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ORIGINAL RESEARCH

Meta-analysis of B-type natriuretic peptide in diagnosis of congestive heart failure in different clinical settings

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Background: B-type natriuretic peptide (BNP) is a neurohormone released from the left ventricle in response to ventricular wall stress and pressure overload. BNP testing has been developed, and aids in identification of patients with suspected congestive heart failure (CHF). The objective of this study was to evaluate the role of BNP as a diagnostic marker of CHF, and determine its value in different clinical settings.

Methods: A systematic review and meta-analysis of clinical studies regarding BNP and CHF was conducted. A comprehensive search of Medline, the Cochrane Library, and the reference sections of the primary studies was done. The methodologic quality of each study that met the inclusion criteria was assessed. The results of individual studies were described. The pooled sensitivity and specificity were calculated. Estimation of the diagnostic accuracy was done using meta-regression of the diagnostic odds ratio and summarized by a summary receiver-operating curve (S-ROC).

Results: In total, 32 studies (n = 11054) met the inclusion criteria. The overall sensitivity and specificity at the optimum cutoff point are 81% (95% confidence interval: 0.76–0.86) and 86% (95% confidence interval: 0.81–0.89), respectively. The area under the S-ROC for all studies is 0.92. Nine papers included patients with dyspnea. The pooled negative likelihood ratio for this group was 0.12. Five studies included patients with chronic CHF and another seven studies included patients who were referred for echocardiography. The remaining studies were patients from the general population, patients with stable coronary artery disease, and patients referred for cardiac catheterization.

Conclusion: BNP is a valuable tool in the diagnosis of CHF. It should be applied in the appropriate clinical setting. The strongest evidence of benefit for use of BNP is in patients presenting to the emergency room with dyspnea.

Keywords: B-type natriuretic peptide, congestive heart failure, neurohormone, summary receiver-operating curve, dyspnea

Introduction

Congestive heart failure (CHF) presently affects five million people in the US, and its diagnosis in frequently challenging.[1] The prevalence of systolic dysfunction is 6%. Fewer than half of the patients with moderate to severe diastolic or systolic dysfunction have recognized CHF.[1] The number of newly diagnosed cases is increasing as the population ages. The incidence of CHF approaches 10 per 1000 population after the age of 65 years. Heart failure causes a huge burden on the health care system. For instance, in 2005 the estimated direct and indirect cost of CHF in the US was $27.9 billion.[1]

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The natriuretic peptides are a group of structurally related peptides.[2] C-type natriuretic peptide is a 22-amino acid peptide produced mainly by the vascular endothelium. Atrial natriuretic peptide is a cyclic 28-amino acid peptide secreted by the atria. B-type natriuretic peptide (BNP) first discovered in porcine brain,[3] is a 32-amino acid peptide that is structurally similar to atrial natriuretic peptide. It is mainly synthesized and secreted by both the atria and ventricles. When the wall of the ventricle is stretched in response to volume or pressure overload a prohormone, proBNP is cleaved by furin to form active BNP and inactive N-terminal BNP molecules. These molecules are secreted into the circulation and then cleared by enzymatic- and receptor-mediated mechanisms.[2]

A competitive radioimmune assay was the first method used for measurement of natriuretic peptides. This was followed by noncompetitive immunoradiometric assays, which are more precise and sensitive.[4] More recently, a rapid point-of-care measurement of BNP was developed. It is fully automated and produces results in about 15 minutes, rather than up to 24 hours with the earlier methods.[5]

Several studies have been done to evaluate the measurement of BNP in CHF. A previous meta-analysis showed that there is significant heterogeneity among the studies.[6,7] The aim of this meta-analysis was not only to determine the overall accuracy of BNP, but also to evaluate its value in different clinical settings. This will facilitate the use of the test in the appropriate clinical setting. Here we assess the methodologic quality of the studies, and synthesize the best available evidence.

Methods

Literature review

We performed a Medline and PubMed search from 1966 to April 2005 using a combination of search terms, ie, "brain natriuretic peptide", "proBNP", "BNP", "B-type natriuretic peptide", and "CHF". A search of the Cochrane Library was conducted, and the reference sections of the relevant studies and reviews were manually searched.

Study eligibility

We included studies that evaluated BNP in the diagnosis of CHF. The BNP should be evaluated by comparing its results with a gold standard. Information should be available to allow construction of the diagnostic 2×2 table. We excluded studies that used N-terminal BNP or atrial natriuretic peptide only. Because the main reason for our study was to evaluate the accuracy of BNP in the diagnosis of CHF, we excluded studies that evaluated asymptomatic patients with diastolic dysfunction. Furthermore, because it is well known that myocardial infarction increases BNP levels, we excluded all studies that included patients within 30 days of myocardial infarction.

Data extraction

We extracted data for the eligible studies using a standard format. This included total number of patients, demographic characteristics of patients, the reference test used, and the manufacturer of the BNP test. Specificity and sensitivity values, area under the receiver-operating curve, and the number of patients with true positive and true negative tests were abstracted. We then constructed the 2×2 table.

