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Natriuretic Peptide Testing in the Emergency Department: Beneficial Effects on Diagnosis; Systematic Review with Meta-Analysis

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ABSTRACT

Dyspnea is a frequent complaint in the emergency department (ED). Testing for amino-terminal pro-B-type natriuretic peptide (NT-proBNP) would increase diagnostic accuracy and decrease diagnostic uncertainty in patients with dyspnea. The current review aimed to assess the usefulness of systematic natriuretic peptide testing in the diagnosis of patients presenting with acute dyspnea in the ED. The literature search was performed between 2000 and 2024 throughout PubMed, MEDLINE, EMBASE, and Cochrane Central for eligible articles on natriuretic peptide (BNP) diagnostic accuracy. All clinical studies evaluating the diagnostic accuracy of BNP among patients with dyspnea were included. Only studies aged 18 or older were reviewed, with exclusions for incomplete records, case reports, languages, and samples other than blood. The present systematic review included 13 articles, encompassing 4524 patients. There were seven cross-sectional studies, and one diagnostic, retrospective, and randomized controlled trial, separately. The pooled sensitivity of serum BNP was 0.94 (95%CI; 0.94, 0.95) and the pooled specificity was 0.87 (95%CI; 0.86, 0.88). The pooled sensitivity of serum NT-proBNP was 0.94 (95%CI; 0.91, 0.96) and the pooled specificity was 0.85 (95%CI; 0.80, 0.88). The review reveals that BNP or NT-proBNP have high rule-out properties for dyspnea in ED cases, potentially adding benefits to CHF management.

Keywords: BNP, B-type natriuretic peptide, NT-proBNP, apnea, dyspnea, diagnosis, accuracy

INTRODUCTION

Heart failure (HF) is one of the most frequent causes of shortness of breath, which is a common reason for patients to arrive at the emergency department (ED). Comorbidities frequently aggravate the symptoms of patients, making diagnosis challenging, with a recommendation to use natriuretic peptides with a class IIa recommendation n 2000, the US FDA approved using brain natriuretic peptide (BNP) as an additional test to help diagnose heart failure[1,2]. The same year, Biosite Inc. (now Alere) introduced BNP as a point-of-care test for use in the emergency department (ED)[3,4]. Undifferentiated dyspnea is a common reason patients go to the emergency department[5]. Undifferentiated dyspnea may arise from a variety of conditions, including acute and chronic congestive heart failure, chronic obstructive pulmonary disease (COPD), asthma, acute coronary syndrome (ACS), pneumonia, and pulmonary embolism. Patients in the emergency room end up staying longer in the hospital and have a higher risk of morbidity and death when clinicians are unsure of the reason for their dyspnea[6].

The sensitivity of natriuretic peptides in diagnosing heart failure has been demonstrated. Using a point-of-care system to measure these levels minimizes errors, increases the precision of physician decision-making, and dramatically lowers the rate of clinical indecision during the initial examination[7,8]. Previous studies revealed highly diagnostic performance of NT-proBNP using age-related cut-off points to define abnormal level[9,10]. The levels of BNP are less affected by age compared to the levels of NT-proBNP. As a result, interpreting NT-proBNP values typically requires the use of age-specific reference values[11]. Otherwise, BNP and NT-proBNP can generally be used interchangeably, as there are no clinically significant differences in overall accuracy[12].

Several studies have validated the use of measuring BNP and NT-proBNP in the plasma of individuals experiencing acute dyspnea[13-17]. In addition, previous studies highlighted the necessity of hospital admission and hospital stay for patients with heart failure based on BNP and NT-proBNP values[18-20]. Patients with heart failure showed lower

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levels of natriuretic peptides after receiving long-term beta-blocker and RAAS blocker medication[21,22]. Adding a single BNP or NT-proBNP measurement could improve diagnostic accuracy compared with standard clinical judgment alone. They have provided cutoff values for BNP and NT-proBNP to "rule out" or "rule in" congestive heart failure (CHF)[23,24]. The current review aimed to assess the usefulness of systematic natriuretic peptide testing in the diagnosis of patients presenting with acute dyspnea in the emergency settings.

METHODOLOGY

This systematic review was executed in parallel with PRISMA guidelines[25], and the recommendations of the Cochrane Collaboration[26].

