Review Article

Relevant Aspects of Natriuretic Peptides in the Etiology of Dyspnea in the Emergency Room: Evidence, Indications, Confounding Factors, and Cost-Effectiveness

Humberto Villacorta[1]
Universidade Federal Fluminense,[1] *Niterói, RJ – Brazil*

Abstract

Natriuretic peptides are hormones released by the heart after acute or chronic aggression. They are produced exclusively by the heart and are, therefore, specific cardiac biomarkers. Recent pivotal studies have confirmed that they are useful in the diagnostic assessment of patients with dyspnea in the emergency room, with a high predictive value in ruling out acute heart failure, and they are indicated when there are doubts in clinical examination. They are also useful as prognostic markers and in monitoring response to treatment. Multiple studies have demonstrated that they are cost-effective in the emergency room. However, it is important to underscore that they should always be used in conjunction with clinical examination, and they have the limitation of reduced accuracy in some subgroups, due to the influence of some clinical variables, such as age, renal function, atrial fibrillation, and obesity. The use of cutoff values stratified by age group and machine learning techniques minimize the influence of confounding factors.

Introduction

Heart failure (HF) is a severe disease, with elevated morbidity and mortality, as well as a high rate of hospitalizations, and it can have unfavorable progression if it is not treated properly.[1] One of the main symptoms of the disease is dyspnea, which can appear as intolerance to exertion in the initial stages, progressing to resting dyspnea, a phase during which the patient usually seeks emergency care for diagnostic clarification and treatment. In other situations, the patient presents with acute dyspnea, immediately seeking emergency care. It is important to highlight that dyspnea is a non-specific symptom common to several disorders, which can make diagnosis difficult, lead to errors, and harm patients.[2,3]

HF syndrome is diagnosed based on the universal definition that defines HF as the presence of signs and symptoms suggestive of HF, in addition to elevated natriuretic peptides or objective evidence of pulmonary or systemic congestion.[4] Often, when typical findings of HF are present (orthopnea, edema, third heart sound, hepatomegaly, jugular vein distention), the diagnosis of HF can be made based only on history and physical examination. In other situations, in patients without specific signs on physical examination, measurement of natriuretic peptides, B-type natriuretic peptide (BNP) and N-terminal pro-B-type natriuretic peptide (NT-proBNP), is used in conjunction with clinical examination for HF diagnosis.[1]

Natriuretic peptides are hormones that are released when the heart suffers stress or aggression, which, as they are produced exclusively by the cardiac ventricles, are useful in the diagnosis of HF.[1,5] When facing aggression, regardless of the etiology, the neurohormonal systems responsible for progression and perpetuation of HF are activated, mainly the renin-angiotensin-aldosterone system and the sympathetic nervous system.[6] To defend itself, the heart produces natriuretic peptides, such as BNP and atrial natriuretic peptide, which have biological properties,[7,8] as demonstrated in Figure 1. Therefore, these peptides are elevated in HF and are useful in its diagnosis. Even when HF is diagnosed clinically, plasma levels of these biomarkers are useful for prognosis and monitoring treatment. The higher they are, the worse the prognosis.[1,5]

In this article, we highlight the studies that have evaluated the diagnostic accuracy of natriuretic peptides in patients with acute dyspnea in the emergency room, the current indications for using these biomarkers, the limitations, and the cost-effectiveness of their use.

Evidence of the use of natriuretic peptides in the diagnosis of acute heart failure

At the beginning of the 2000s, two studies with a small number of patients showed that the use of BNP measurement using a point-of-care system could be useful in diagnosing HF in the emergency room.[9,10] Dao et al. demonstrated that BNP was accurate in diagnosing HF, with a C statistic of 0.97, and would have corrected 29 of the 30 incorrect diagnoses made by the emergency physician.[9] Similar results were obtained by Villacorta et al., with an area under the curve (AUC) of 0.99, correcting all 16 cases of diagnostic error.[10]

These initial findings were definitively confirmed by the publication of the first multicenter study, Breathing Not Properly (BNP) Multinational Study,[2,11] led by Professor Alan S. Maisel, after which these biomarkers began to be included in HF guidelines. In this pivotal publication, which studied 1586 patients with acute dyspnea, Maisel et al. demonstrated