The methodologic quality of the studies was assessed using a checklist developed by Lijmer et al.[8] We assessed the studies for selection bias as to whether the study was randomized or not. Verification bias was excluded if investigators were blinded to the results of the reference test, and if it was not clear from the text if the study was labeled as unblinded. The study was considered to be cross-sectional if the test was evaluated in patients known to have the disease and compared with healthy subjects. In addition, methods for data collection were categorized as either prospective or retrospective.

Statistical analysis

We described the results of individual studies. Heterogeneity in the results of the studies was assessed using the Chi-square test and Q-test. The pooled sensitivity and specificity was calculated using the random effect model. The summary receiver-operating curve (S-ROC) was performed using the methods described by Moses et al[9] and the area under the S-ROC was calculated. A subgroup analysis was performed according to the clinical application of the test. Pooled specificity and sensitivity, and the S-ROC were calculated for each subgroup that included five or more studies. We also calculated the pooled likelihood ratios (LR) and the diagnostic odd ratios for the studies. Meta-Test version 0.6[10] and Meta-DiSc version 1.1.1[11] was used for the analysis.

Results

The strategy for the literature search is explained in Figure 1. More than 1500 citations were retrieved for the initial search from all sources. Of the 1500 citations we searched, the abstracts of 204 studies and 80 articles were identified for

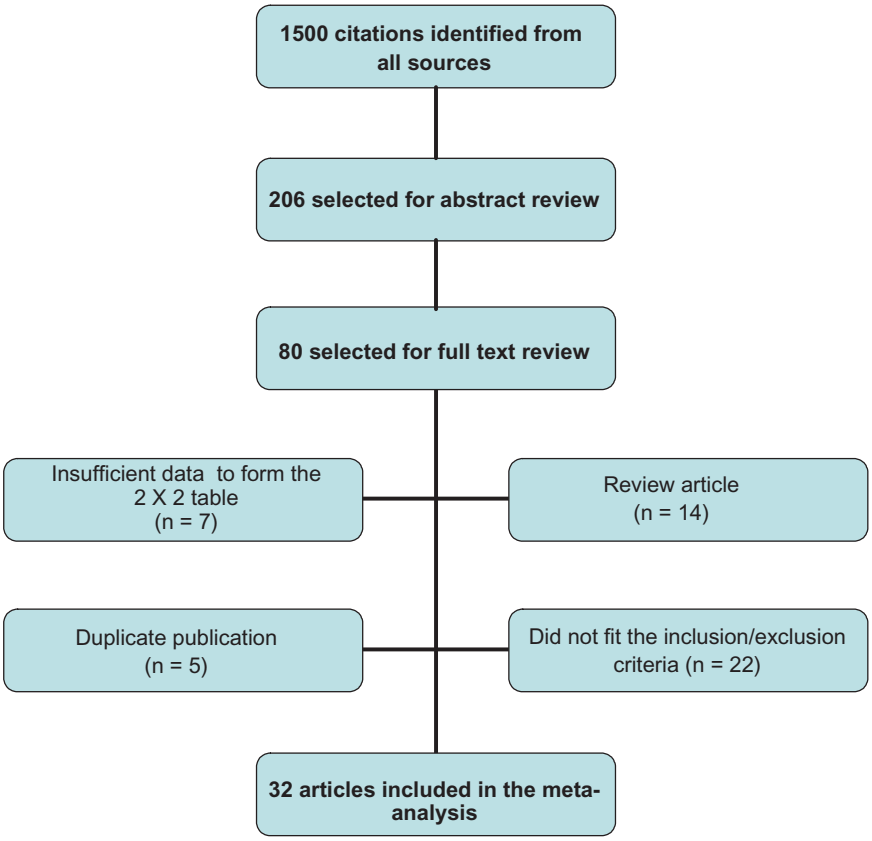

Figure 1 Strategy for literature search.

full text review. Of the 80 articles, seven were excluded because of insufficient information to form the 2 × 2 table, 14 were review articles, five were duplicate publications, and 22 articles did not fit the inclusion or the exclusion criteria. Finally we included 32 articles in the meta-analysis.[12–43] The total number of patients included in all the studies was 11,054. The summary data for the studies included in the meta-analysis are shown in the Table 1. The overall sensitivity and specificity at the optimum cutoff point as defined by the authors of each study was 81% (95% confidence interval [CI]: 0.76–0.86) and 86% (95% CI: 0.81–0.89), respectively (Figure 2). The area under the S-ROC for all the studies was 0.92 (Figure 3).

Subgroup analysis

We divided the studies into eight distinct subgroups according to the clinical application of BNP (see Table 1). The pooled analysis was done to subgroups that had five or more studies included. Nine studies (n = 2943) evaluated patients presenting to the emergency department with dyspnea. Five studies (n = 3679) included patients with chronic CHF and another seven studies (n = 1359) included patients who were referred for echocardiography. The remaining studies were patients from the general population, patients with stable coronary artery disease, and patients referred for cardiac catheterization.

In the studies that evaluated patients presenting to the emergency department with dyspnea, the pooled sensitivity and specificity was 88% and 80%, respectively. For patients with a history of CHF when compared with healthy subjects, the pooled specificity was 77% and 95% for sensitivity. The pooled sensitivity and specificity for patients referred for echocardiography was 85% and 77%, respectively (Figure 4).