Search strategy: PubMed, MEDLINE, EMBASE, and Cochrane Central were searched for eligible articles until September 2024. Articles included were articles published in the English language using the following search string: (natriuretic peptide OR BNP OR NT-proBNP OR natriuretic factor-32) AND [(Apnea) OR (Emergency department) OR (respiratory distress)]. The following criteria were used to include studies: (1) availability of cross-sectional, observational, prospective studies, clinical trials, and screening studies data (2) Studies with complete data (assessing the testing benefits and factors associated with use), (3) Studies published during the period from 2000 to 2024, (4) Studies with indexed publication, (5) use of a validated or standardized diagnostic tool for assessing the BNP diagnostic accuracy. The study included only human subjects who were 18 years of age or older were the reviewed studies. Exclusion criteria were: (1) studies with incomplete records, (2) case reports, abstracts, letters, or reviews, (3) studies in a language other than English, and (4) studies conducted on animals or human samples other than blood (e.g., urine or cell cultures). A specific exclusion criterion for enrollment was for studies including cases diagnosed with disorders raising B-type natriuretic peptides independent of cardiac failure (e.g., renal disease, atrial fibrillation, respiratory disease, pulmonary hypertension, heart transplant, etc.). The assay types were restricted to the most commercially known tests for BNP.

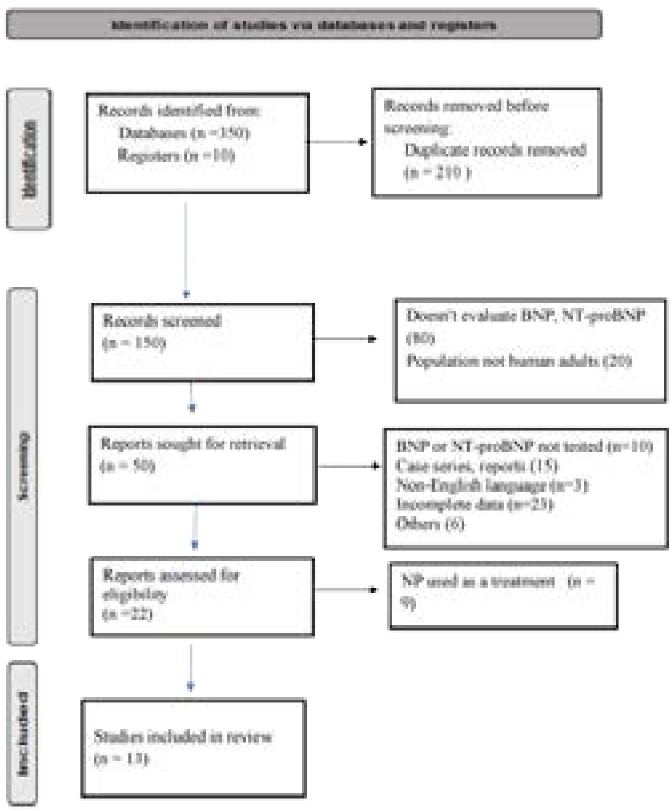

Figure 1. Flowchart (www.prismastatemant.org) depicting the selection of articles.

Study selection: The literature review was carried out by the corresponding author, and the eligibility of the studies was separately evaluated by two other independent reviewers. If an agreement couldn't be reached, disagreements were settled by conversation and, if needed, the assistance of a third reviewer was asked for consensus.

Data extraction: A pre-structured data extraction sheet was used for data collection, which the study researchers designed to avoid inter-rater and intra-rater bias. Items collected for each study population included the type of study, study age, country, BNP data (index test), reference (standard) test, and BNP diagnostic ability (sensitivity/specificity).

Statistical analysis: Pooled sensitivity, specificity, positive likelihood ratio (PLR), negative likelihood ratio (NLR), diagnostic odds ratio (DOR), and their 95% confidence intervals (CI) were calculated as a whole and were displayed as forest plots. The summary receiver operating characteristic curve (SROC), area under the curve (AUC), and Q* index (point at which the sensitivity and specificity are equal) were calculated. AUC values of more than 80% represented the greatest potential for actual clinical application. Statistical heterogeneity was determined using Higgins I^2 statistic, at the value of $>50\%$, and the Cochrane Q (Chi^2 test), at the value of $p<0.10$. Review Manager version 5.4 and MetaDisc software were used to analyze the data[27,28].

RESULTS

Searching the literature revealed 360 articles of which 210 duplicates were removed. Furthermore, 150 articles were included for title and abstract screening, in which 128 were excluded. Finally, 13 articles were finally included for data extraction and systematic review. All criteria for inclusion or removal of the review studies were illustrated in PRISMA (Figure 1).

