The Diagnostic Utility of Brain Natriuretic Peptide in Heart Failure Patients Presenting with Acute Dyspnea: A Systematic Review and Meta-analysis

Mohammad Amin Karimi[1#], Zahra Kazemi Ferezghi[2#], Reza Khademi[3#], Seyed Amirhossein Mazhari[4], Fatemeh Chichagi[5], Asma Rasouli[6], Reyhaneh Alikhani[7], Anis Sani[8], Shima Akhavan Rezayat[9], Nima Shakouri[10], Seyed Iraj Azimi[11], Faezeh Jadidian[2], Golnaz Nikeghbali[2], Mahfam Edrisian[12], Alaleh Alizadeh[9], Niloofar Deravi[2], Mohadeseh Poudineh[13*], Mahsa Asadi Anar[2*]

[1]School of Medicine, Shahid Beheshti University of Medical Sciences, Tehran, Iran.
[2]Student Research Committee, School of Medicine, Shahid Beheshti University of Medical Sciences, Tehran, Iran.
[3]Student Research Committee, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran.
[4]Student Research Committee, Azerbaijan Medical University, Baku, Azerbaijan, Iran.
[5]Tehran Heart Center, Tehran University of Medical Sciences, Tehran, Iran.
[6]School of Medicine, Zanjan University of Medical Sciences, Zanjan, Iran.
[7]Tehran University of Medical Sciences, Tehran, Iran.
[8]Student Research Committee, Tabriz University of Medical Sciences, Tabriz, Iran.
[9]Student Research Committee, Faculty of Medicine, Islamic Azad University of Mashhad, Mashhad, Iran.
[10]School of Medicine, Guilan University of Medical Sciences, Rasht, Iran.
[11]Student Research Committee, Iran University of Medical Sciences, Tehran, Iran.
[12]Student Research Committee, School of Medicine, Iran University of Medical Sciences, Tehran, Iran.
[13]Student Research Committee, School of Medicine, Zanjan University of Medical Sciences, Zanjan, Iran.
#The authors contributed equally to the article.

Corresponding Authors:
Mahsa Asadi Anar, MD. Shahid Beheshti University of Medical Sciences. Arabi Ave, Daneshjoo Blvd, Velenjak, Tehran 19839-63113, Iran. Email: mahsa.boz@gmail.com.
Mohadeseh Poudineh, MD. School of Medicine, Zanjan University of Medical Sciences. 12th Street, Shahrake Karmandan, Zanjan 45139-56111, Iran. Email: mo.poudineh@gmail.com.

ABSTRACT

Background: *Patients with heart failure are often diagnosed based on clinical signs and serological markers. Finding biomarkers with greater sensitivity and specificity for heart failure patients who also have episodic dyspnea is a challenge for researchers. Thus, we conducted a systematic review and meta-analysis of previous research to determine the diagnostic value of B-type natriuretic peptide as a potential biomarker in heart failure patients experiencing acute dyspnea.* ***Methods:*** *By searching PubMed/Medline, Scopus, and Google Scholar up to March 2023, all cross-sectional and cohort studies were selected according to the PRISMA guidelines and assessed by the Deeks' funnel plot asymmetry test for bias.* ***Results:*** *A total of thirty-five qualifying studies had their data extracted. In 26 investigations (n=16002), the precision of B-type natriuretic peptide was evaluated. There were significant differences in the reported sensitivity and specificity between trials. One research study yielded the lowest sensitivity of 0.76 (0.68, 0.82), with a prevalence of 46% for heart failure and a BNP level of ≥500 pg/ml. Specificity grew but stayed variable as the threshold rose, whereas sensitivity declined. A diagnostic meta-analysis was carried out on 14 trials (n=6313) to determine the accuracy of N-terminal probrain natriuretic*

peptide. When the threshold is raised, the pattern in NTproBNP is similar to that of B-type natriuretic peptides, with sensitivity falling and specificity increasing. Following the final analysis, the confidence areas surrounding the pooled sensitivity and specificity for BNP vs NTproBNP showed a distinct overlap. The overlap indicated that there was no statistically significant difference between the tests at the <100 pg/ml and ≤300 pg/ml rule-out levels, respectively (P>0.05). ***Conclusion:*** *The meta-analysis reveals a substantial degree of congruity in the sensitivity and specificity between the levels of BNP and NTproBNP as biomarkers. Nevertheless, it's worth noting that, in the end, there exists a potential for overlooking heart failure diagnoses. Larger future studies, overcoming past limitations, could likely establish a consensus.*

Keywords: *NTproBNP, heart failure, B-type natriuretic peptide, BNP, meta-analysis*

INTRODUCTION

Breathlessness, often known as dyspnea, is one of the most prevalent reasons for visits to emergency departments. Dyspnea is a subjective perception of breathing difficulty characterized by qualitatively diverse sensations of varying intensity.[1] During the initial hours, the primary diagnosis is occasionally ambiguous. Some of the most prevalent underlying causes of acute dyspnea are cardiovascular disease (CVD), congestive heart failure (CHF), and chronic obstructive pulmonary disease (COPD). For many patients with acute dyspnea, clinical evaluations based on symptoms, physical indicators, and chest radiography remain inconclusive.[2]

The most frequent presenting symptom in patients with heart failure (HF) is dyspnea; more specifically, dyspnea at rest was prevalent in 38.0% of patients in North America and 70.1% of patients worldwide.[3] Dyspnea is commonplace in all phases of heart failure, and its underlying cause and severity must be evaluated to comprehend disease progression and treatment efficacy. Even individuals with stable HF have many symptoms, with dyspnea being the most noticeable and prevalent. In an HF outpatient clinic, up to 85 percent of patients judged shortness of breath to be the most significant symptom.[4] In the United States, the emergency department commences hospital-based care for more than 80% of patients with HF, and these Patients typically present with dyspnea. Given the broad differential for such a primary complaint, particularly in patients with numerous comorbidities, obtaining an accurate diagnosis is essential but can be challenging.[5]

The discovery and creation of novel biomarkers that aim to improve physicians' ability to diagnose and predict their patients' prognosis has been a significant development in medicine over the past decade. One of these biomarkers is brain natriuretic peptide (BNP).

Many studies have shown how crucial BNP is in the differential diagnosis of patients with acute dyspnea and how closely its level is correlated with the degree of heart failure. Thirty-two amino acids make up BNP, which is created as the pre-prohormone protein proBNP. ProBNP is secreted from cardiac myocytes in response to myocardial stretch, volume overload, and increased end-diastolic pressure. It is then cleaved into an active BNP and an inactive N-terminal pro-B-type natriuretic peptide (NT-proBNP) with 76 amino acids. BNP and NT-proBNP are typically used to evaluate cardiac function because they are biologically distinct from one another. They also play a significant role in the control of natriuresis, diuresis, and vascular tone. ACC/AHA guidelines recommend BNP and NT-proBNP for the sole diagnosis of heart failure. Testing for BNP and NT-proBNP is an advantageous diagnostic and predictive method for heart failure.[6] To the best of our knowledge, this systematic review, for the first time, is going to critically elucidate the diagnostic utility of brain natriuretic peptide in heart failure patients presenting with acute dyspnea.

METHODS

This systematic review/meta-analysis followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Our design protocol was registered in the International Prospective

Register of Systematic Reviews, known as PROSPERO (CRD42023421800). (https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42023421800)

Literature Search

Firstly, a comprehensive search was done in PubMed (Medline) and Scopus databases on March 12th, 2023. The search strategy was conducted based on the title, abstract, and suitable keywords and tags using advanced search features for each search engine. No limitation regarding time and language was set. The summary of our search strategy is available in Table 1. After searching, removing duplicates, and retrieving initiated articles, two researchers independently reviewed the studies' titles and abstracts, and conflicts were resolved by discussion with a third member. The next step was reviewing the full text of identified articles for exact inclusion criteria. All studies met the inclusion criteria included in the study.

Inclusion and Exclusion Criteria

In the present study, the authors included published papers discussing the diagnostic utility of BNP in patients presenting with dyspnea with a history of HF. We included Randomized Controlled Trials (RCTs), cross-sectional studies, and cohorts. Other studies were excluded, including reviews, case reports, case series, letters to the editor, abstracts, and posters.

Methodological Quality Assessment

We used the JBI criteria appraisal checklist to assess the included studies' quality, which is available at https://jbi.global/critical-appraisal-tools. Two team members evaluated all included studies' full texts independently, and disagreements were resolved by scientific consensus. Then, a data extraction form including author, country, study design, follow-up duration, sex, mean age, participants, index test, the reference standard for HF, adjustment, threshold, and outcomes was prepared, and two independent authors conducted this process.

Statistical Analysis

From every study, we retrieved data on binary diagnostic accuracy and created 2x2 tables at every threshold. To provide a general idea of test accuracy, we created a receiver operating characteristic plot of estimations for sensitivity and specificity for each threshold for each natriuretic peptide test. These charts show the data divided by research design and index test. One of two study designs—case-control or cross-sectional/cohort—was specified. Studies involving chosen healthy and unhealthy populations were included in the category of case-control studies. We did not include case-control studies in our analysis since their results are prone to bias.

For every natriuretic peptide, we created matched forest plots along with matching 95 percent confidence intervals. Based on these thresholds, we divided the data into two groups: <100 and ≥500 for BNP, and ≤300 and ≥1800 for NT-proBNP.

For every natriuretic peptide, we generated average summary receiver operating characteristic (sROC) curves and forest plots with estimates of the paired observed sensitivities and specificities at the predetermined threshold. The charts illustrate how the accuracy of the studies varies. We performed diagnostic meta-analyses when sufficient data were available. We needed five or more studies for each criterion to pool data. To pool test accuracy for the investigations, we employed the bivariate technique modeled in Winbugs (Medical Research Council Biostatistics Unit). Logistic regression is employed in the bivariate approach to analyze the true positives, true negatives, false positives, and false negatives that were documented in the research. We constructed sROCs and plotted confidence regions (using methods outlined by Novielli and colleagues.[7] From every study, we retrieved data on binary diagnostic accuracy and created 2x2 tables at every threshold. To provide a general idea of test accuracy, we created a receiver operating characteristic plot of estimations for sensitivity and specificity for each threshold for each natriuretic peptide test. These charts show the data divided by research design and index test. One of two study designs—case-control or cross-sectional/cohort—was specified. Studies involving chosen healthy and unhealthy populations were included in the category of

case-control studies. We did not include case-control studies in our analysis since their results are prone to bias.