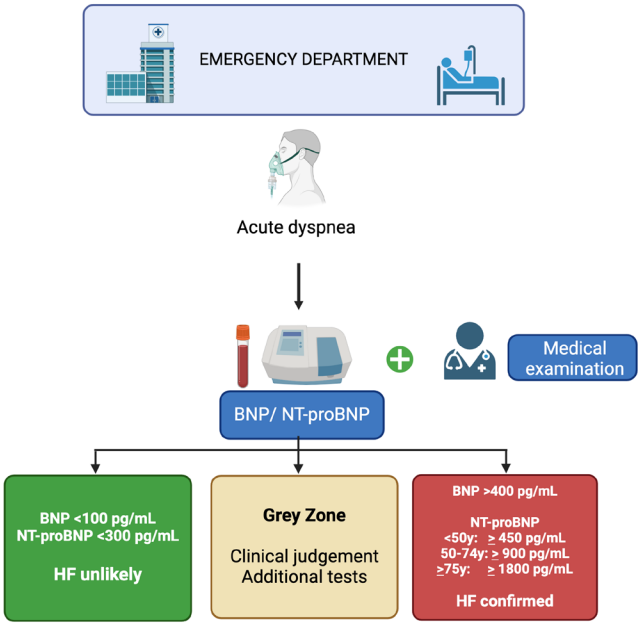
Keywords

Natriuretic Peptides; Heart Failure; Emergency Medical Services; Dyspnea; Diagnosis.

Mailing Address: Humberto Villacorta •
Universidade Federal Fluminense - Rua Marquês do Paraná, 303. Postal Code 24033-900, Niterói, RJ - Brazil
E-mail: hvillacorta@cardiol.br
Manuscript received March 05, 2024, revised manuscript March 25, 2024, accepted April 09, 2024
Editor responsible for the review: Luis Beck-da-Silva

DOI: https://doi.org/10.36660/abchf.20240017i

Central Illustration: Relevant Aspects of Natriuretic Peptides in the Etiology of Dyspnea in the Emergency Room: Evidence, Indications, Confounding Factors, and Cost-Effectiveness



ABC Heart Fail Cardiomyop. 2024; 4(1):e20240017

Flowchart for the use of natriuretic peptides in the diagnosis of heart failure in patients with acute dyspnea in the emergency room. BNP: B-type natriuretic peptide; HF: heart failure; NT-proBNP: N-terminal pro-B-type natriuretic peptide.

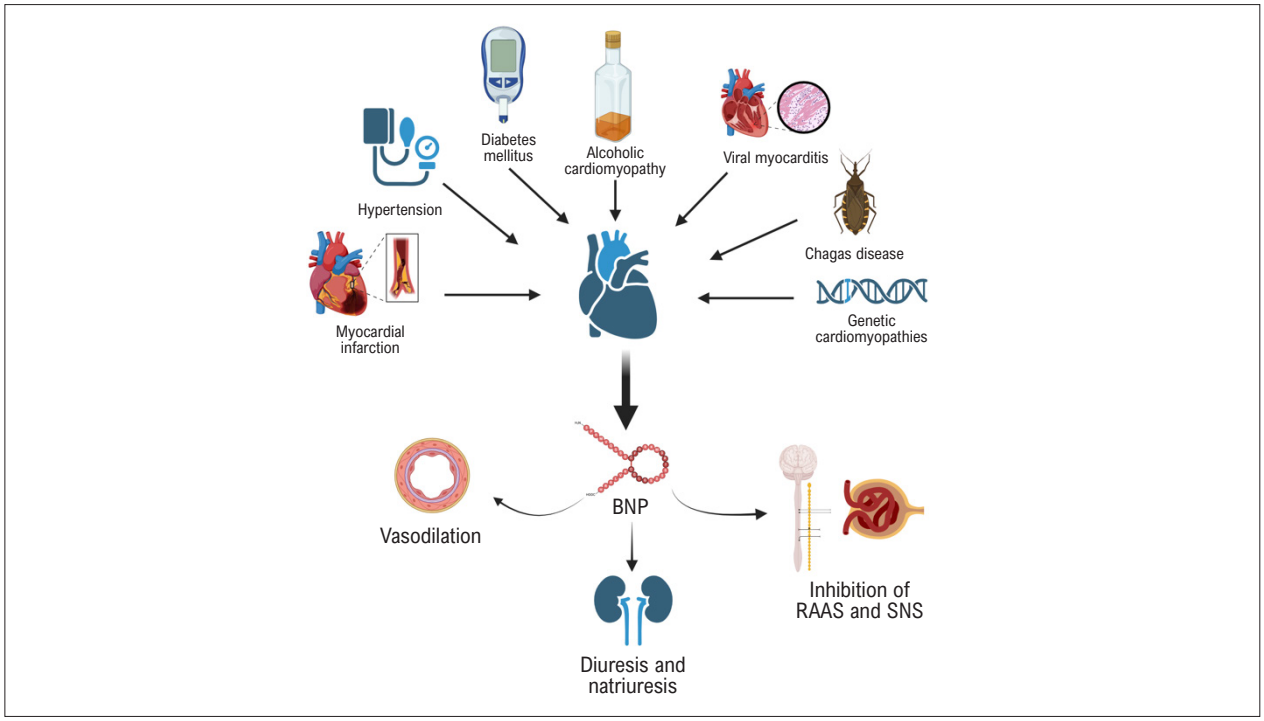


Figure 1 – *The natriuretic peptide system. After aggression to the heart, regardless of the etiology, the heart releases peptides, such as BNP and atrial natriuretic peptide, which are molecules that protect the heart, promoting vasodilation, diuresis, natriuresis, and inhibition of the renin-angiotensin-aldosterone system and sympathetic nervous system. BNP: B-type natriuretic peptide; RAAS: renin-angiotensin-aldosterone system; SNS: sympathetic nervous system.*