The pooled negative likelihood ratio was lowest for patients presenting to the emergency department with dyspnea at 0.12. The positive likelihood ratio was highest for patients with a history of CHF, at 12.2 (Figure 5). The pooled diagnostic odd ratio for patients presenting to the emergency department with dyspnea was 48.53 and was highest for patients with history of CHF, at 62.01 (Figure 6).

The area under the S-ROC was best for patients with a history of CHF at 0.96; for patient presenting to the emergency department with dyspnea it was 0.94, and for patients referred for echocardiography was 0.91 (Figure 7).

Table 1 Study characteristics and diagnostic test performance by clinical application of test

Reference	Year	Patients (n)	Mean age	Population details	Gold standard	Manufacturer	Threshold	Sensitivity	Specificity	PPV*	NPV*	Quality criteria met**
Patients presenting to the emergency department with dyspnea												
Morrison et al[12]	2002	321	NA*	Patients presenting to emergency department with acute dyspnea	Cardiologist	Biosite, San Diego, CA	94 pg/mL#	86%	98%	97%	91%	b, c, d
							105 pg/mL	86%	94%	91%	90%	
							135 pg/mL	90%	90%	87%	93%	
							195 pg/mL	94%	85%	82%	95%	
							240 pg/mL	96%	79%	77%	96%	
Dao et al[13]	2001	250	63	Patients presenting to emergency department with acute dyspnea	Cardiologist	Biosite	80 pg/mL#	98%	92%	89%	99%	b, c, d
							100 pg/mL	94%	94%	91%	96%	
							115 pg/mL	90%	96%	93%	94%	
							120 pg/mL	90%	96%	93%	94%	
							150 pg/mL	87%	97%	95%	92%	
Villacorta et al[14]	2002	70	72.4	Patients presenting to emergency department with acute dyspnea	Cardiologist	Biosite	200 pg/mL	10%	97%	78%	50%	a, b, c, d
Maisel[15]	2002	1586	64	Patients presenting to emergency department with acute dyspnea	Cardiologist	Biosite	100 pg/mL#	90%	76%	77%	90%	a, b, c, d
							50 pg/mL	97%	62%	69%	96%	
							80 pg/mL	93%	74%	76%	92%	
							125 pg/mL	87%	79%	79%	87%	
							150 pg/mL	85%	83%	82%	86%	
Davis et al[16]	1994	52	74	Patients admitted and treated for acute dyspnea	Cardiologist		22 pmol/L	93%	90%	94%	89%	b, c, d
Knudsen et al[17]	2004	86	78	Female patients presenting to emergency department with acute dyspnea	Cardiologist	Biosite	50 pg/mL	100%	37%	52%	100%	a, b, c, d
							100 pg/mL#	94%	55%	59%	93%	
							150 pg/mL	91%	59%	60%	91%	
							200 pg/mL	89%	63%	62%	89%	
		69	69	Male patients presenting to emergency department with acute dyspnea			50 pg/mL	95%	38%	68%	85%	
							100 pg/mL#	90%	55%	73%	80%	
							150 pg/mL	93%	62%	77%	87%	
							200 pg/mL	90%	72%	82%	84%	
Mueller et al[18]	2005	251	76	Patients presenting to emergency department with acute dyspnea	Cardiologist	AxSYM (Abbott Laboratories, Abbott Park, IL)	100 ng/L	96%	61%	75%	93%	a, b, c, d
							118 ng/L	95%	64%	76%	91%	
							160 ng/L	90%	73%	80%	86%	
							295 ng/L#	80%	86%	87%	78%	
Alibay et al[19]	2005	160	80	Patients presenting to emergency department with acute dyspnea	Cardiologist	Biosite	50 pg/mL	99%	31%	46%	98%	b, c, d
							100 pg/mL	98%	47%	53%	98%	
							150 pg/mL #	94%	61%	59%	94%	
							200 pg/mL	87%	64%	59%	89%	
Barcarse et al[20]	2004	98	64	Patients presenting to emergency department with acute dyspnea	Cardiologist	Biosite	110 pg/mL #	97%	93%	95%	96%	c, d
							170 pg/mL	82%	95%	96%	79%	
							300 pg/mL	70%	99%	99%	70%	