For every natriuretic peptide, we created matched forest plots along with matching 95 percent confidence intervals. Based on these thresholds, we divided the data into two groups: <100 and ≥500 for BNP, and ≤300 and ≥1800 for NT-proBNP.

For every natriuretic peptide, we generated average summary receiver operating characteristic (sROC) curves and forest plots with estimates of the paired observed sensitivities and specificities at the predetermined threshold. The charts illustrate how the accuracy of the studies varies. We performed diagnostic meta-analyses when sufficient data were available. We needed five or more studies for each criterion to pool data. To pool test accuracy for the investigations, we employed the bivariate technique modeled in Winbugs (Medical Research Council Biostatistics Unit). Logistic regression is employed in the bivariate approach to analyze the true positives, true negatives, false positives, and false negatives that were documented in the research.

Table 1. Curated search strategies across databases

Search Engine	Search strategy	Time	Results
Scopus	TITLE-ABS-KEY (heart) AND (TITLE-ABS-KEY (dyspnea) OR TITLE-ABS-KEY (short AND of AND breath) OR TITLE-ABS-KEY (breathlessness) OR TITLE-ABS-KEY (breath AND shortness) OR TITLE-ABS-KEY (recumbent AND dyspnea) OR TITLE-ABS-KEY (rest AND dyspnea)) AND (TITLE-ABS-KEY (brain AND natriuretic AND peptide) OR TITLE-ABS-KEY (bnp-32) OR TITLE-ABS-KEY (brain AND natriuretic AND peptide-32) OR TITLE-ABS-KEY (natriuretic AND factor 32) OR TITLE-ABS-KEY (BNP AND gene AND product) OR TITLE-ABS-KEY (type-b AND natriuretic AND peptide) OR TITLE-ABS-KEY (Nesiritide) OR TITLE-ABS-KEY (b-type AND natriuretic AND peptide) OR TITLE-ABS-KEY (BNP) OR TITLE-ABS-KEY (Natrecor))	March 12th, 2023	5740
PubMed	(heart[Title/Abstract]) AND ((dyspnea[Title/Abstract]) OR (Shortness of Breath[Title/Abstract]) OR (Breath Shortness[Title/Abstract]) OR (Breathlessness[Title/Abstract]) OR (Orthopnea[Title/Abstract]) OR (Recumbent Dyspnea[Title/Abstract]) OR (Dyspnea, Recumbent[Title/Abstract]) OR (Platypnea [Title/Abstract]) OR (Trepopnea[Title/Abstract]) OR (Rest Dyspnea[Title/Abstract]) OR (Dyspnea, Rest[Title/Abstract]) OR (Dyspneas, Rest[Title/Abstract])) AND ((brain natriuretic peptide[Title/Abstract]) OR (Peptide, Brain Natriuretic[Title/Abstract]) OR (BNP-32[Title/Abstract]) OR (BNP 32[Title/Abstract]) OR (Brain Natriuretic Peptide-32[Title/Abstract]) OR (Brain Natriuretic Peptide 32[Title/Abstract]) OR (Natriuretic Peptide-32, Brain[Title/Abstract]) OR (Peptide-32, Brain Natriuretic[Title/Abstract]) OR (Natriuretic Factor-32[Title/Abstract]) OR (Natriuretic Factor 32[Title/Abstract]) OR (BNP Gene Product[Title/Abstract]) OR (Type-B Natriuretic Peptide[Title/Abstract]) OR (Natriuretic Peptide, Type-B[Title/Abstract]) OR (Type B Natriuretic Peptide[Title/Abstract]) OR (Natriuretic Peptide Type-B[Title/Abstract]) OR (Natriuretic Peptide Type B[Title/Abstract]) OR (Nesiritide[Title/Abstract]) OR (B-Type Natriuretic Peptide[Title/Abstract]) OR (Natriuretic Peptide, B-Type[Title/Abstract]) OR (Natrecor[Title/Abstract]))	March 12th, 2023	722

RESULTS

Study Selection

A PRISMA flow diagram offers an overview of the exclusions and screening procedure (**Figure 1**). Searches through PubMed, Scopus, and Google Scholar produced 6228 papers that might be of interest. 498 of these 6228 documents were identical hits, so we decided not to give them any further thought. After evaluating the abstracts and titles of 5730 papers, we eliminated 5410 as being unrelated to the review. After obtaining and examining 320 full-text papers, we formally eliminated 285 of them (which had no relevant outcomes). A total of 35 studies were deemed eligible and incorporated into the review.

After searching in (PubMed/Medline, Scopus, and Google Scholar) databases, a total of 6228 articles were obtained, and 498 duplicates were removed. After reviewing the title & abstract screening, 320 studies remained. The final review includes 35 articles of the final full-text results; the rest of which had unrelated data were deleted.

Baseline Characteristics

In total, 35 cohort studies were included in our systematic review and meta-analysis, which included 16102 patients. The patients' average age was 68.3, and 45.5% of them were female. The years of investigation were 2002 through 2023. The studies came from over ten different

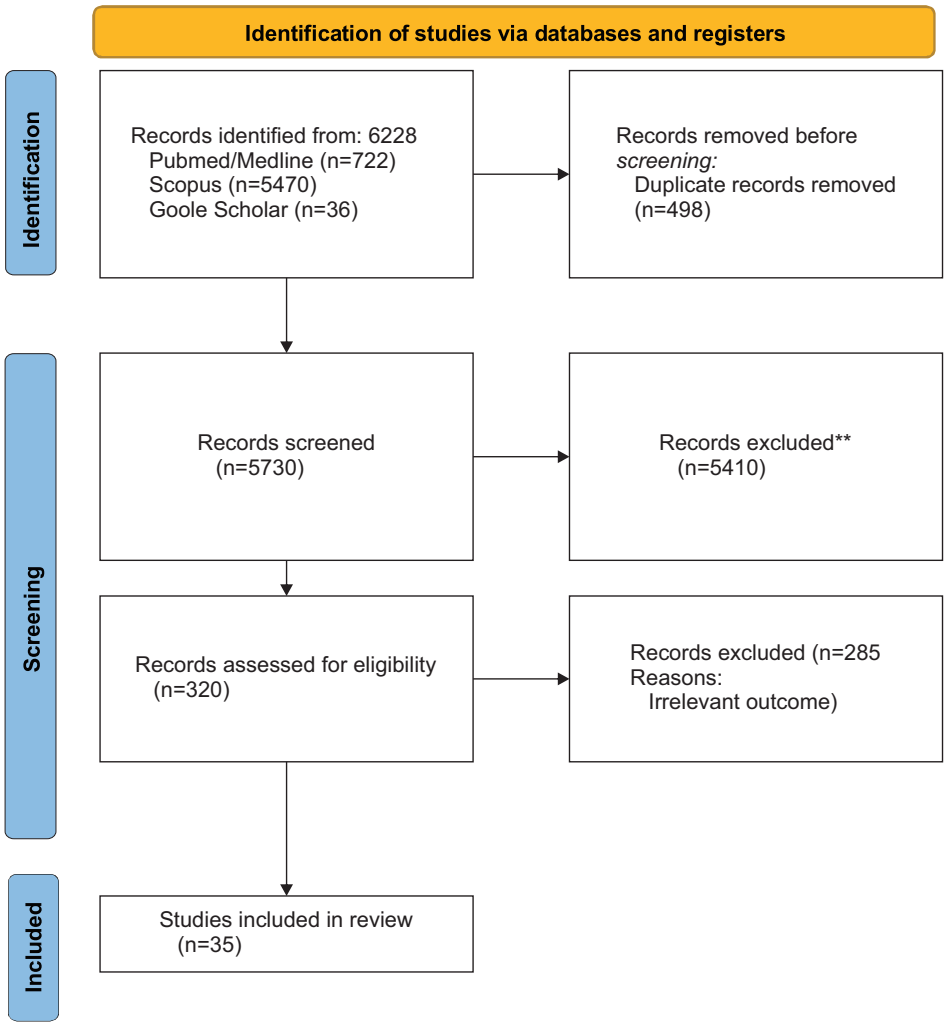


Figure 1. Flowchart of literature inclusion following PRISMA guidelines.

countries in a variety of geographical situations. The USA was the primary location for participant recruitment, with sample sizes varying from 41 to 1586 patients. A thorough explanation of the data retrieved from the listed research is provided in **Table 2**.

B-type Natriuretic Peptide

26 studies evaluated the accuracy of B-type natriuretic peptide. Data were reported at the <100 ng/L criterion in 7 studies (including 4434 people), the 100-500 ng/L threshold in 21 studies (involving 9371 participants), and the ≥500 ng/L threshold in 6 studies (involving 2297 participants). The majority of research used a cross-sectional/cohort design to evaluate the accuracy of the Triage test in comparison to clinical assessment.

There were significant differences in the reported sensitivity and specificity between trials. One study's findings, with a heart failure prevalence of 46%, had the lowest sensitivity.[8] The pooled sensitivity and specificity of B-type natriuretic peptide at a threshold of less than 100 were 0.92 (0.89, 0.94) and 0.69 (0.60, 0.77), respectively, when diagnostic meta-analysis was performed. The combined sensitivity and specificity at a B-type natriuretic peptide concentration of 100–500 pg/ml were 0.87 (0.83, 0.91) and 0.77. (0.70, 0.83). The combined sensitivity and specificity at a B-type natriuretic peptide concentration of ≥500 pg/ml were 0.76 (0.68, 0.82) and 0.79. (0.72, 0.85). Sensitivity dropped and specificity rose, but stayed unstable as the threshold rose (**Figure 2**). More details are included in **Figure 3**, which shows the summary sensitivity and specificity points concerning the forest plots in **Figure 1**. While the specificity was higher, the summary point for the threshold of ≥500 pg/ml is lower in the sROC space than the criterion of <100 pg/ml, indicating that heart failure diagnoses might be overlooked.