Characteristics of the included studies

The present systematic review included 13 articles, encompassing 4524 patients. There were seven cross-sectional studies, and one diagnostic, retrospective, and randomized controlled trial, separately[8,29-40]. Most studies were conducted in the USA (4 studies), France (2 studies), Australia (2 studies), and other countries were also included such as Spain, Brazil, India, New Zealand, and Pakistan. The mean age of participants ranged from 49 to 80 years old. Heart failure or cardiac disorder diagnosis ranged from 34% to 83% of assessed cases. All cases in the studies included showed shortness of breath (SOB), which may be associated with limited physical activity or ventricular arrhythmia. BNP was the most tested screening method among studies while NT-proBNP was used in four studies. Cardiologists blinded to BNP results were used for diagnosis as a standard method for most studies cases but in some studies, the standard diagnosis is based on cardiologist with pneumologist and ER physician Table 1.

Diagnostic accuracy of the study tests (BNP and NT-proBNP)

The pooled sensitivity of serum BNP was 0.94 (95%CI; 0.94, 0.95) with a statistical heterogeneity between the analyzed articles (I^2=97.6%, P<0.001)[29-31,33,34,36-40]. The pooled specificity was 0.87 (95%CI; 0.86, 0.88) with a statistical heterogeneity between the analyzed articles (I^2=98%, P<0.001). The pooled PLR and NLR were 6.50 (95%CI; 3.29, 12.84) and 0.10(95%CI; 0.04, 0.23), respectively. The pooled AUC was 0.9486 with a standard error of 0.0160 (Figures. 2A, 2B, 2C, 2D, and 2E).

Table 1. Summary of characteristics of the studies included the study review of Natriuretic Peptide diagnostic accuracy in ED (n=13)

No	Study ID	Study year	Study country	Study design	Study cases	Sample size	Mean age	HF rate	Standard diagnostic test	Used standard method	Screening test	Sensitivity	Specificity	AUC
1	Dao et al., [40]	2001	USA	Cross-sectional	SOB	250	64	39%	Blinded cardiologist report	Clinical	BNP	98%	95%	0.98
2	Logert et al., [29]	2002	France	Cross-sectional	SOB	63	67	71%	Cardiologist +pneumologist report	Clinical	BNP	97%	27%	0.93
3	Maisel et al., [30]	2002	USA	Cross-sectional	SOB	1586	64	47%	Blinded cardiologist report	Clinical	BNP	97%	62%	0.91
4	Villacorta et al., [31]	2002	Brazil	Cross-sectional	SOB	70	72	51%	Blinded cardiologist report	Clinical	BNP	100%	97%	0.99
5	Jose et al., [32]	2003	India	Cross-sectional	SOB	119	54	61%	Not mentioned	ECHO-based	NT -proBNP	97%	89%	0.94
6	Lainchbury et al., [33]	2003	New Zealand	Diagnostic screening	SOB	205	70	34%	Blinded cardiologist report	Clinical	NT -proBNP	87%	71%	0.89
7	Barcarse et al., [34]	2004	USA	Prospective study	VA with SOB	98	65	58%	Blinded cardiologist report	Clinical	BNP	96%	91%	0.98
8	Bayés-Genís et al., [35]	2004	Spain	Prospective study	SOB	100	71	83%	Blinded cardiologist report	Clinical	NT -proBNP	98%	47%	0.96
9	Ray et al., [36]	2004	France	Cross-sectional	SOB	308	80	46%	Cardiologist +pneumologist +geriatrician +ER physician report	Clinical	BNP	78%	90%	0.87
10	Smit et al., [37]	2008	Australia	Prospective study	SOB	406	NR	43%	Blinded cardiologist report	Clinical	BNP	78%	88%	0.86
11	Green et al., [8]	2008	USA	Retrospective	SOB	592	69	56%	Cardiologist review	Clinical	NT -proBNP	92%	86%	0.96
12	Lokuge et al., [38]	2010	Australia	RCT	SOB	612	74	45%	Blinded cardiologist + emergency or respiratory physician report	Clinical	BNP	65%	92%	0.81
13	Saghir et al., [39]	2023	Pakistan	Cross-sectional	NYHA Class III and IV	115	49.1	66%	Blinde cardiologist report	ECHO-based	BNP	94%	75%	0.92

The pooled sensitivity of serum NT-proBNP was 0.94 (95%CI; 0.91, 0.96) with a statistical heterogeneity between the analyzed articles (I^2=68.6%, P=0.0413)[32, 35]. The pooled specificity was 0.85 (95%CI; 0.80, 0.88) with a statistical heterogeneity between the analyzed articles (I^2=85.8%, P=0.009). The pooled PLR and NLR were 4.66 and 0.07, respectively. The pooled AUC was 0.9709 with a standard error of 0.0246 (Figures. 3A, 3B, 3C, 3D, and 3E).