Patients with chronic congestive heart failure versus healthy subjects												
Seino et al[21]	2004	172	64	Patients with chronic CHF vs healthy subjects	TTE*	Shionoria, Japan	135 pg/mL	72%	73%	81%	62%	a, d
Prontera et al[22]	2004	278		Patients with cardiomyopathy vs healthy subjects	History	Two-site IRMA	117 pg/mL	81%	94%	97%	69%	d
Fonseca et al[23]	2004	104	70	Patients with chronic CHF vs healthy subjects	TTE	Shionoria, Japan	32 pg/mL	92%	94%	99%	71%	a, d
							50 pg/mL	99%	55%	91%	92%	
							100 pg/mL	98%	95%	99%	91%	
							136 pg/mL#	96%	99%	100%	84%	
							150 pg/mL	96%	99%	100%	84%	
							200 pg/mL	93%	100%	100%	75%	
Wu et al[24]	2004	2243	67	Patients with chronic CHF vs healthy subjects	History	Bayer	80 ng/L#	72%	96%	90%	88%	d
							100 ng/L	70%	97%	92%	87%	
							120 ng/mL	68%	98%	94%	87%	
Wieczorek et al[25]	2002	882	79	Patients with the diagnosis of CHF vs individuals with no evidence of CHF (controls)	History	Biosite	100 pg/mL	82%	97%	96%	86%	d
Patients referred for transthoracic echocardiography												
Landray et al[26]	2000	126	74.4	Patients with suspected heart failure referred by GP for further evaluation and TTE	TTE	Shionoria, Japan	17.9 pg/mL#	88%	34%	38%	86%	c, d
							76 pg/mL	66%	87%	70%	85%	
							10 pg/mL	92%	18%	34%	83%	
Epshteyn et al[27] Part 1*	2003	172	54	Diabetic patients with clinical indication for echocardiography	TTE		79 pg/mL#	86%	92%	95%	78%	b, c, d
							39 pg/mL	90%	65%	83%	78%	
							60 pg/mL	88%	83%	91%	79%	
							90 pg/mL	81%	93%	96%	72%	
							102 pg/mL	79%	95%	97%	71%	
Kirshnaswamy et al[28]	2001	400	65	Patients referred for echocardiography to evaluate LV function.	TTE	Biosite	75 pg/mL#	85%	97%	98%	79%	b, c, d
							345 pg/mL	36%	99%	98%	47%	
							160 pg/mL	65%	99%	99%	62%	
							110 pg/mL	75%	98%	98%	69%	
							62 pg/mL	89%	90%	94%	83%	
							49 pg/mL	91%	82%	90%	84%	
Maisel[29]	2001	200	65	Patients referred for echocardiography to evaluate LV function	TTE	Biosite	75 pg/mL#	86%	98%	97%	89%	a, b, c, d
							65 pg/mL	88%	91%	90%	89%	
							55 pg/mL	92%	86%	86%	92%	
							46 pg/mL	93%	80%	81%	93%	
							38.5 pg/mL	95%	66%	72%	94%	
Cowie er al[30]	1997	106	?	Patients with suspected heart failure referred by GPs for further evaluation and echocardiography	Cardiologist	RIS (BNP RIK 9086, Peninsula Lab)	22.2 pmol/L	97%	84%	70%	99%	a, c, d
Valli et al[31]	2001	153	54	Patients referred for WMS	WMS*	IRMA-BNP, CIS Bio International, France),	52 pg/mL	85%	82%	74%	90%	a, b, c, d

(*Continued*)

Table 1 (*Continued*)

Reference	Year	Patients (n)	Mean age	Population details	Gold standard	Manufacturer	Threshold	Sensitivity	Specificity	PPV*	NPV*	Quality criteria met**
Atisha et al[32]	2004	202	65	Patients referred for echo to assess LV dysfunction	TTE	Biosite	20 pg/mL[#]	79%	44%	57%	69%	c, b, d
							40 pg/mL	65%	56%	58%	63%	
							60 pg/mL	55%	68%	62%	62%	
							100 pg/mL	42%	78%	64%	59%	
Screening of general population												
McDonagh et al[33]	1998	1252	50.9	Randomly selected community member who completed a questionnaire and had analyzable echocardiograms	TTE	RIS	17.9 pg/mL	77%	87%	15%	99%	a, c, d
Smith et al[34]	2000	155	75.6	Elderly patients from general practice	TTE	RIS	18.7 pmol/mL[#]	92%	65%	18%	99%	a, c, d
							19.8 pmol/L	83%	70%	19%	98%	
							26.7 pmol/L	75%	80%	24%	97%	
Luchner et al[35]	2000	479	59	Subjects originated from a gender-stratified random sample of general population who had analyzable echocardiograms	TTE	Shionoria	34 pg/mL	28%	86%	15%	93%	b, c, d
Patients with stable coronary artery disease												
McClure et al[36]	1998	134	67	Long term survivors of myocardial infarction recalled for echocardiography as part of primary care secondary prevention	TTE	RIS	46 pg/mL	27%	88%	43%	78%	a, b, c, d
Bibbins-Domingo et al[37]	2004	293		Patients with stable CAD	TTE	Biosite	100 pg/mL[#]	65%	80%	17%	97%	b, c, d
							30 pg/mL	76%	48%	8%	97%	
High-risk groups (special disease)												
Epshteyn et al[27] Part 2*	2003	91	54	Diabetic patients without clinical indication for TTE	TTE	Biosite	60 pg/mL[#]	84%	76%	65%	90%	b, c, d
							39 pg/mL	88%	66%	58%	91%	
							79 pg/mL	75%	76%	63%	85%	
							90 pg/mL	71%	83%	69%	84%	
							102 pg/mL	66%	88%	75%	83%	
Talvani et al[38]	2004	63	40s	Patients with Chagas disease vs healthy controls	TTE	Biosite	60 pg/mL	92%	83%	53%	98%	b, d
Law et al[39]	2005	62	11.7	Pediatric and adult patients with congenital heart disease	TTE/Cath	Biosite	40 pg/mL	85%	81%	93%	65%	c
Other												
Mueller et al[40]	2004	180		Patients admitted for extensive cardiac evaluation	TTE	Bayer	113 pg/mL	81%	96%	86%	94%	a, b, c, d