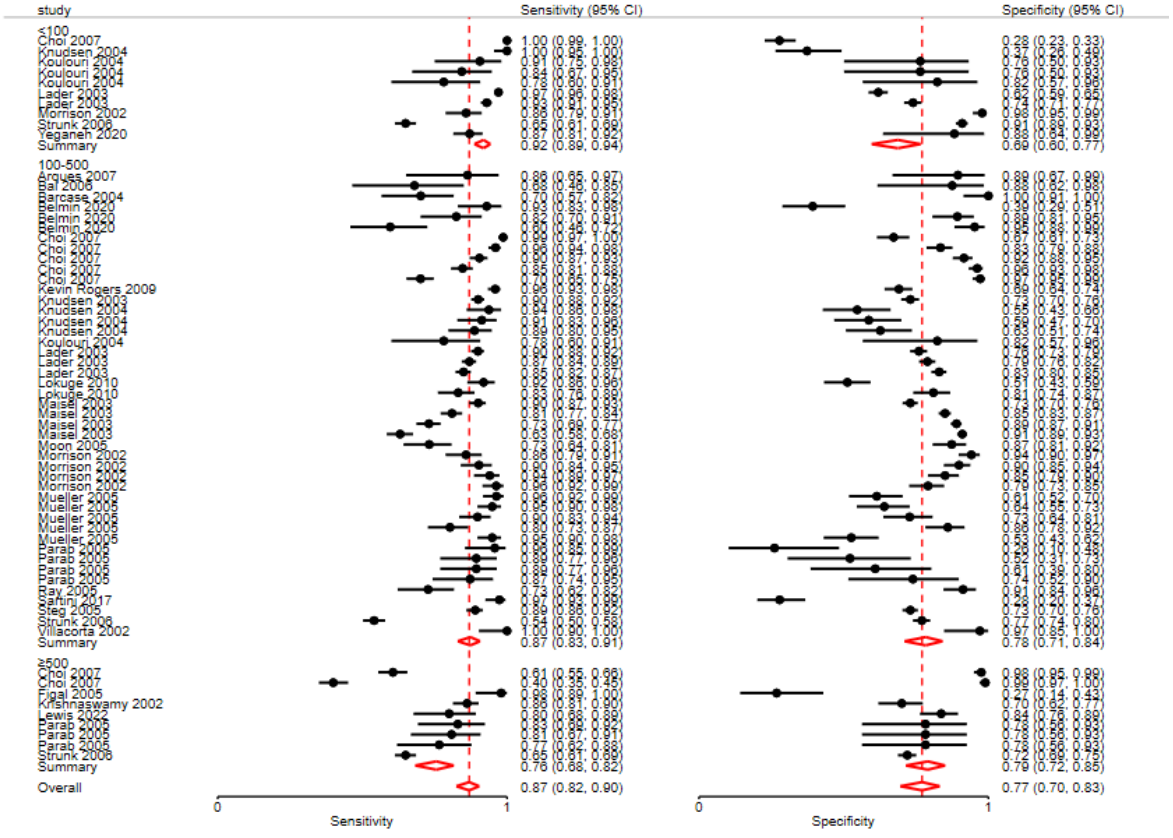


Figure 2. Paired sensitivity and specificity plots for B-type natriuretic peptide at three threshold levels

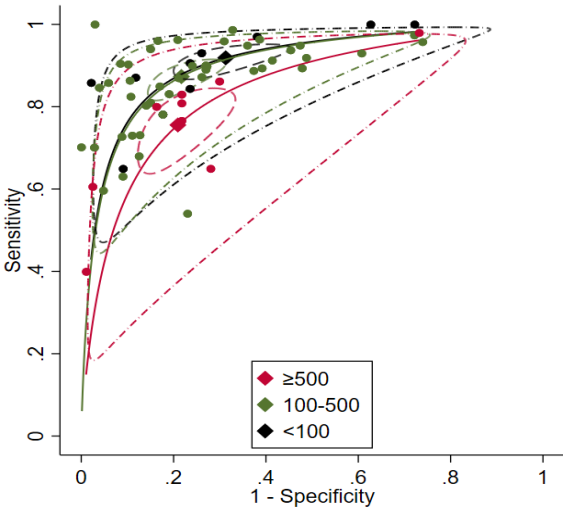


Figure 3. Results for B-type natriuretic peptide (separated by threshold) displayed in summary receiver operating characteristic space.

N-terminal Pro-brain Natriuretic Peptide

In 14 studies, the accuracy of B-type natriuretic peptide was evaluated. Data at the ≤300 pg/ml level were reported in 5 investigations, including 1671 people. At the 300–1800 pg/ml barrier in 11 investigations, including 4056 people, and the ≥1800 pg/ml threshold in two studies involving 586 participants.

The results of the diagnostic meta-analysis showed that, at a threshold of ≤300 ng/L, the pooled sensitivity, specificity, positive predictive value, and negative predictive value of NTproBNP were, respectively, 0.92 (0.87, 0.95) and 0.64 (0.57, 0.71). The pooled sensitivity and specificity were 0.87 (0.82, 0.91) and 0.80 at an NTproBNP level of 300–1800 pg/ml (0.75, 0.84). The pooled sensitivity and specificity were 0.62 (0.49, 0.72) and 0.90 at an NTproBNP level of ≥1800 pg/ml (0.85, 0.93). **Figures 4** and **5** show how B-type natriuretic peptides behave at various thresholds: as the threshold is raised, specificity increases and sensitivity decreases. **Figure 5** summary points unmistakably show a drop in mean sensitivity by threshold.

Comparisons Between Natriuretic Peptides

Following diagnostic meta-analysis, the confidence areas encompassing the pooled sensitivity and specificity for B-type natriuretic peptide and NTproBNP overlapped. The overlap indicated that there was no statistically significant difference between the tests conducted at the <00 ng/L and ≤300 ng/L rule-out thresholds, respectively (P>0.05). (**Figure 6**).

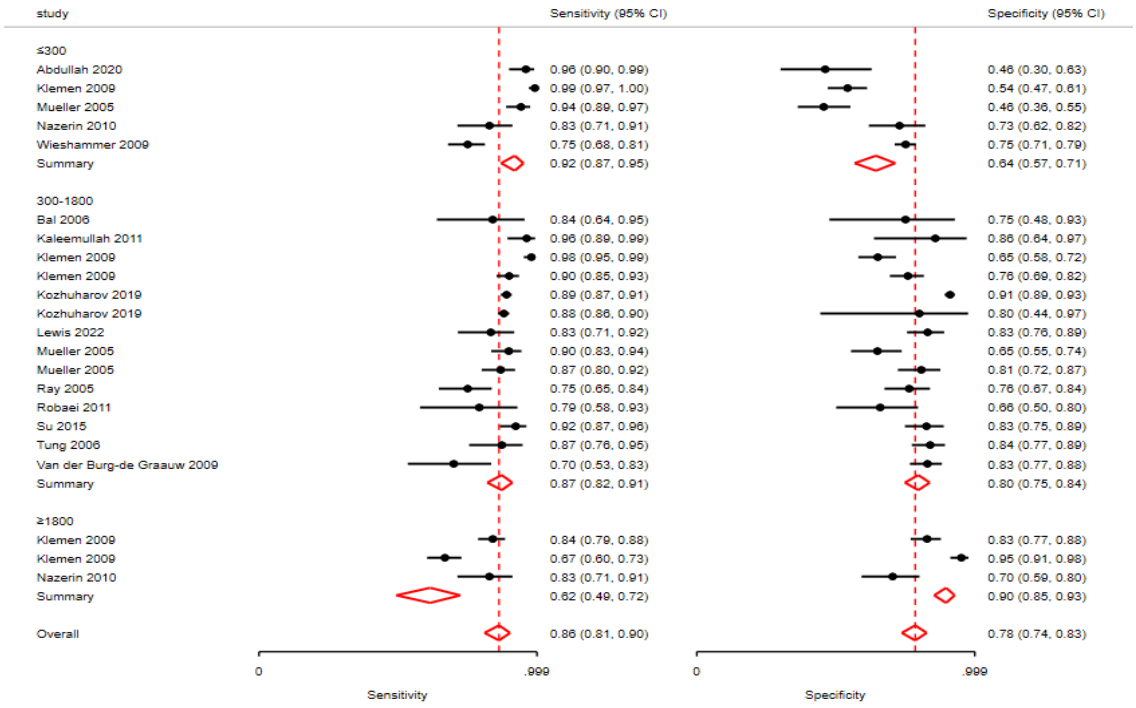


Figure 4. Paired sensitivity and specificity plots for N terminal probrain natriuretic peptide at three threshold levels.

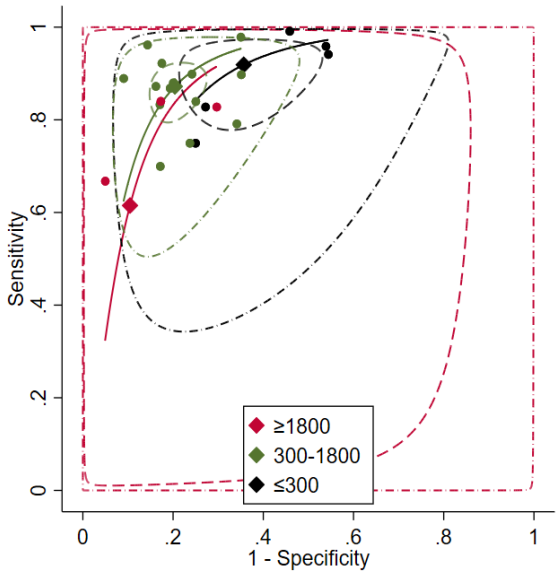


Figure 5. Results for N terminal pro-brain natriuretic peptide (separated by threshold) displayed in summary receiver operating characteristic space.

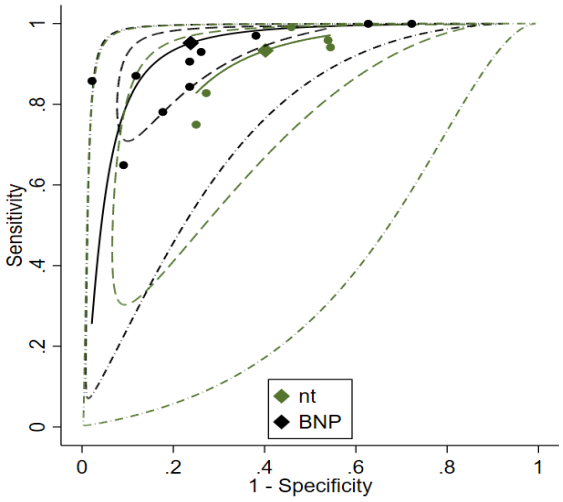


Figure 6. Comparison of pooled B type natriuretic peptide and N terminal pro-brain natriuretic peptide diagnostic accuracy results at lowest threshold

Publication Bias and Heterogeneity

No indication of publication bias was found for BNP<100, 100≤BNP<500, 300<NTproBNP<1800, and NTproBNP≥1800 according to Deeks' funnel plot asymmetry test (see supplementary file). The I2 data for every peptide at every threshold are shown in **Table 3**. I2 statistics were consistently greater than 50%, as anticipated in diagnostic meta-analyses, due to variations in the underlying diagnoses and comorbidities of the patients.