DISCUSSION

Dyspnea in the emergency settings is challenging to distinguish between the several possible causes[41]. One of the most significant causes of dyspnea is acutely destabilized heart failure (ADHF), which is prevalent and carries a significant risk of morbidity and death if it is not identified promptly[42,43]. Herein, careful clinical decisions are essential when assessing the patient with dyspnea[44,45]. The clinical uncertainty with diagnosis may be minimized by using new diagnostic technology to enhance clinical judgment[13,46,47]. It has recently been demonstrated that biomarkers like BNP and amino-terminal pro-B type natriuretic peptide (NT-proBNP) increase clinician accuracy for the diagnosis of ADHF in the ED scenario[47].

The current meta-analysis showed high sensitivity with lower specificity for both BNP and NT-proBNP in diagnosing dyspnea cases in ED. The findings also clearly show that BNP and NT-proBNP have similar diagnostic performance features that may be useful in treating individuals with acute dyspnea. In particular, the low specificities and high sensitivities suggest that these peptides can be used in the acute clinical emergency to exclude HF as the source of acute dyspnea.

These findings were similar to a previous meta-analysis conducted by Worster A et al. 2008[47] who reported that the pooled estimates of sensitivity and specificity were the same for the BNP studies as for the NT-proBNP studies. All indicated the same conclusion that using BNP NT-proBNP has a very similar diagnostic value and can be used to exclude heart failure among ED cases.

On the other hand, Trinquart L et al. 201[48] in their meta-analysis concluded that evidence remains inconclusive on whether systematic natriuretic peptide testing is useful for the management of patients presenting to ED with acute dyspnea. Also, Lokuge A et al. 2010[38] reported that the non-BNP group's ED diagnosis of HF had an accuracy, specificity, and sensitivity of 81%, 92%, and 65%, respectively. For the diagnosis of HF in the ED, the BNP group's sensitivity, specificity, and accuracy were comparable at 66%, 90%, and 78%, respectively. The BNP and non-BNP groups did not significantly vary from one other in any of the HF diagnosis accuracy metrics. This means that the availability of BNP levels in ED did not significantly improve the accuracy of a diagnosis of HF.