that BNP alone was more accurate than any data from medical history, physical examination, or laboratory tests in diagnosing HF.[11] A cutoff of 100 pg/mL showed accuracy of 83.4%, and the negative predictive value for BNP values < 50 pg/mL was 96%.[11] In an additional publication from the same study, McCullough et al. demonstrated that, even when the clinical probability estimated by the emergency physician was > 80%, BNP added information, increasing accuracy from 74% to 81.2%.[2] In patients with intermediate clinical probability (between 21% and 79%), the cutoff of 100 pg/mL for BNP correctly classified 74% of cases.[2] It is important to highlight that the best AUC observed was for clinical judgment combined with BNP, with AUC of 0.86, 0.90, and 0.93 for clinical judgment alone, BNP alone, and clinical judgment combined with BNP, respectively.[2]

The use of NT-proBNP was validated shortly afterwards by the PRIDE study,[12] led by Professor James L. Januzzi, which found results similar to those observed with BNP. The study included 600 patients with dyspnea in the emergency department. A cutoff point of 300 pg/mL for NT-proBNP had excellent performance in ruling out the diagnosis of HF, with a negative predictive value of 99%. The authors of the study tested a strategy to minimize the effects of age on natriuretic peptides. To rule in the diagnosis of HF, stratified cutoff points by age group were validated. Cutoffs of 450 pg/mL and 900 pg/mL had good sensitivity and specificity for the diagnosis of HF for the age groups of < 50 and ≥ 50 years, respectively.[12] NT-proBNP was the main predictor of HF diagnosis and was superior to clinical judgment (AUC 0.90 versus 0.94). However, the combination of clinical judgment with NT-proBNP obtained the highest AUC (0.96).

One year later, in a multicenter study with 1,256 patients, Januzzi et al. derived and validated NT-proBNP cutoffs stratified by 3 age groups, using bootstrapping and multi-variable logistic regression techniques.[13] Cutoffs of 450, 900, and 1800 pg/mL, for age groups < 50, 50 to 75, and > 75 years of age, showed a sensitivity of 90% and specificity of 84%. It is worth mentioning that patients with admission values > 5180 pg/mL had an elevated risk of death within 76 days.[13]

More recently, these age-stratified cutoffs were revalidated in the ICON-RELOADED study,[14] in 1461 patients with acute dyspnea. The cutoffs showed good sensitivity and specificity. The cutoff of 300 pg/mL had a negative predictive value of 98% for ruling out HF. Additionally, several meta-analyses and systematic reviews have confirmed the findings of these pivotal studies, showing good diagnostic accuracy of BNP and NT-proBNP in patients with acute dyspnea.[15-18]

Indications and practical use

The main HF guidelines recommend the use of natriuretic peptides to assist in diagnosis of acute HF, in patients with acute dyspnea, and in conjunction with clinical examination when there are doubts regarding diagnosis based solely on clinical examination.[1,19,20] Even in cases where HF has been diagnosed on clinical grounds, measurement of these biomarkers is indicated for prognostic purposes and to monitor the response to treatment.[1,19,20]

The Central Illustration displays the suggested cutoffs for natriuretic peptides as diagnostic aids for HF in the emergency room. The cutoffs to rule out the diagnosis of HF are BNP < 100 pg/mL or NT-proBNP < 300 pg/mL.[1,5,19,20] To confirm diagnosis, the cutoff for BNP is 400 pg/mL. For NT-proBNP, Januzzi et al. created stratified cutoff points by age group, corrected for age and renal function. For patients in the age groups < 50 years, 50 to 75 years, and > 75 years, the suggested cutoffs are 450, 900, and 1800 pg/mL, respectively.[5] The range between both cutoff points, ruling out and ruling in, is known as the gray zone. When values are in this range, the biomarker is of little use, given that it cannot exclude or confirm the diagnosis. The gray zone may include patients with HF or other diagnoses, such as chronic obstructive pulmonary disease, pneumonia, bronchoaspiration, pulmonary thromboembolism, and others. In this situation, clinical reasoning should be used, and other diagnostic tests should be requested as necessary.