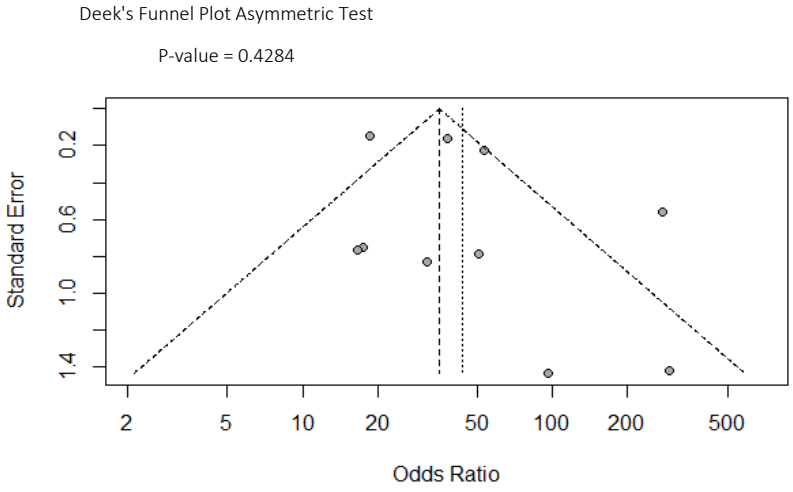
DISCUSSION

This systematic study investigated the effectiveness of Brain Natriuretic Peptide (BNP) and N-terminal pro-B-type brain natriuretic peptide (NT-proBNP) as diagnostic tools for heart failure patients experiencing acute dyspnea. The research included a total of 16102 Participants from 35 separate studies. The findings revealed an intriguing pattern, as the threshold values for both BNP and NT-proBNP increase, there is a noticeable decrease in sensitivity, while specificity tends to rise.

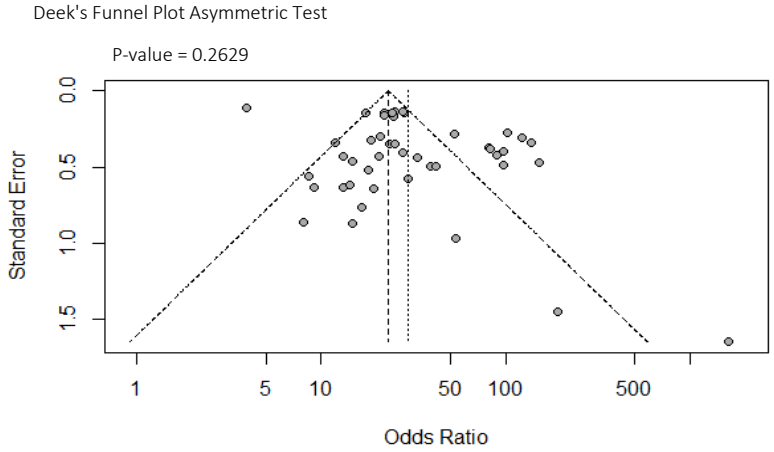
The meta-analysis unveiled that at a threshold of less than 100 pg/ml, BNP exhibited a sensitivity of 0.92 (with a confidence interval of 0.89 to 0.94) and a specificity of 0.69 (with a confidence interval of 0.60 to 0.77). Notably, Koulouri et al.[9] suggested that BNP thresholds below 100 pg/mL were optimal for maximizing sensitivity to rule out congestive heart failure (CHF). However, 100 pg/mL provided higher specificity for diagnosing CHF, especially in pediatric patients with respiratory distress. BNP cut-offs of 40 pg/mL and 60 pg/mL displayed even higher sensitivity at 91% and 83%, respectively, compared to 78% for 100 pg/mL.

Table 3. Sensitivity and Specificity for All Peptides

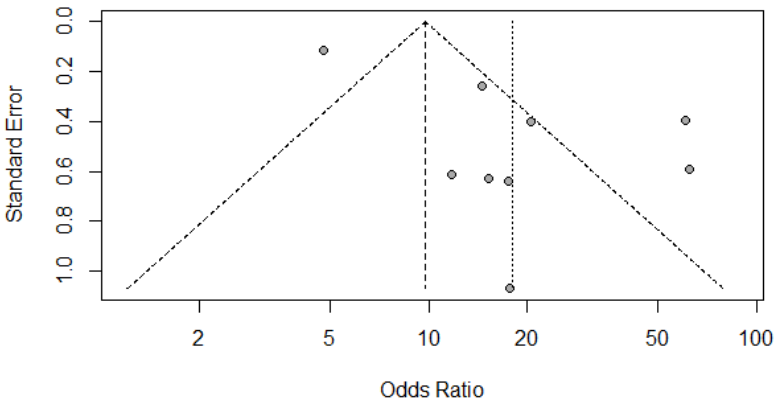
Natriuretic peptide (threshold)		Number of studies	Total patients	Sensitivity (%)	Specificity (%)	I^2
BNP	<100	7	4434	0.92 (0.89, 0.94)	0.69 (0.60, 0.77)	76.9%
	100-500	21	9371	0.87 (0.83, 0.91)	0.77 (0.70, 0.83)	90%
	≥500	6	2297	0.76 (0.68, 0.82)	0.79 (0.72, 0.85)	89.2%
NTproBNP	≤300	5	1671	0.92 (0.87, 0.95)	0.64 (0.57, 0.71)	72.1%
	300-1800	11	4056	0.87 (0.82, 0.91)	0.80 (0.75, 0.84)	83.4%
	≥1800	2	586	0.62 (0.49, 0.72)	0.90 (0.85, 0.93)	61.2%


Deek's Funnel Plot Asymmetric Test
P-value = 0.4284
Standard Error
0.2
0.6
1.0
1.4
2
5
10
20
50
100
200
500
Odds Ratio

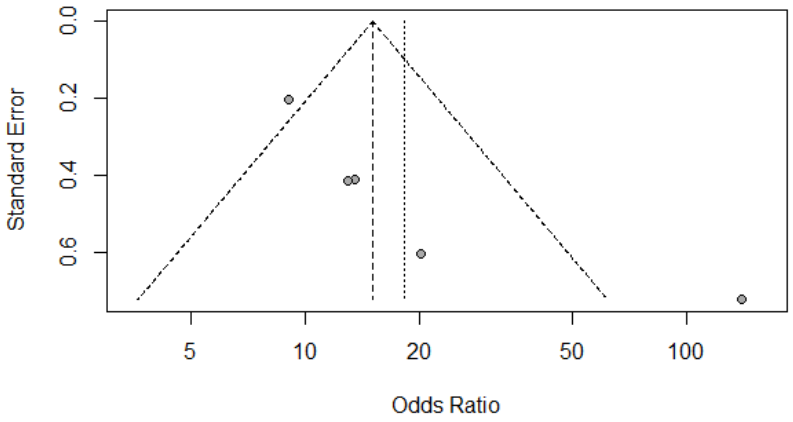
(A)


Deek's Funnel Plot Asymmetric Test
P-value = 0.2629
Standard Error
0.0
0.5
1.0
1.5
1
5
10
50
100
500
Odds Ratio

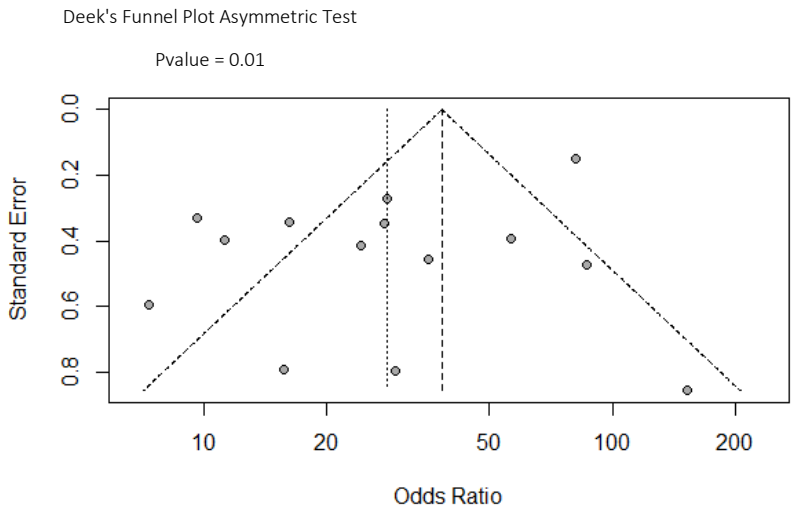
(B)


Standard Error
0.0
0.2
0.4
0.6
0.8
1.0
2
5
10
20
50
100
Odds Ratio

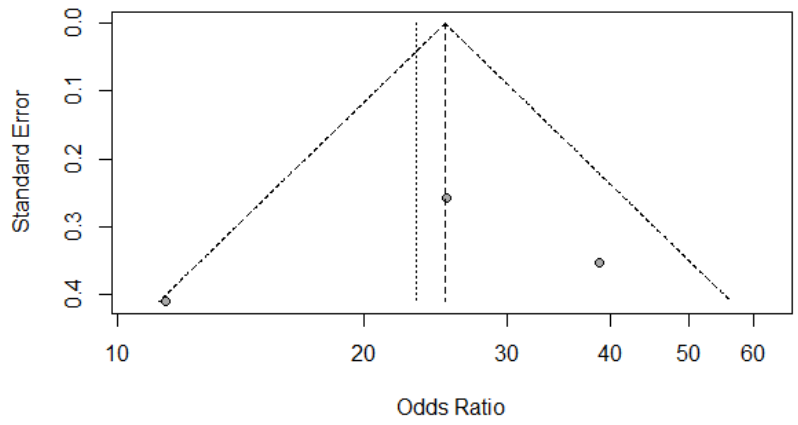
(C)



(D)



(E)



(**F**)

Figure 7. Thoroughly evaluates publication bias across distinct subsets of studies. Funnel plots are depicted for specific B-type natriuretic peptide (BNP) and N-terminal pro-B-type natriuretic peptide (NTproBNP) concentration ranges, including: (A) BNP < 100 pg/ml (B) 100 ≤ BNP < 500 pg/ml (C) BNP ≥ 500 pg/ml (D) NTproBNP ≤ 300 pg/ml (E) 300 < NTproBNP < 1800 pg/ml (F) NTproBNP ≥ 1800 pg/ml. Each plot illustrates the distribution of effect sizes relative to their standard errors, providing insights into potential publication bias within individual study subsets.

