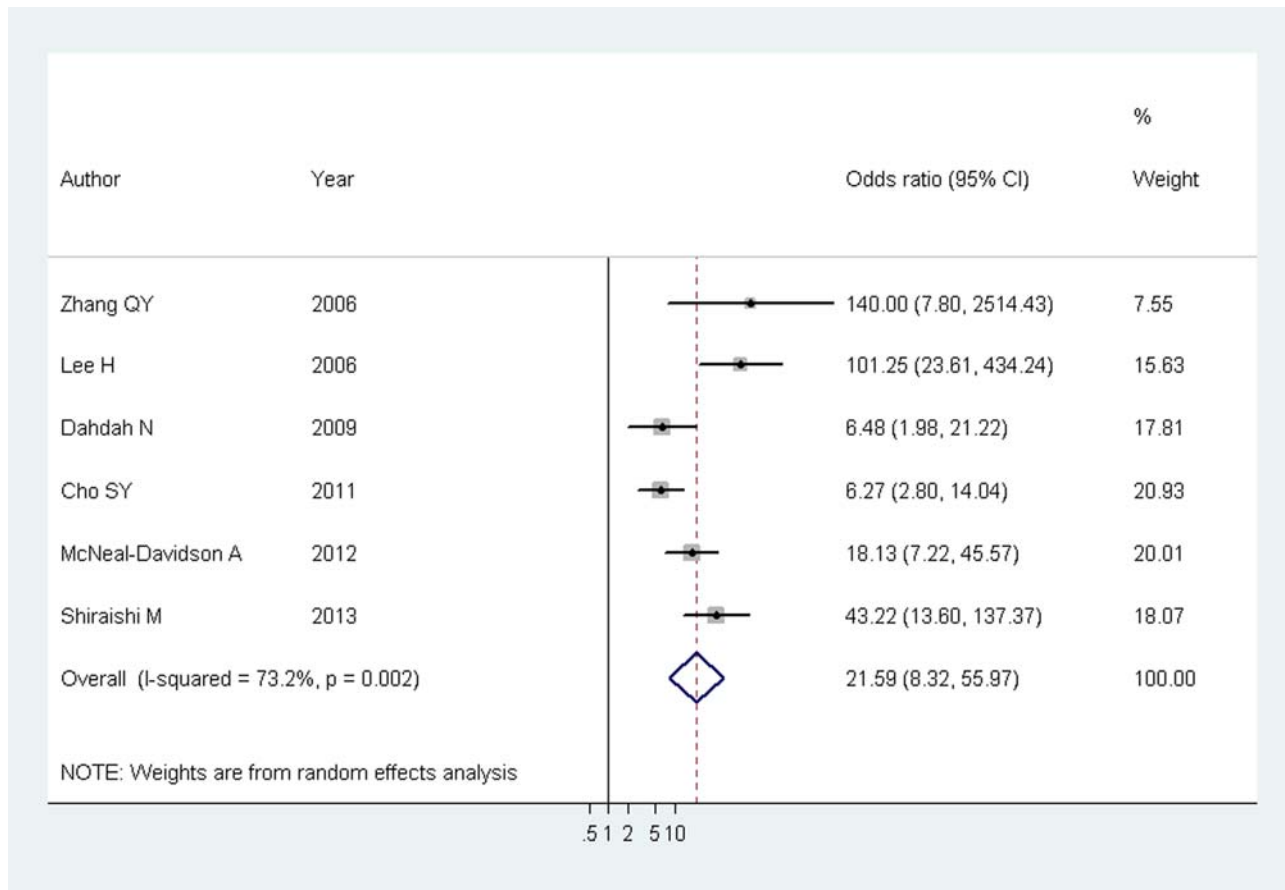


Figure 4 Forest plot showing the diagnostic value of serum B-type natriuretic peptide in acute Kawasaki disease (KD) in different studies.

value for NT-proBNP or BNP testing in the diagnosis of KD would be to carry out a prospective, cohort study in consecutive patients with clinical suspicion of KD. Before this type of study is available, individual data meta-analysis may also provide better insight into the age-specific best cut-off value in this clinical setting.

CONCLUSIONS

To date, KD is diagnosed on clinical grounds alone. Our review shows determination of BNP in clinical routine may represent a valuable addition to the current diagnostic work up of patients with suspected KD. The measurement of this biomarker is likely to help screen out some patients with incomplete KD presentations who may need cardiac imaging studies for early identification of possible cardiac complications. Considering the small sample size and suboptimal case-control design of the currently available studies, a sufficiently powered prospective cohort study is needed to conclusively address the usefulness of serum NT-proBNP as a diagnostic aid in KD.

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