Koulouri et al[41]	2004	49		Infants and children presenting with finding of respiratory distress	History	Biosite	40 pg/mL[#]	91%	77%	78%	91%	c, d
							60 pg/mL	83%	77%	76%	84%	
							80 pg/mL	78%	81%	78%	81%	
							100 pg/mL	78%	85%	82%	81%	
Patient referred for cardiac catheterization												
Muders et al[42]	1997	221	60	Consecutive patients undergoing diagnostic cardiac catheterization	Cath	RIAs (Phoenix Pharmaceuticals Inc., Belmont, CA)	75 pg/mL	54%	82%	38%	90%	a, c, d
Yamamoto et al[43]	1996	94	62	Consecutive patients undergoing diagnostic cardiac catheterization	Cath/TTE	Shionoria	17.1 pmol/L	83%	77%	55%	93%	a, c, d

Abbreviations: a, randomized; b, blinded; c, cross-sectional; d, prospective; *this study was divided into two separate studies according the population; NA, not available; #, reported optimum cutoff point; PPV, positive predictive value; NPV, negative predictive value; TTE, transthoracic echocardiography; WMS, wall motion score; cath, cardiac catheterization; CHF, congestive heart failure; LV, left ventricular; GP, general practitioner.

Discussion

In this metanalysis we showed that the overall sensitivity and specificity of BNP in the diagnosis of CHF was 81% and 86%, respectively. Because of the heterogeneity among the studies, these results should be taken with caution, because pooling specificity and sensitivity might underestimate or overestimate the test accuracy.[44] An alternative method to determine accuracy is the area under the S-ROC, which was 0.92 for all studies. Although the value of the S-ROC is difficult to interpret in the clinical setting,[45] it indicates that the overall accuracy of the test is reasonable. To decrease the heterogeneity between the studies[46] and to make the meta-analysis more clinically relevant, we divided the studies into eight different groups according to the clinical applications of BNP.

The largest group was patients who presented to the emergency department with dyspnea. This group included nine studies with a total of 2943 patients. More than 50% are from a single study known as the "Breathing Not Properly" study.[15] The pooled negative and positive likelihood ratios for patient presenting to the emergency department with dyspnea was 0.12 and 5.2, respectively. To put this into perspective, we used a theoretical patient who presented to the emergency department with shortness of breath of unknown cause. If his pretest probability was 40%, the post-test probability of the test if it was positive would be 74%, but, if the test was negative, it would be only 7%. This indicates that BNP is more appropriate for ruling out rather than ruling in CHF in this clinical scenario. Several authors have arrived at the same conclusion, given the high sensitivity and negative predictive value of the test.[47] Ruskoaho[2] suggested that in those patients in whom the plasma BNP level is normal, other causes of dyspnea should be considered. Most of the studies used 80–100 pg/mL as the optimum cutoff point.

The BNP is more specific when healthy subjects are compared with patients having chronic CHF. The positive likelihood ratio is also higher at 12.2. This indicates that, in asymptomatic patients, a positive test is highly suspicious for CHF, although a negative test does not rule out the disease. Given the limited data in the studies, these results may not represent the true value. Furthermore, the application of these studies to clinical practice is uncertain.

For patients referred for assessment of LV function, the pooled specificity and sensitivity is not as good compared with the previous population. This may be as a result of variability between the studies. In addition the diagnostic odds ratio is also low, which indicates the poor diagnostic