In contrast, the 100 pg/mL cut-off showed a better specificity of 85% compared to 77% for both 40 pg/mL and 60 pg/mL. These findings indicate that BNP thresholds below 100 pg/mL are more effective at excluding cases of CHF due to their high sensitivity. However, given its higher specificity, a 100 pg/mL threshold appears more appropriate for confirming CHF diagnosis.

Focusing on investigations with BNP values in the 100-500 pg/ml range, the sensitivity and specificity were 0.87 (with a confidence interval of 0.83 to 0.91) and 0.77 (with a confidence interval of 0.70 to 0.83), respectively. Furthermore, our data demonstrated that at a BNP level of 500 pg/ml or higher, sensitivity and specificity were 0.76 (with a confidence interval of 0.68 to 0.82) and 0.79 (with a confidence interval of 0.72 to 0.85), respectively. In the study conducted by Strunk et al.[10] A diagnostic performance evaluation of brain natriuretic peptide (BNP) for congestive heart failure (CHF) was carried out across various cut-off levels, ranging from 80 pg/mL to 500 pg/mL. The researchers observed a trade-off between sensitivity and specificity as the BNP cut-off value increased. Lower BNP thresholds within the 80-100 pg/mL range exhibited very high sensitivity, exceeding 90%, although specificity was somewhat suboptimal, falling below 75%. On the contrary, higher BNP cut-offs nearing 500 pg/mL demonstrated excellent specificity, exceeding 90%, but at the expense of considerably lower sensitivity, dropping below 60%. The researchers suggested that an optimal balance between sensitivity and specificity is achieved by utilizing mid-range BNP levels, specifically between 200-400 pg/mL. These thresholds seem to strike a reasonable compromise between maintaining reasonably high sensitivity while enhancing specificity, as opposed to the extremes of the tested range. This study highlights an interesting and potentially unfavorable association between sensitivity and specificity, which appears to depend on the chosen diagnostic BNP cut-off.

Parab et al.[11] conducted a study focusing on different brain natriuretic peptide (BNP) cut-offs for diagnosing congestive heart failure (CHF) in elderly individuals, with cut-offs ranging from 100 pg/mL to 700 pg/mL. The study revealed a gradual reduction in sensitivity with increasing BNP thresholds, ranging from 95.7% at the 100 pg/mL threshold to 76.5% at the 700 pg/mL threshold. In contrast, specificity exhibited an opposite trend, rising as the cut-offs increased, from a mere 26% at 100 pg/mL to 78.2% within the 600-700 pg/mL range. The commonly used 100 pg/mL threshold showcased outstanding sensitivity but poor specificity. Overall, an inverse relationship between sensitivity and specificity was observed, strongly influenced by the chosen BNP threshold, particularly in the context of diagnosing CHF in elderly patients.

Choi et al.[12] conducted a study involving BNP cut-offs ranging from 12.5 pg/mL to 983.5 pg/mL for diagnosing congestive heart failure in Korean patients experiencing dyspnea. Their findings indicated a gradual decrease in sensitivity from 100% at 12.5 pg/mL to 39.9% at 983.5 pg/mL; at the same time, specificity exhibited a converse trend, climbing from 27.8% to 98.8% across the same range of thresholds. The researchers achieved an optimal balance between sensitivity (90.5%) and specificity (91.4%) at a BNP cut-off of 296.5 pg/mL. Below this threshold, sensitivity exceeded specificity, whereas specificity surpassed sensitivity beyond 296.5 pg/mL. This pattern illustrates the typical negative relationship between sensitivity and specificity as dictated by the chosen diagnostic BNP threshold. Furthermore, this observation, suggesting a decline in sensitivity and an increase in specificity with higher cardiac BNP thresholds, resonates with several other studies that have explored the utility of BNP in detecting heart failure and acute dyspnea.[13-16]

Regarding the assessment of NT-proBNP, a total of 14 articles were considered. Among these, five studies (involving 1671 participants) presented results using the threshold of ≤300 pg/ml, while 11 studies (encompassing 4056 participants) utilized the 300-1800 pg/ml threshold. Additionally, two studies (comprising 586 participants) applied the≥1800 pg/ml threshold. Our findings indicated that at the ≤300 ng/L level, the sensitivity and specificity for NT-proBNP were 0.92 (with a confidence interval of 0.87 to 0.95) and 0.64 (with a confidence interval of 0.57 to 0.71), respectively. For the NT-proBNP cut-off range of 300-1800 pg/ml, sensitivity and specificity were 0.87 (with a

confidence interval of 0.82 to 0.91) and 0.80 (with a confidence interval of 0.75 to 0.84), respectively. Furthermore, at an NT-proBNP level of ≥1800 pg/ml, the pooled sensitivity and specificity were 0.62 (with a confidence interval of 0.49 to 0.72) and 0.90 (with a confidence interval of 0.85 to 0.93), respectively. In a study conducted by Kozhuharov et al.[17] An NT-proBNP threshold of 300 pg/mL exhibited a high sensitivity of 98%, albeit at the cost of low specificity at 22%, making it suitable for ruling out acute heart failure (AHF). In contrast, a cut-off of 2200 pg/mL demonstrated a specificity of 70% but a lower sensitivity of 83%, making it more suitable for ruling in AHF. Another study by Mueller et al.[14] established an NT-proBNP threshold of 825 pg/mL, ideally balancing sensitivity at 87% with specificity at 81% for AHF diagnosis. Nazerian et al.[18] identified an NT-proBNP cut-off below 450 pg/mL for patients under 50 years old and below 900 pg/mL for patients over 50. These thresholds achieved good sensitivity, exceeding 90%, but featured lower specificity at around 50%, allowing for the exclusion of AHF. Also, Klemen et al.[19] reported that an NT-proBNP threshold of 2000 pg/mL exhibited a sensitivity of 84% and specificity of 83% for AHF diagnosis, while a threshold of 300 pg/mL yielded a high sensitivity of 99% but lower specificity at 54%, making it suitable for ruling out AHF. In conclusion, the collective findings from these studies suggest that lower NT-proBNP cut-offs, ranging from 450-300 pg/mL, optimize sensitivity for excluding AHF, whereas higher thresholds in the range of 2000-900 pg/mL provide greater specificity for ruling in AHF. The best compromise between sensitivity and specificity is observed within the 825-2000 pg/mL range.

The relationship between sensitivity and specificity based on thresholds for both BNP and NT-proBNP has never been thoroughly studied before the publication of this systematic review and meta-analysis. Our study shed light on the intricate relationship between sensitivity and specificity based on the chosen diagnostic thresholds for both BNP and NT-proBNP, providing valuable insights into the diagnostic utility of these biomarkers in detecting heart failure and acute dyspnea. High heterogeneity in the results of studies included in our analysis is the main drawback of this study, and it is advised to carry on further studies to support our findings.

CONCLUSION

In summary, our findings suggest that elevating the B-type natriuretic peptide (BNP) and N-terminal pro-B-type natriuretic peptide (NT-proBNP) cut-off values, utilized as diagnostic tests for heart failure and for distinguishing the underlying causes of acute dyspnea, exhibits a direct correlation with heightened specificity and an inverse correlation with sensitivity. This implies that adopting a higher threshold may result in an increased occurrence of overlooked heart failure diagnoses, notwithstanding the enhancement in specificity. Determining the optimal threshold hinges upon whether the clinical priority pertains to optimizing sensitivity or specificity. The principal limitations of this study stem from the substantial heterogeneity observed in the outcomes of the studies subjected to our analysis. Consequently, further research is advisable to substantiate our outlined conclusions.

CONFLICT OF INTEREST

The authors declare there is no conflict of interest for this study.

FUNDING

None

ACKNOWLEDGMENTS

The authors would like to thank the researchers whose works were included in this article.

REFERENCES

1. Campbell ML. Dyspnea. AACN Adv Crit Care. 2011;22(3):257-64.
2. Wessman T, Tofik R, Ruge T, Melander O. Associations between biomarkers of multimorbidity burden and mortality risk among patients with acute dyspnea. Intern Emerg Med. 2022;17(2):559-67.
3. Filippatos G, Angermann CE, Cleland JGF, et al. Global differences in characteristics, precipitants, and initial management of patients presenting with acute heart failure. JAMA Cardiol. 2020;5(4):401-10.
4. Kjellström B, van der Wal MH. Old and new tools to