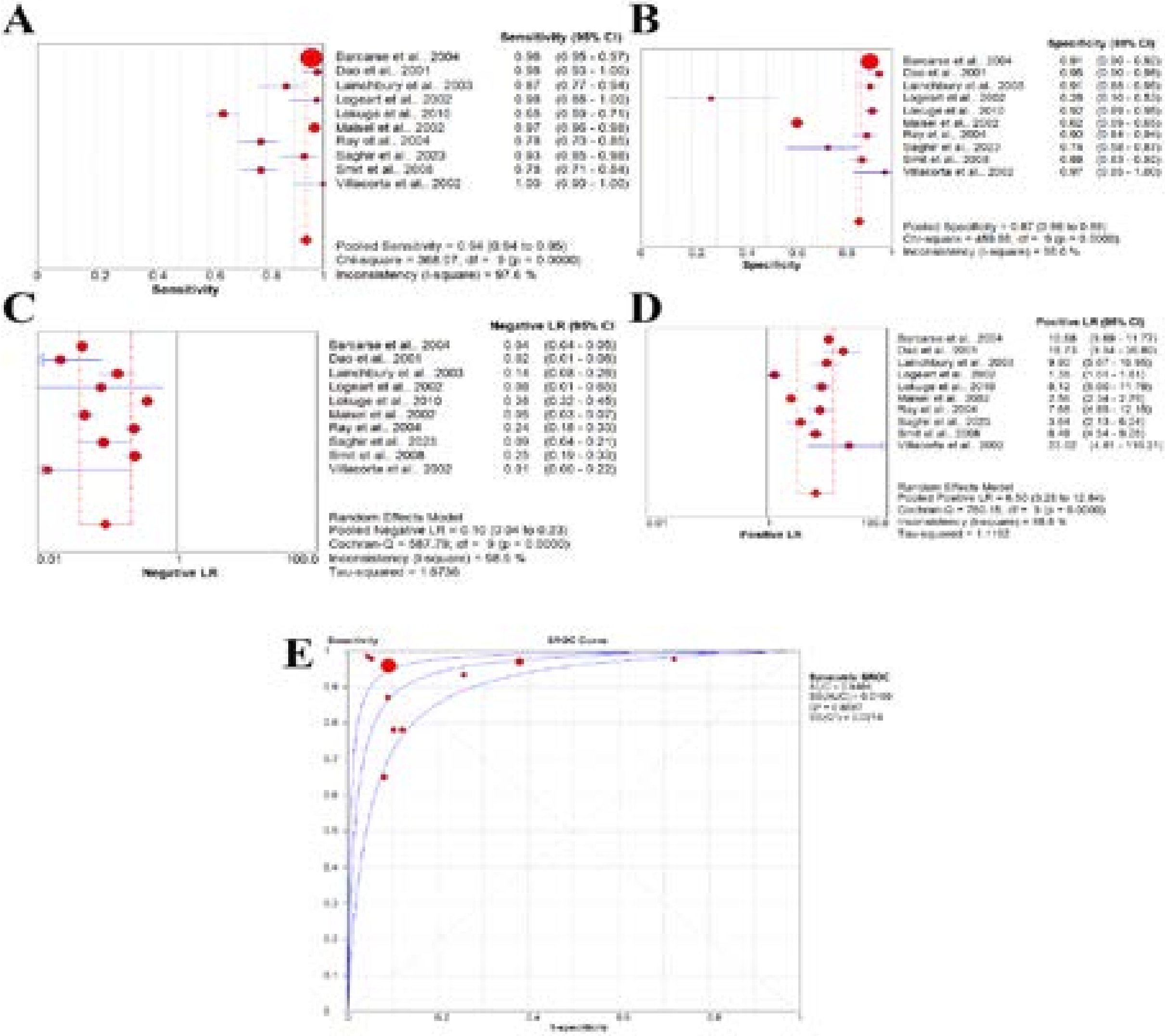

Figure 2. Diagnostic test accuracy meta-analysis of BNP for diagnosis patients with acute Dyspnea in the emergency settings **(A)** Pooled sensitivity and 95%CI of BNP for diagnosis patients with acute Dyspnea in the emergency settings **(B)** Pooled Specificity and 95%CI of BNP for diagnosis patients with acute Dyspnea in the emergency settings**. (C)** Pooled Positive likelihood ratio and 95%CI of BNP for diagnosis patients with acute Dyspnea in the emergency settings**. (D)** Pooled Negative likelihood ratio and 95%CI of BNP for diagnosis patients with acute Dyspnea in the emergency settings**. (E)** Summary receiver operating characteristics curve with pooled area under curve and 95%CI of BNP for diagnosis patients with acute Dyspnea in the emergency settings

To rule out acute heart failure, Januzzi et al. 2006 published an NT-proBNP cut point value of 300 pg/mL with corresponding 99% sensitivity and 60% specificity[10]. In a meta-analysis of 22 BNP trials, Battaglia et al.[9] found no cut-point value but rather a summary negative likelihood ratio of 0.18. Doust et al.[48] reported a high sensitivity BNP or NT-proBNP with a cut point value of around 15 pmol/L (52 pg/mL and 127 pg/mL, respectively) in their meta-analysis. Like us, Doust et al.[48]discovered that estimates of diagnostic accuracy vary throughout studies, and that variance does not appear to be explained by variations in the clinical situation or the kind of test employed. Although

Differences in the peptides tested (BNP or NT-proBNP) and the measurement technique account for variations in diagnostic accuracy[49,50]. For example, the Triage BNP assay regularly yields greater results than the Shionoria assay, and the size of the differential grows with concentration (and heart failure severity)[51].

CONCLUSIONS AND RECOMMENDATIONS

In conclusion, the current review showed that BNP or NT-proBNP showed significantly high rule-out properties for dyspnea with lower rule-in criteria in ED cases. Also, their use may add extra benefits to managing patients with CHF in the ED. There was a high discrepancy in their sensitivity and specificity values across studies, mainly observational studies with small sample sizes. The extra benefit of the clinical examination is still controversial. However, peptide measurement should be restricted to cases where the cause of dyspnea is still unclear after a complete clinical assessment.