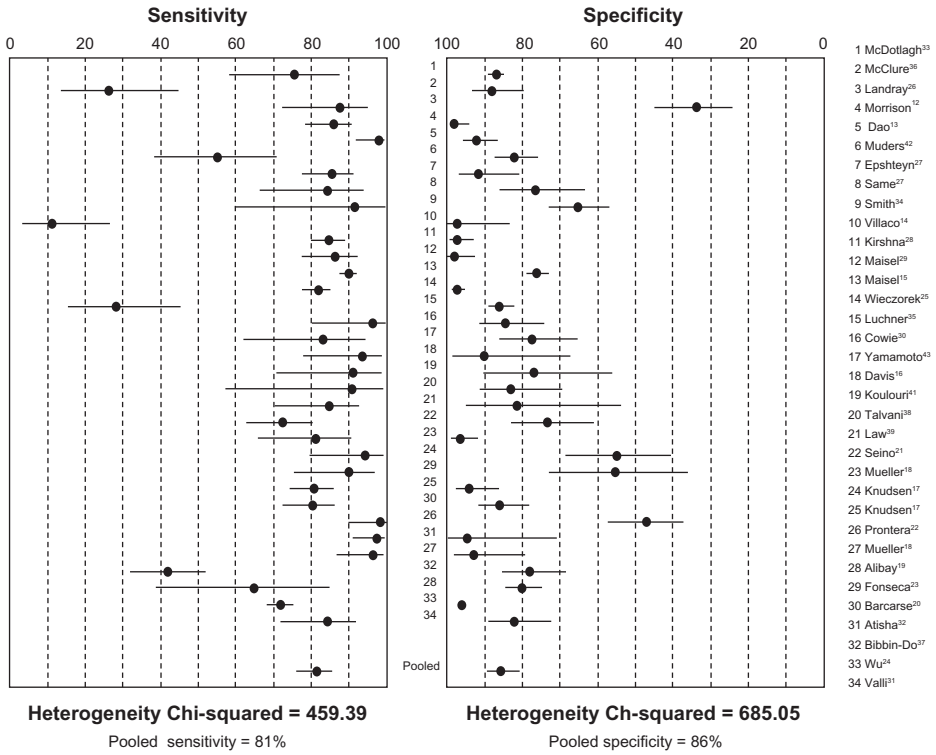

Figure 2 Pooled specificity and sensitivity for all studies (95% confidence interval) with Chi-square test for heterogeneity.

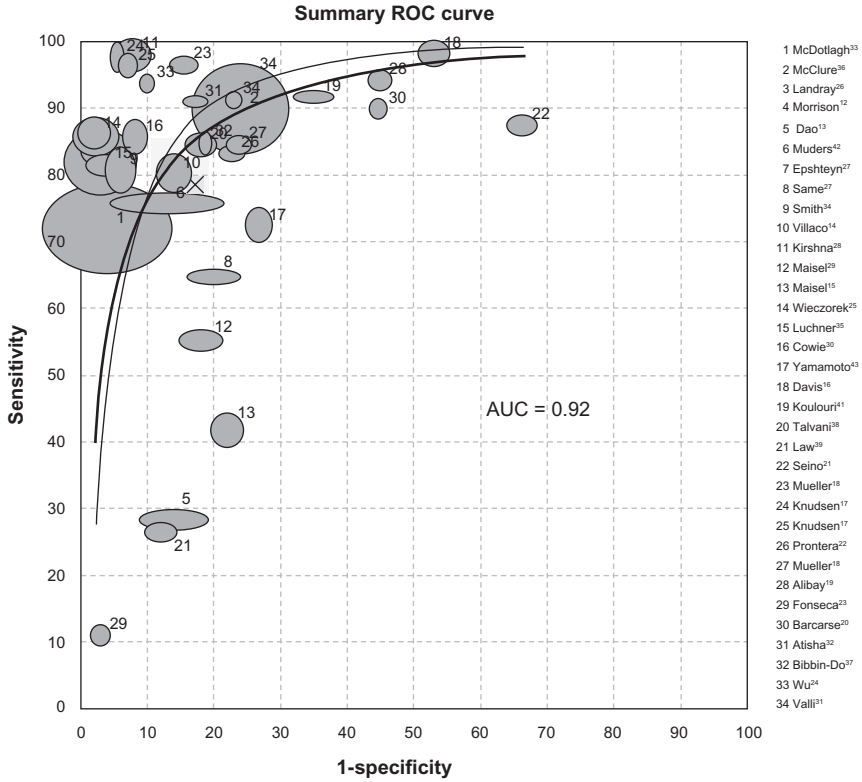

Figure 3 Summary receiver-operating curve for all studies (n = 34). Individual studies are depicated as ellipse. The x and y dimensions of the ellipses are proportional to the square root of the number of patients available to study the specificity and sensitivity, respectively, within the analysis. The cross (x) represents the independent random effect pooling of sensitivity and specificity values of the studies. The numbers next to the ellipse represents the identification number for the study. The area under the concentration time-curve is 0.92.