assess dyspnea in the hospitalized patient. Curr Heart Fail Rep. 2013;10(3):204-11.
5. Kuo DC, Peacock WF. Diagnosing and managing acute heart failure in the emergency department. Clin Exp Emerg Med. 2015;2(3):141-9.
6. Su Q, Liu H, Zhang X, et al. Diagnostic values of NT-proBNP in acute dyspnea among elderly patients. Int J Clin Exp Pathol. 2015;8(10):13471-6.
7. Hypoglycemia in the Diabetes Control and Complications Trial. The Diabetes Control and Complications Trial Research Group. Diabetes. 1997;46(2):271-86.
8. Strunk A, Bhalla V, Clopton P, et al. Impact of the history of congestive heart failure on the utility of B-type natriuretic peptide in the emergency diagnosis of heart failure: results from the breathing not properly multinational study. The American Journal of Medicine. 2006;119(1):69, e1-, e11.
9. Koulouri S, Acherman RJ, Wong PC, Chan LS, Lewis AB. Utility of B-type natriuretic peptide in differentiating congestive heart failure from lung disease in pediatric patients with respiratory distress. Pediatric Cardiology. 2004;25(4):341-6.
10. Strunk A, Bhalla V, Clopton P, et al. Impact of the history of congestive heart failure on the utility of B-type natriuretic peptide in the emergency diagnosis of heart failure: Results from the breathing not properly multinational study. American Journal of Medicine. 2006;119(1):69.e1-.e11.
11. Parab R, Vasudevan A, Brensilver J, Gitler B. Utility of brain natriuretic peptide as a diagnostic tool for congestive heart failure in the elderly. Critical Pathways in Cardiology. 2005;4(3):140-4.
12. Choi S. Cut-off values for B-type natriuretic peptides in Korean patients visiting emergency departments [2]. Emergency Medicine Journal. 2008;25(4):246.
13. Belmin J, Donadio C, Jarzebowski W, Genranmayeh K, Valembois L, Lafuente-Lafuente C. The value of B-type natriuretic peptide plasma concentrations in very old people with chronic peripheral oedema. Archives of Cardiovascular Diseases. 2020;113(5):332-40.
14. Mueller T, Gegenhuber A, Poelz W, Haltmayer M. Diagnostic accuracy of B-type natriuretic peptide and amino terminal proBNP in the emergency diagnosis of heart failure. Heart. 2005;91(5):606-12.
15. Lader E. BNP levels had high sensitivity but moderate specificity for detecting congestive heart failure in the emergency department. ACP J Club. 2003;138(1):23.
16. Maisel A. B-type natriuretic peptide measurements in diagnosing congestive heart failure in the dyspneic emergency department patient. Reviews in Cardiovascular Medicine. 2002;3(SUPPL. 4):S10-S7.
17. Kozhuharov N, Sabti Z, Wussler D, et al. Prospective validation of N-terminal pro B-type natriuretic peptide cut-off concentrations for the diagnosis of acute heart failure. European Journal of Heart Failure. 2019;21(6):813-5.
18. Nazerian P, Vanni S, Zanobetti M, et al. Diagnostic accuracy of emergency Doppler echocardiography for identification of acute left ventricular heart failure in patients with acute dyspnea: Comparison with Boston criteria and N-terminal prohormone brain natriuretic peptide. Academic Emergency Medicine. 2010;17(1):18-26.
19. Klemen P, Golub M, Grmec S. Combination of quantitative capnometry, N-terminal pro-brain natriuretic peptide, and clinical assessment in differentiating acute heart failure from pulmonary disease as cause of acute dyspnea in pre-hospital Emergency setting: Study of diagnostic accuracy. Croatian Medical Journal. 2009;50(2):133-42.
20. Maisel AS, McCord J, Nowak RM, et al. Bedside B-type natriuretic peptide in the emergency diagnosis of heart failure with reduced or preserved ejection fraction: results from the Breathing Not Properly Multinational Study. Journal of the American College of Cardiology. 2003;41(11):2010-7.
21. Moon JY, Bae JH, Kim TH, et al. The role of plasma B-type natriuretic peptide measurements in the differential diagnosis of acute dyspnea. Tuberculosis and Respiratory Diseases. 2005;59(6):656-63.
22. Figal DAP, Sánchez MCC, Velasco JAN, et al. Usefulness of NTproBNP in the emergency management of patients with severe dyspnea and an uncertain heart failure diagnosis. Revista Española de Cardiología (English Edition). 2005;58(10):1155-61.
23. Sartini S, Frizzi J, Borselli M, et al. Which method is best for an early, accurate diagnosis of acute heart failure? Comparison between lung ultrasound, chest X-ray, and NT pro-BNP performance: a prospective study. Internal and emergency medicine. 2017;12:861-9.
24. Kevin Rogers R, Stehlik J, Stoddard GJ, et al. Adjusting for clinical covariates improves the ability of B-type natriuretic peptide to distinguish cardiac from non-cardiac dyspnoea: a sub-study of HEARD-IT. Eur J Heart Fail. 2009;11(11):1043-9.
25. Ray P, Arthaud M, Birolleau S, et al. Comparison of brain natriuretic peptide and probrain natriuretic peptide in the diagnosis of cardiogenic pulmonary edema in patients aged 65 and older. J Am Geriatr Soc. 2005;53(4):643-8.
26. Bal L, Thierry S, Brocas E, et al. B-type natriuretic peptide (BNP) and N-terminal-proBNP for heart failure diagnosis in shock or acute respiratory distress. Acta Anaesthesiol Scand. 2006;50(3):340-7.
27. Barcarse E, Kazanegra R, Chen A, Chiu A, Clopton P, Maisel A. Combination of B-type natriuretic peptide levels and non-invasive hemodynamic parameters in diagnosing congestive heart failure in the emergency department. Congest Heart Fail. 2004;10(4):171-6.
28. Arques S, Roux E, Sbragia P, Pieri B, Gelisse R, Luccioni R, et al. Usefulness of bedside tissue Doppler echocardiography and B-type natriuretic peptide

(BNP) in differentiating congestive heart failure from noncardiac causes of acute dyspnea in elderly patients with a normal left ventricular ejection fraction and permanent, nonvalvular atrial fibrillation: insights from a prospective, monocenter study. Echocardiography. 2007;24(5):499-507.
29. Nazerian P, Vanni S, Zanobetti M, et al. Diagnostic accuracy of emergency Doppler echocardiography for identification of acute left ventricular heart failure in patients with acute dyspnea: comparison with Boston criteria and N-terminal prohormone brain natriuretic peptide. Acad Emerg Med. 2010;17(1):18-26.
30. Morrison LK, Harrison A, Krishnaswamy P, Kazanegra R, Clopton P, Maisel A. Utility of a rapid B-natriuretic peptide assay in differentiating congestive heart failure from lung disease in patients presenting with dyspnea. Journal of the American College of Cardiology. 2002;39(2):202-9.
31. Kaleemullah S, Mansoor A. Diagnostic significance of NT-proBNP estimation in patients with acute dyspnea. 2011.
32. Lader E. B type natriuretic peptide levels had high sensitivity but moderate specificity for detecting CHF in the emergency department.
33. Choi S, Park D, Lee S, Hong Y, Kim S, Lee J. Cut-off values of B-type natriuretic peptide for the diagnosis of congestive heart failure in patients with dyspnoea visiting emergency departments: a study on Korean patients visiting emergency departments. Emergency Medicine Journal. 2007;24(5):343-7.
34. Mueller T, Gegenhuber A, Poelz W, Haltmayer M. Diagnostic accuracy of B-type natriuretic peptide and amino terminal proBNP in the emergency diagnosis of heart failure. Heart. 2005;91(5):606-12.
35. Knudsen CW, Westheim A, Omland T. B-type natriuretic peptide and clinical judgement in the diagnosis of heart failure in patients presenting with acute dyspnoea. Tidsskr Nor Laegeforen. 2003;123(15):2045-8.
36. Knudsen CW, Riis JS, Finsen AV, et al. Diagnostic value of a rapid test for B-type natriuretic peptide in patients presenting with acute dyspnoea: effect of age and gender. Eur J Heart Fail. 2004;6(1):55-62.
37. Kozhuharov N, Sabti Z, Wussler D, et al. Prospective validation of N-terminal pro B-type natriuretic peptide cut-off concentrations for the diagnosis of acute heart failure. Eur J Heart Fail. 2019;21(6):813-5.
38. Koulouri S, Acherman RJ, Wong PC, Chan LS, Lewis AB. Utility of B-type natriuretic peptide in differentiating congestive heart failure from lung disease in pediatric patients with respiratory distress. Pediatr Cardiol. 2004;25(4):341-6.
39. Klemen P, Golub M, Grmec S. Combination of quantitative capnometry, N-terminal pro-brain natriuretic peptide, and clinical assessment in differentiating acute heart failure from pulmonary disease as cause of acute dyspnea in pre-hospital emergency setting: study of diagnostic accuracy. Croat Med J. 2009;50(2):133-42.
40. Villacorta H, Duarte A, Duarte NM, et al. The role of B-type natriuretic peptide in the diagnosis of congestive heart failure in patients presenting to an emergency department with dyspnea. Arq Bras Cardiol. 2002;79(6):569-72, 4-8.
41. Lewis LK, Raudsepp SD, Whitlow JC, et al. Assays specific for BNP1-32 and NT-proBNP exhibit a similar performance to two widely used assays in the diagnosis of heart failure. Clin Chem. 2022;68(10):1292-301.
42. Krishnaswamy P, Lubien E, Clopton P, et al. Utility of B-natriuretic peptide levels in identifying patients with left ventricular systolic or diastolic dysfunction. Am J Med. 2001;111(4):274-9.
43. Abdullah A, Iqbal A, Ishtiaq W, Hussain SW, Qadeer A, Rasheed G. Diagnostic utility of N-terminal pro-brain natriuretic peptide and C-reactive protein in diagnosing heart failure in patients with acute hypoxemic respiratory failure. Cureus. 2020;12(1):e6835.
44. Robaei D, Koe L, Bais R, Gould I, Stewart T, Tofler GH. Effect of NT-proBNP testing on diagnostic certainty in patients admitted to the emergency department with possible heart failure. Annals of Clinical Biochemistry. 2011;48(3):212-7.
45. Lokuge A, Lam L, Cameron P, et al. B-type natriuretic peptide testing and the accuracy of heart failure diagnosis in the emergency department. Circ Heart Fail. 2010;3(1):104-10.
46. Su Q, Liu H, Zhang X, et al. Diagnostic values of NT-proBNP in acute dyspnea among elderly patients. International Journal of Clinical and Experimental Pathology. 2015;8(10):13471.
47. Tung RH, Camargo CA, Jr., Krauser D, et al. Amino-terminal pro-brain natriuretic peptide for the diagnosis of acute heart failure in patients with previous obstructive airway disease. Ann Emerg Med. 2006;48(1):66-74.
48. van der Burg-de Graauw N, Cobbaert CM, Middelhoff CJ, Bantje TA, van Guldener C. The additive value of N-terminal pro-B-type natriuretic peptide testing at the emergency department in patients with acute dyspnoea. Eur J Intern Med. 2009;20(3):301-6.
49. Wieshammer S, Dreyhaupt J, Basler B, Marsovszky E. NT-proBNP for pulmonologists: not only a rule-out test for systolic heart failure but also a global marker of heart disease. Respiration. 2009;77(4):370-80.
50. Yeganeh M, Jaweed SS, Woei KSS, Zakaria MIb, Loch A. Accuracy of B-type natriuretic peptide in a multiethnic Asian population with acute dyspnea. Hong Kong Journal of Emergency Medicine. 2022;29(2):101-7.
51. Steg PG, Joubin L, McCord J, et al. B-type natriuretic peptide and echocardiographic determination of ejection fraction in the diagnosis of congestive heart failure in patients with acute dyspnea. Chest. 2005;128(1):21-9.

Table 2. Detailed summary of the extracted data from the included studies.