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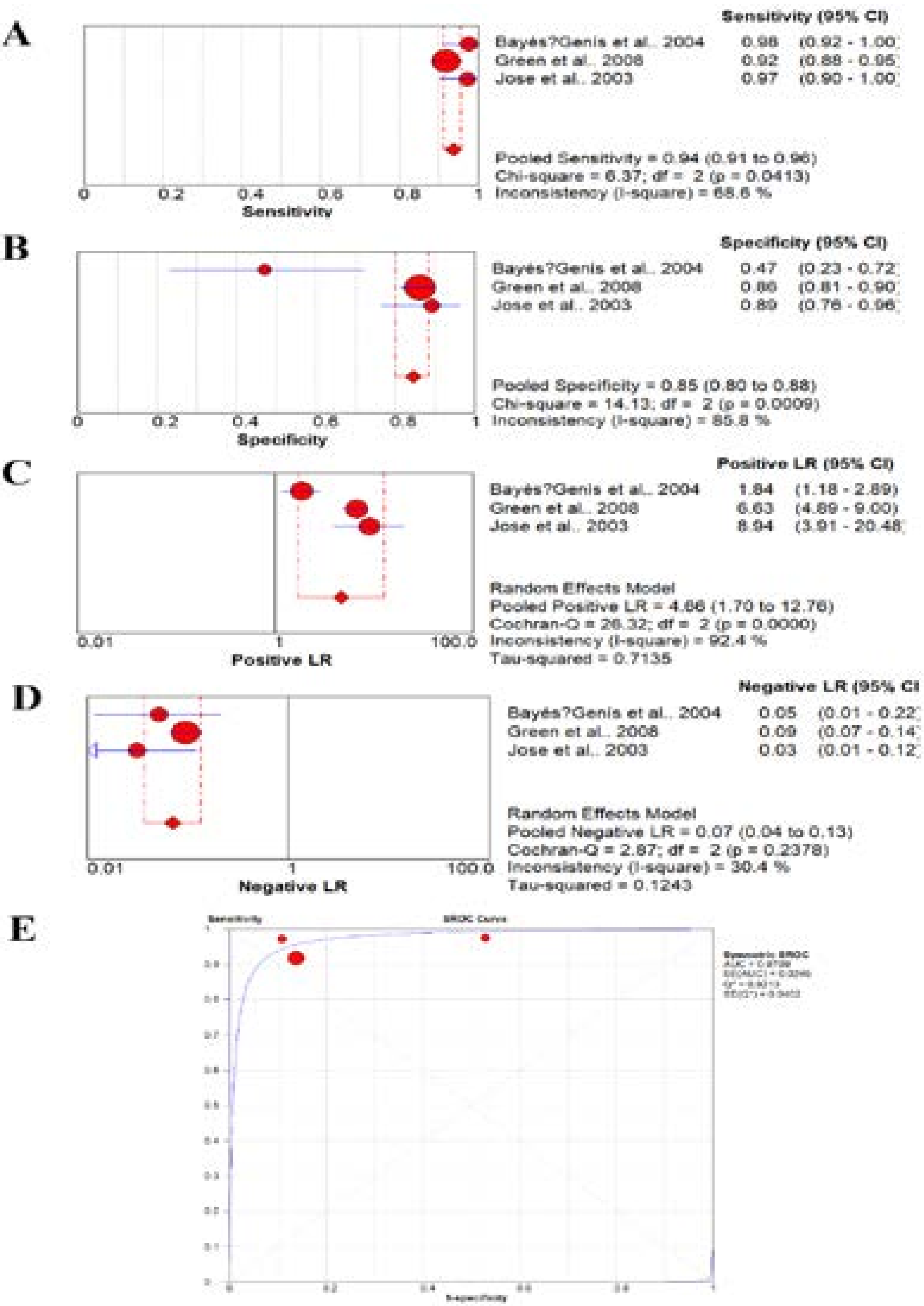

Figure 3. Diagnostic test accuracy meta-analysis of NT-PROBNP for diagnosis patients with acute Dyspnea in the emergency settings **(A)** Pooled sensitivity and 95%CI of NT-PROBNP for diagnosis patients with acute Dyspnea in the emergency settings **(B)** Pooled Specificity and 95%CI of NT-PROBNP for diagnosis patients with acute Dyspnea in the emergency settings**. (C)** Pooled Positive likelihood ratio and 95%CI of NT-PROBNP for diagnosis patients with acute Dyspnea in the emergency settings**. (D)** Pooled Negative likelihood ratio and 95%CI of NT-PROBNP for diagnosis patients with acute Dyspnea in the emergency settings**. (E)** Summary receiver operating characteristics curve with pooled area under curve and 95%CI of NT-PROBNP for diagnosis patients with acute Dyspnea in the emergency settings

Potential Conflicts of Interest: None

Competing Interest: None

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