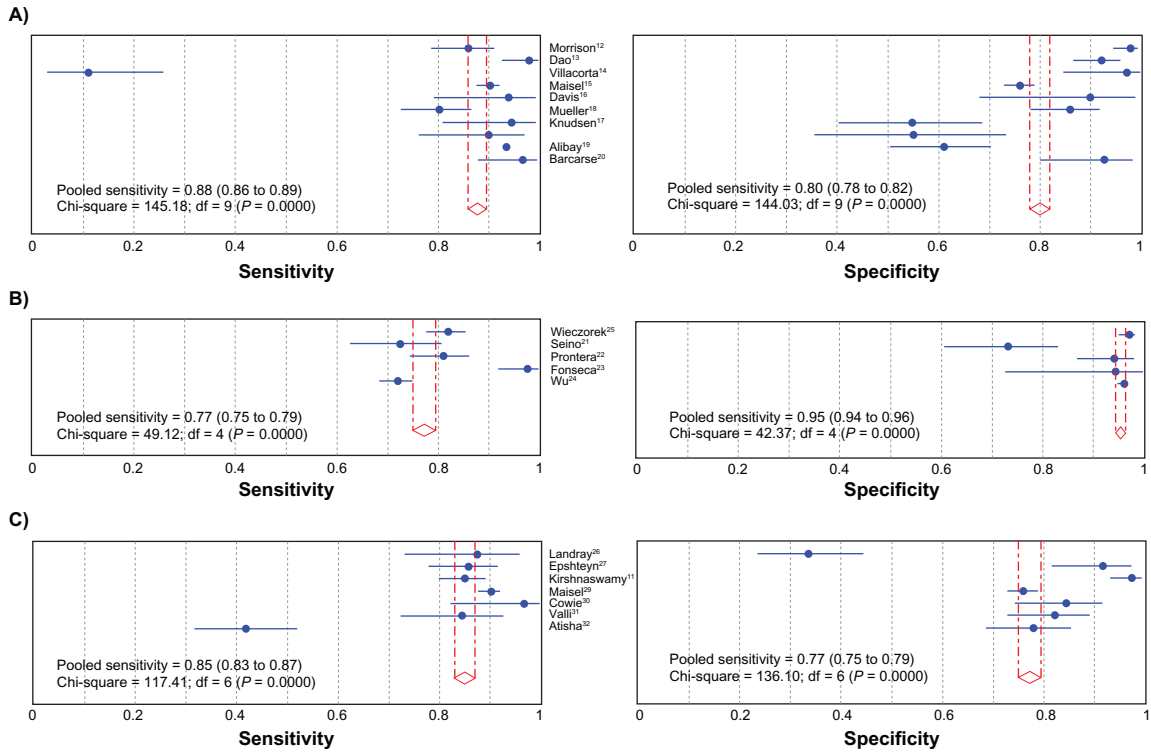

Figure 4 Pooled sensitivity and specificity (95% confidence interval) for **A**) patients presenting to the emergency department with dyspnea, **B**) patients with chronic congestive heart failure versus healthy subjects, and **C**) patients referred for echocardiography.

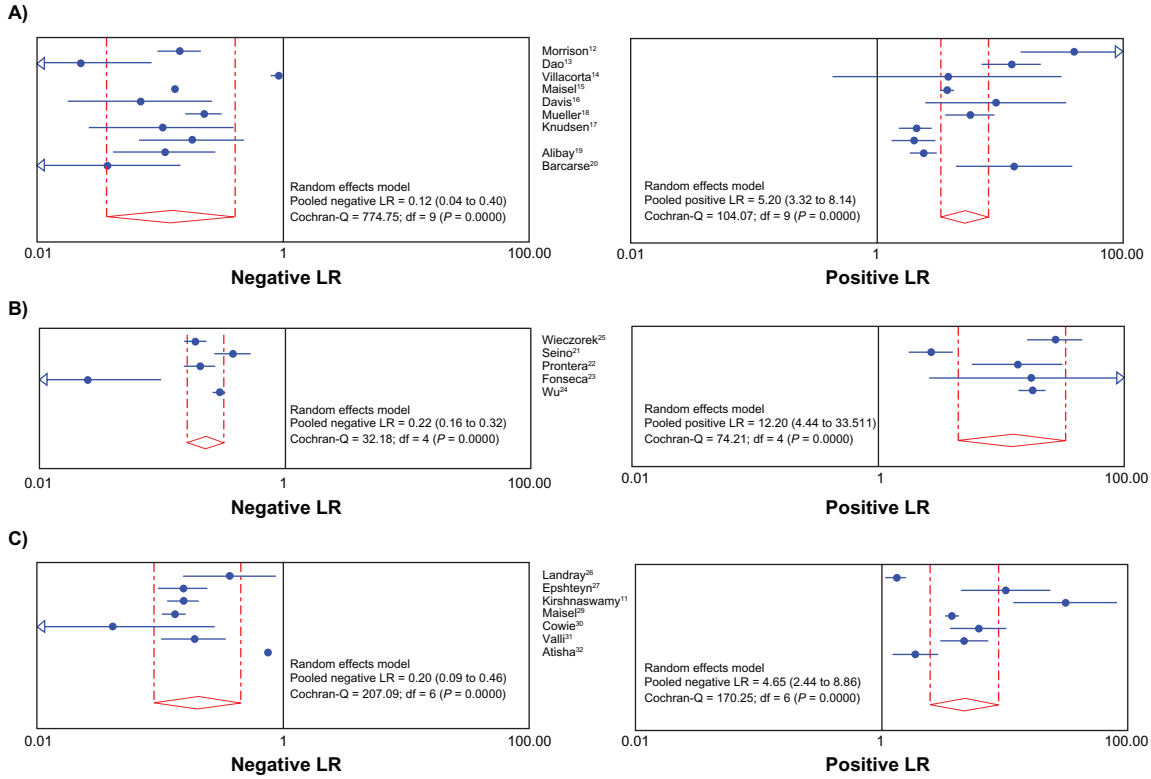

Figure 5 Positive and negative likelihood ratio (95% confidence interval) for **A**) patients presenting to the emergency department with dyspnea, **B**) patients with chronic congestive heart failure versus healthy subjects, and **C**) patients referred for echo.