Author (year) (reference)	Country	Study design	Duration of follow-up	Participants	Mean age	Sex (percentage of females)	Index test	Reference standard for heart failure	Adjustments	Threshold	Sensitivity %	Specificity %
Maisel et al.(2003) (20)	USA	Prospective cohort study	30 days	452 patients with a final diagnosis of CHF	64 (SD= 16.7)	44.3% female	Blood sample was collected into tubes containing potassium ethylenediaminetetraacetic acid. The BNP was measured in triplicate using the Triage B-Type Natriuretic Peptide test (Biosite Inc., San Diego, California). The Triage BNP test is a fluorescence immunoassay for the quantitative determination of BNP in whole blood and plasma specimens. The precision, analytical sensitivity, and stability characteristics of the system have been previously described (16,17). Triplicate BNP values were determined on site using the Triage BNP test with either whole blood or plasma samples.	Two cardiologists reviewed all medical records pertaining to the patient and made independent initial assessments of the final diagnosis: 1) CHF; 2) history of CHF but acute dyspnea due to a non-cardiac cause; or 3) not CHF. The cardiologists were presented the components and summary of the Framingham (two major or one major and two minor criteria) CHF score and the National Health and Nutrition Examination Survey (score 3) CHF score, calculated from the case report form.	-	BNP: 100 pg/ml BNP: 200 pg/ml BNP: 300: pg/ml BNP: 400 pg/ml	90 81 73 63	73 85 89 91
Moon et al. (2005) (21)	Korea	Retrospective cohort study	-	261 patients with acute dyspnea	66±15	54% female	The serum BNP levels of the patients were measured using the ELISA method.	Admitted to the emergency department of Hanyang University Hospital due to acute dyspnea	-	BNP: 133 pg/ml	73	87
Figal et al. (2005) (22)	Spain	Prospective cohort study	180 days	70 patients with shortness of breath	74±11% (SD)	57% female	Samples were collected in tubes containing a lithium heparin anticoagulant, and centrifuged for 30 min at 4°C. NTproBNP levels were then immediately determined using the proBNP assay method (Roche Diagnostics, Germany) and an Elecsys 2010 analyzer (Roche Diagnostics, Germany). The reactant consists of polyclonal antibodies that recognize epitopes at the N-terminal (1-76) of the proBNP (1-108) molecule. A 20 mL sample was incubated with a biotinylated polyclonal antibody specific for NTproBNP and another labeled with a ruthenium chelate to form a sandwich complex. After incubation, the bound fraction was separated with microparticles covered in streptavidin and quantified by chemiluminescence. The assay precision ranged from 1.8% at 800 pmol/L to 2.7% at 20.7 pmol/L. The detection limits were 0.6 and 4.130 pmol/L. The pmol/L—pg/mL conversion ratio was 8.457.	The emergency room physicians (internal medicine specialists and family doctors trained in emergency medicine) took initial charge of these patients and attempted to make a diagnosis based on anamnesis, a physical examination, a chest x-ray, an ECG, a pulse oximeter, and emergency blood analysis. The patients included in the study were those whose dyspnea was of unclear origin and who had an uncertain diagnosis of HF (i.e., they had two equally likely possible diagnoses, one of which was HF).	-	BNP: 900 pg/mL	97.59	NR

Sartini et al. (2017) (23)	Italy	prospective cohort study	540 days	236 patients with acute dyspnea	80 (SD=12)	50.4% female	analyzed with ECLIA	The NT-proBNP level was considered indicative of heart failure when C300 pg/ml, following European Society of Cardiology recommendations. Chest radiography images were analyzed and reported by consultant radiologists available in the ED 24 h/day. They were considered suggestive of decompensated heart failure if cardiothoracic ratio [1:2 plus one of the following was present: vascular congestion, interstitial edema, pulmonary edema, and bilateral pleural effusion. Echocardiography has been performed in all admitted patients, but full results are not reported in the current analysis as they were not part of the initial workup.	-	BMP ≥300 pg/ml	97.59	27.56
Kevin Rogers et al. (2009) (24)	USA	Prospective Cohort	3 Months	740 Dyspneic patients of more than 40 years	66 ± 13	46% Female	BNP (5 sites Triage, Biosite, USA, two sites Abbott, Netherlands)	A retrospective review by two cardiologists	-Age -Gender -Ethnicity -BMI -BUN -Creatinine -Atrial fibrillation -BUN BNP -BUN ethnicity -Atrial fibrillation creatinine -Age BUN -Age creatinine	BNP to 100 pg/mL	96	69
Ray et al. (2005) (25)	France	Prospective Cohort	20 Months	202 Patients aged 65 and older presenting with acute dyspnea	Control Group (n=114): 78 ± 9 Cardiogenic Pulmonary Edema Group (n=88): 82 ± 9	49.5 % male	BNP Triage (Biosite, USA) and NTproBNP Elecsys (Roche, USA)	Two independent experts (pulmonologist, cardiologist, emergency physician, geriatric or internal medicine physician) made the final diagnosis	-	BNP ≥250 pg/mL proBNP greater than 1,500 pg/mL	73 75	91 76

Bal et al. (2006) (26)	France	Retrospective Cohort	9 months	41 patients within 24 h of the onset of shock or acute respiratory distress	52.9 ± 20	41% male	-Triage BNP (Biosite Europe, Velizy, France) -NTproBNP Elecsys (Roche Diagnostics GmbH, Mannheim, Germany)	Diagnosed according to clinical history, physical examination, laboratory test, TTE, and TEE. Two echocardiographers interpreted the echocardiograms	-	BNP >221 pg/mL proBNP ≥443 pg/mL	68 84	88 75
Barcarse et al. (2004) (27)	USA	Cohort	11 months	98 patients presented to the urgent care center or ED with acute shortness of breath	64.6±1.2	100% male	Triage BNP (Biosite Inc., San Diego, CA) assay.	Retrospective review by a Cardiologist	-	BNP >100 pg/mL.	70	100
Arques et al. (2007) (28)	France	Prospective Cohort	-	41 consecutive elderly patients with an ejection fraction ≥ 50% were hospitalized for acute dyspnea	Heart failure (N = 22): 84.3 ± 5.2 Noncardiac (N = 19): 83.6 ± 5.1	63% female	Triage BNP (Biosite Inc., San Diego, CA) assay.	The diagnosis was recorded at discharge based on clinical and instrumental investigations. The final diagnosis was established at discharge by two cardiologists and one chest physician.	-	-BNP: 250 pg/mL	86.4	89.5
Nazerian et al (2010) (29)	Italy	Prospective Cohort	3 months	145 patients with acute dyspnea	aLVHF (n = 64): 81 ± 8 Other (n = 81): 75 ± 12	51% female	NTproBNP Elecsys (Roche, USA)	Three independent reviewers, including two cardiologists and one respiratory physician	-	-NT-proBNP ≤ 300 pg /mL -NT-proBNP ≥2,200 pg /mL	83 98	70 22

Parab et al. (2005) (11)	USA	Cross-sectional	_	70 dyspneic patients who had a BNP level drawn	76.5 (34-102)	65.71 % female (46/70)	BNP level drawn as a part of their evaluation	Framingham Criteria for CHF 15	Age They computed the age-specific sensitivity and specificity of BNP measurements for several age groups (65,65, 75, and85). It was found that these analyses did not affect the above results	BNP ≥100 pg/mL BNP ≥200 pg/mL BNP ≥300 pg/mL BNP ≥400 pg/mL BNP ≥500 pg/mL BNP ≥600 pg/mL BNP greater BN to 700 pg/mL	95.7 89.3 89.3 87.2 83 80.8 76.5	26 52 60.8 73.9 78.2 78.2 78.2
Morrison et al.(2002) (30)	USA	Cross-sectional	-	321 patients presenting to the ED with acute dyspnea	-	-	Triage BNP assay	The diagnosis of CHF was based on independent confirmation of two cardiologists and was based on generally accepted Framingham criteria (9) with corroborative information, including hospital course (response to diuretics, vasodilators, inotropes, or hemodynamic monitoring) and results of further cardiac testing, including echocardiography, nuclear medicine ejection fractions, or left ventriculography done at cardiac catheterization	-	BNP: 94 pg/mL BNP: 105 pg/mL BNP: 135 pg/mL BNP: 195 pg/mL BNP: 240 pg/mL	86 86 90 94 96	98 94 90 85 79

Belmin et al.(2020) (13)	France	Cross sectional Observational study	-	141 aged > 75 years with chronic peripheral edema and no dyspnea	86.5+- 6.0	Men: 28 (20%) Women: 113 (80%)	immunoassay (Triage; Biosite Systems Ltd., Solihull, UK)	ESC guidelines for the diagnosis and treatment of acute and chronic heart Failure 2008: The Task Force for the diagnosis and treatment of acute and chronic heart failure, 2008, of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association of the ESC (HFA) and endorsed by the European Society of Intensive Care Medicine (ESICM).	-	BNP: 100 pg/mL BNP: 274 pg/mL BNP: 400 pg/mL	93 82 59	39 89 95
Kaleemullah et al. (2011) (31)	Pakistan	Cross-sectional	6 months	100 patients were selected with purposive non-probability sampling who had presented to the emergency department with acute dyspnea	61±14 years	female (52%)	NT-proBNP analysis was performed with a commercially available immunoassay (Elecsys proBNP, Roche Diagnostics, Indianapolis, Indiana) on an Elecsys 1010 analyzer according to the established methods	Clinical diagnosis All information was used to calculate the Framingham scores (requiring 2 major or 1 major and 2 minor criteria for CHF). Major The criteria included paroxysmal nocturnal dyspnoea, neck vein distention, rales, radiographic cardiomegaly (Increasing heart size on chest radiography), acute pulmonary oedema, S3 gallop, increased central venous pressure (> 16 cm H2O at right atrium), hepatojugular reflux and weight loss > 4.5 kg in 5 days in response to treatment. Minor criteria included bilateral ankle oedema, nocturnal cough, dyspnoea on ordinary exertion, hepatomegaly, pleural effusion, decrease in vital signs capacity by one-third of the maximum recorded and tachycardia (heart rate >120 beats/minute)	Age	proBNP: 900 pg/mL	96.2	86

Lader et al.(2003) (32)	USA	Cross-sectional	-	1586 ED patients who had shortness of breath as the most prominent symptom.	mean age 64 years	(56% men)	Triage B type natriuretic fluorescence immunoassay (Biosite Diagnostics, La Jolla, CA, USA)	2 cardiologists (blinded to the BNP levels) Independently reviewed all medical records about each patient and classified the diagnosis as dyspnea caused by CHF, acute dyspnea caused by noncardiac causes in a patient with a history of left ventricular dysfunction, or dyspnea not caused by CHF. Information reviewed by the cardiologists included a reading of the chest roentgenogram, medical history, results of tests of ventricular function, and the hospital course for admitted patients.	-	BNP: 50 pg/mL BNP: 80 pg/mL BNP: 100 pg/mL BNP: 125 pg/mL BNP: 150 pg/mL	97 93 90 87 85	62 74 76 79 83
Choi et al.(2007) (33)	South Korea	Cross-sectional	-	1040 Korean patients with dyspnea visiting emergency departments	63 years	582 men (56%) 458 women	Triage BNP test; Biosite, San Diego, California, USA	CHF was diagnosed at the beginning of the visit based on Framingham's criteria, followed by a transthoracic echocardiography (Philips Sonos 5500, Andover, Massachusetts, USA) Conducted within 24 h by two independent echocardiologists who were blinded to the BNP assay. The final diagnosis of CHF was defined by transthoracic echocardiography. The findings from the transthoracic echocardiography that led to the Diagnosis of CHF was as follows: Systolic dysfunction: left ventricular ejection fraction (LVEF) ,50% of the inner diameter of the left ventricle at diastole .5.2 cm or global hypokinesia detected. -Diastolic dysfunction: the E-wave/A-wave (E/A) ratio was ,1 and the deceleration time.240 ms or the E/A ratio was .1.5 and the deceleration time,150 ms.	age, sex, and underlying disease	BNP: 12.5 pg/mL BNP: 100 pg/mL BNP: 191 pg/mL BNP: 296.5 pg/mL BNP: 400 pg/mL BNP: 496 pg/mL BNP: 601 pg/mL BNP: 983 pg/mL	100 98.7 96.1 90.5 84.7 70.1 60.6 39.9	27.8 67.1 83.5 91.4 96.2 97.3 97.7 98.8

Muller et al.(2005) (34)	Austria	Cross-sectional	_	251 consecutive patients presenting to the emergency department with dyspnea as a chief complaint complaint	74	93% of men 7% of women	BNP was assayed on an AxSYM analyser (Abbott Laboratories, Abbott Park, Illinois, USA). The AxSYM BNP assay is a fully automated microparticle enzyme immunoassay with two monoclonal mouse antibodies antibodies in a two-step sandwich format. 12 NT-proBNP was measured on an Elecsys 2010 instrument (Roche Diagnostics). (Abbott and Roche methods).	The Diagnosis of CHF was based on the Framingham score for CHF, plus echocardiographic evidence of systolic or diastolic dysfunction. The final classification was based on The Framingham criteria for the clinical diagnosis of CHF. 10 For the diagnosis of CHF, both of the following had to be present: Framingham CHF score with two major or one major and two minor criteria, and evidence of systolic or diastolic dysfunction as determined by echocardiography.	-	BNP: 100 pg/ml BNP: 118 pg/ml BNP: 160 pg/ml BNP: 292 pg/ml BNP: 295 pg/ml proBNP: 125 pg/ml proBNP: 476 pg/ml proBNP: 825 pg/ml	96 95 90 95 80 94 90 87	61 64 73 53 86 46 65 81
Knudsen et al. (2003) (35)	Norway	Prospective Cohort	-	155 patients presenting with acute dyspnea	76 years	55% Female	There was no significant interaction between age and BNP or between gender and BNP about the accuracy of diagnosing CHF.	The diagnostic ‘gold’ standard for CHF was adjudicated by two independent cardiologists who were blinded to the BNP data.	-In a multivariate model, BNP provided additional prognostic information to patient age and gender, radiographic evidence of pulmonary congestion and cardiomegaly, and the presence of pulmonary rales and jugular vein distention by physical examination.	BNP ≥100 pg/ml	90	73

Knudsen et al.(2004) (36)	Norway	Prospective Cohort	18 months	In total, 292 patients had permanent/ paroxysmal AF.	75.5 years	37.65% Female	recruited patients from seven centers (5 U.S. and 2 European)	A retrospective review by two cardiologists	Age Gender Medical history Congestive heart failure Myocardial infarction Arterial hypertension Diabetes mellitus Clinical findings Jugular vein distension Orthopnea Lower extremity edema Rales Body mass index	BNP ≥50 pg/ml BNP ≥100 pg/ml BNP ≥150 pg/ml BN greaterP ≥200 pg/ml	100 94.3 91.4 88.6	37.3 54.9 58.8 62.7
Kozhuharov et al. (2019) (37)	Switzerland	Prospective Cohort	-	2053 patients presenting with acute dyspnea	50–75 years	-	-	Two independent cardiologists/ internists centrally adjudicated the final diagnosis using all individual patient's information including chest X-ray, natriuretic peptide, renal dysfunction (defined as estimated glomerular filtration rate < 60 mL/min/1.73 m 2 at presentation), echocardiography, pulmonary function test, and 90-day follow-up, in consistence with current guidelines.	-	proBNP: 450 pg/ml proBNP: 900 pg/ml	89 88	91 84

Koulouri et al. (2004) (38)	USA	prospective randomized controlled	11 Months	immunoassay in 49infant infants and children presenting With acute respiratory distress.	(30 ± 59 versus 13 ± 23 months,	(2 ± 2 vs 81 ± 80 months).	BNP Triage (Biosite, USA)	According to clinical They were diagnosed history, physical examination, pulse oximetry, blood tests including arterial blood gas analysis, chest X-ray, Echocardiography, and pulmonary function tests.	.Age Gender Medical history Congestive heart failure Myocardial infarction Aterial hypertension Diabetes mellitus Clinical findings Jugular vein distension Orthopnea Lower extremity edema Rales Body mass index	BNP: 40 pg/ml BNP: 60 pg/ml BNP: 80 pg/ml BNP: 100 pg/ml	91 83 78 78	77 77 81 85
Klemen et al. (2009) (39)	Slovenia	Prospective Cohort	25 months	Acute HF-related dyspnea (n = 238)	was 68.9 ± 10.5 years	58% male	Triage BNP (Biosite Inc., San Diego, CA) assay.	Retrospective review by a Cardiologist	Analysis includes age, nocturnal dyspnea, orthopnea, cough, Sputum production, fever, wheezing, rales, wheezing, jugular	proBNP: 300 pg/ml proBNP: 700 pg/ml proBNP: 1000 pg/ml proBNP: 2000 pg/ml proBNP: 3000 pg/ml	99 98 90 84 67	54 65 76 83 95
Villacorta et al. (2002) (40)	Brazil	Cross-sectional	-	70 patients With acute dyspnea	72±16 years	47% male	rapid (15 min) bedside test	Physical examination, chest radiography, and electrocardiography.		BNP: 200 pg/mL	100	97

Lewis et al. (2022) (41)	New Zealand	Cross sectional	-	195 patients with acute dyspnea	73 years (IQR 64-80) for males and 68 years (IQR 58-76) for females,	60.5% male	The study compared the performance of three different BNP assays: Roche NT-proBNP, BNP1-32, and Abbott BNP	clinical assessment and echocardiography	sex, age, BMI	BNP: 12000 pg/ml proBNP: 1536 pg/ml	80 83	84 83
Krishnaswamy et al. (2002) (42)	USA	Cross-sectional	-	400 patients who were referred for echocardiography to evaluate ventricular function	*In patient with Normal Left Ventricular Function (n 5 147):60±12 *In patient with Abnormal Left Ventricular Function (n 5 253):69±11	*Male sex in patient with Normal Left Ventricular Function: 97% *Male sex in patient with Abnormal Left Ventricular Function: 96%	Triage B-type natriuretic assay immunoassay.	determined by cardiologists blinded to the echocardiogram (ECG) results, based on standard Framingham criteria, admission and treatment for heart failure, and emergency department visits for heart failure.	-	BNP ≥2200 pg/ml	86	70
Abdullah et al. (2020) (43)	Pakistan	Cohort	1 year	137 Patients with Acute Hypoxemic Respiratory Failure	>18	43.7%	Sandwich enzyme immunoassay	was performed according to the guidelines of the hospital	Age	proBNP >300 pg/ml	95.56	46.81
Robaei et al. (2011) (44)	Australia	RCT	-	68 patients presenting to the ED with dyspnea	73±16	56%	the NT proBNP concentration	-	Final diagnosis of HF Age sex	proBNP >450 pg/ml proBNP >900 pg/ml	81	66
Lokuge et al. (2010) (45)	Australia	Cohort	19 months	799 Patients with a chief complaint of dyspnea	71±11	46.5%	Triage BNP	-	-	BNP: 101 pg/ml BNP: 265 pg/ml	92 83	51 81

Strunk et al. (2006) (8)	USA	Cohort	20 months	1475 patients with dyspnea	63	54% female	Triage B-type natriuretic peptide test (Biosite Incorporated, San Diego, Calif)	by consensus decision of 2 cardiologists	-	BNP <100 pg/ml 100 pg/ml <BNP <500 pg/ml BNP> 500 pg/ml	65 54 65	91 77 72
Su et al. (2015) (46)	China	Cohort	2 years	268 patients with dyspnea	74.1±7.9 yr	43.66% female	Canada RAMP NT-proBNP Assay	based on Framingham Standards, color Doppler echocardiography, chest X-ray, and patient responsiveness to drug treatments	-	proBNP >600 pg/ml	92	82.2
Tung et al. (2005) (47)	USA	Cohort	36 months	216 dyspneic patients	21	55%female	-	By 2 study physicians	-	proBNP >450 pg/ml proBNP >900 pg/ml	87	84
van der Burg-de Graauw et al. (2009) (48)	The Netherlands	Cohort	-	221 patients with acute dyspnea	71.1±14.3	43% female	(1st generation, Elecsys 1010, Roche Diagnostics)	an independent interdisciplinary panel of a cardiologist, clinical chemist, internist and pneumonologist not involved in the patients' care, reviewed all available data including serum NT-proBNP, and made a final diagnosis with respect to the cause of dyspnea	-	proBNP >450 pg/ml proBNP >900 pg/ml	71	83
Wieshammer et al. (2009) (49)	Germany	Cohort	24 months	697 patients with dyspnea	57.5 ± 16.4	38.6%	-	The diagnosis oh HF was made by paraclinical work-up like ECG, CWR, exercise ECG and doppler echocardiography	-	proBNP: 144 pg/ml	75	75
Yeganeh et al. (2022) (50)	USA	Cross-sectional	-	203 patients with the presenting complaint “dyspnea” were recruited	67	45.3%	The bedside BNP measurement was performed with the SOB panel (Biosite® Diagnostics Inc., San Diego, CA) following the patient’s clinical examination	Heart failure diagnosis was adjudicated by two cardiologists	-	BNP: 186 pg/ml	91	80
Steg et al. (2005)(51)	Five sites in the United States, one in France, and one in Norway	Cohort	7 months	1,586 patients with acute dyspnea	68.5 ± 14.1(CHF) 61.6 ± 14.8(no CHF)	55.6	BNP was measured using a fluorescence immunoassay kit	Seven hundred nine of the 1,586 patients underwent echocardiography; 492 patients (69.4%) had a final diagnosis of CHF	-	BNP ≥100 pg/ml	89	73