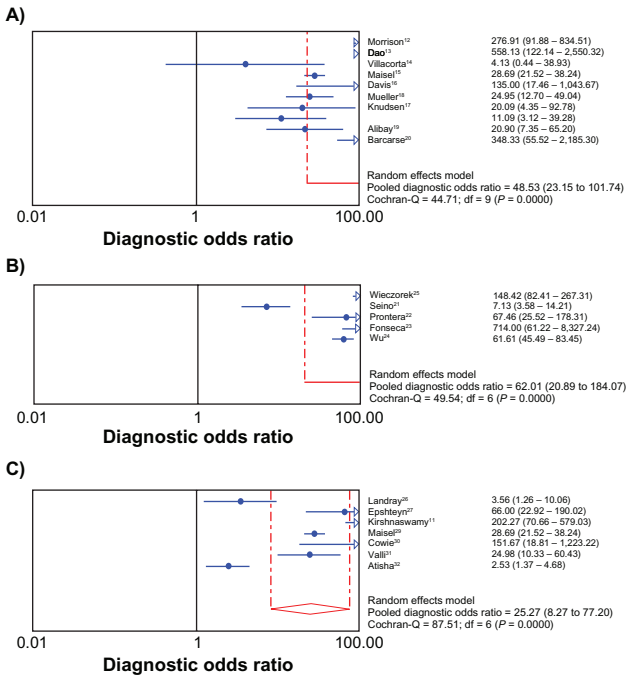

Figure 6 Pooled diagnostic odds ratio (95% confidence interval) for **A**) patients presenting to the emergency department with dyspnea, **B**) patients with chronic congestive heart failure versus healthy subjects, and **C**) patients referred for echocardiography.

accuracy of BNP in this clinical setting. This may be due to the fact that some studies included both symptomatic and asymptomatic patients. Another factor could be the type of practice of the referring physician.

The use of BNP as a screening tool in the general population was evaluated in three studies. The individual studies showed that BNP has a high negative predictive value. A value less than 50 pg/mL may have the best negative predictive value. Given the poor sensitivity and positive predictive value, BNP is not a useful screening tool for identifying patients with CHF.

A previous meta-analysis for BNP of CHF has been published.[48] This included patients with diastolic dysfunction and patients with recent acute coronary syndrome. Furthermore it divided the studies according to the reference test used. In this review we excluded studies that evaluated patient with only diastolic dysfunction and recent acute coronary syndrome. Similar to this study, Mastandrea[6] suggested that BNP could be more indicated for patients with acute CHF diagnosis. They concluded that the reference method used, disease prevalence, and degree of heart failure resulted in significant heterogeneity. Another study[49] compared BNP with N-terminal proBNP. The overall BNP specificity and sensitivity was similar to that of our study, at 85% and 84%, respectively. In this meta-analysis, we divided the studies into eight different subgroups according to the clinical application of the test. This facilitates the use and application of BNP to the appropriate patient population.

Conclusion

BNP is a valuable tool to aid in the diagnosis of CHF. It should be applied in the appropriate clinical setting. Based on the quality of the studies and the large number of patients, the best clinical evidence for use of BNP is available for patient presenting to the emergency department with symptomatic dyspnea. Further studies needed to evaluate BNP in additional patient groups, including asymptomatic or mildly symptomatic patients. BNP should be used in the right clinical setting in conjunction with other diagnostic tools to confirm CHF.

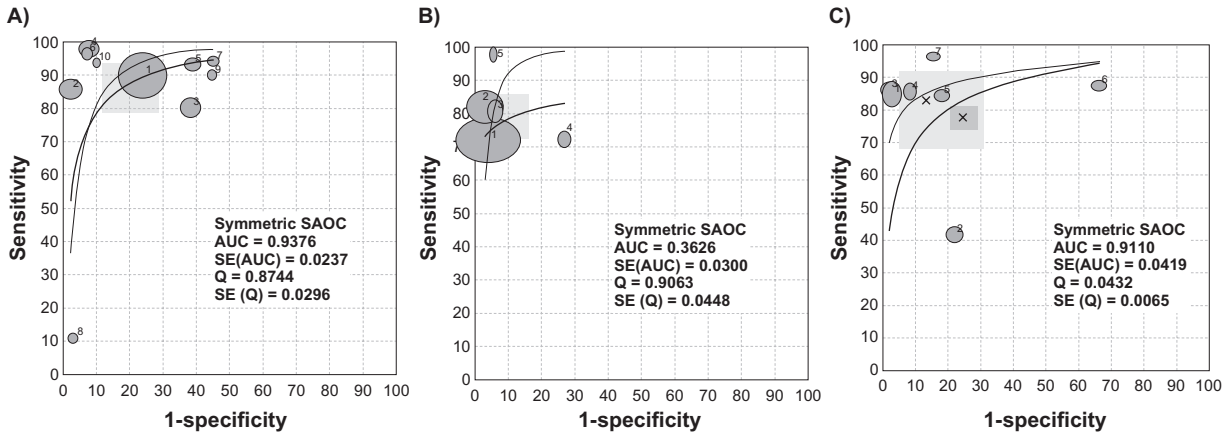

Figure 7 Summary receiver-operating curve for **A**) patients presenting to the emergency department with dyspnea, **B**) patients with chronic congestive heart failure versus healthy subjects, and **C**) patients referred for echocardiography.

Abbreviations: AUC, area under the concentration-time curve; SE, standard error; Q*, Q* index defined by the point where sensitivity and specificity are equal, which is the point closest to the ideal top left corner of the ROC space.

Disclosure

The authors report no conflicts of interest in this work.

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