Confounding factors and limitations to the use of natriuretic peptides

In addition to the gray zone, other limitations should be taken into account when interpreting natriuretic peptide results.[21] Some variables influence their levels. Age, reduced renal function (glomerular filtration rate < 60 mL/min), and atrial fibrillation increase the concentrations of these biomarkers. On the other hand, obesity reduces BNP and NT-proBNP levels, for the same severity, compared to non-obese patients.[21] In some situations, natriuretic peptides may be unexpectedly low during the first few hours, such as rapid onset cardiogenic shock, acute mitral insufficiency, and flash pulmonary edema.[21] Finally, it is worth noting that the medication sacubitril/valsartan targets the inhibition of neprilysin, an enzyme that degrades BNP. Therefore, in patients using this medication, BNP values may be elevated, although there are variations depending on the test brand used.[22] In these cases, measurement of NT-proBNP, which is not the target of the medication, would be indicated.

Therefore, although natriuretic peptides generally have good accuracy in diagnosing acute HF, this accuracy is reduced in some subgroups, mainly elderly patients, patients with glomerular filtration rates below 60 mL/min, and patients with obesity. For example, in the collaborative study by Januzzi et al., the AUC was 99%, 93%, and 86% for age groups < 50 years, 50 to 75 years, and > 75 years.[13]

One way to minimize the effects on ruling-in diagnosis is to use cutoffs stratified by age group, given that atrial fibrillation and renal dysfunction are more common in elderly patients.[5] In the case of obesity, the problem lies in ruling out the diagnosis of HF, because obese patients may present HF with values below the traditional cutoffs. Some authors suggest reducing the cutoff for ruling out diagnosis in patients with obesity. In a study with NT-proBNP, compared to the traditional cutoff of 300 pg/mL, cutoffs stratified by body mass index (33% reduction in the cutoff for body mass index between 30 and 34.9 and 50% for index of body mass ≥ 35) improved the accuracy of the test.[23]

Another strategy to minimize the effects of confounding factors on the diagnostic accuracy of natriuretic peptides is the use of models created by machine learning techniques. Lee et al., in an international collaborative project led by Professor Nicholas L. Mills, created a machine learning model called CODE-HF.[24] The model consists of 10 clinical variables combined with NT-proBNP as a continuous variable. This tool ruled out and ruled in the diagnosis of acute HF more accurately than any other approach using NT-proBNP cutoffs alone. It is important to highlight that the traditional cutoffs had limited accuracy in some subgroups, such as elderly patients, patients with obesity, and patients with renal dysfunction, while CODE-HF worked consistently in all subgroups.[24]

Finally, the accuracy of natriuretic peptides in diagnosing HF can be improved with the joint use of other tools, such as lung ultrasound and echocardiography.[25]

Cost-effectiveness of natriuretic peptides in the diagnosis of acute heart failure

Multiple studies have evaluated the cost-effectiveness of using natriuretic peptides in the diagnosis of acute HF in patients with dyspnea in the emergency room.[26-30] The first study to assess this question was led by Professor Christian Mueller, at the University of Basel, Switzerland.[26] In this randomized study including 452 patients with acute dyspnea, the use of BNP reduced the average cost from USD 7,264 to USD 5,410 per patient, saving USD 1,854 per patient. The cost reduction was basically caused by less need for hospitalization and use of intensive therapy and by the reduced length of hospital stay, a median of 3 days less, in the BNP group.[26] Similar results were observed for NT-proBNP.[27,28] Siebert et al. demonstrated that the use of NT-proBNP would be associated with a 9.4% reduction in costs, with savings of USD 474 per patient.[27] Data from the IMPROVE-CHF study showed savings of USD 949 per patient with the use of NT-proBNP, due to reduced length of emergency room stay, reduced direct medical costs in the emergency room, reduced hospitalizations, and reduced costs of outpatient services within 60 days of inclusion in the study.[28]

A recent study carried out by Ontario Health concluded that the use of BNP or NT-proBNP would be cost-effective in Ontario, reducing the length of hospital stay by at least one day.[30] In Brazil, Araújo and de Souza[29] demonstrated that use of BNP through the public network, Unified Health System (SUS), would reduce the need for echocardiogram exams by 58% and hospitalizations by 12%. The costs per patient in the BNP group and the group with clinical diagnosis alone were BRL 652.04 and BRL 659.53, respectively.[29] Analyses carried out by the Brazilian Ministry of Health also concluded that natriuretic peptides are cost-effective in the SUS.[31,32] Table 1 summarizes the main cost-effectiveness studies on natriuretic peptides in HF diagnosis in the emergency room.

Conclusions

Natriuretic peptides are useful in the diagnostic evaluation of patients with dyspnea in the emergency room. They have a high predictive value in ruling out acute HF, and they are indicated when there are doubts in clinical examination. Even with confirmed clinical diagnosis, their measurement is indicated for prognostic purposes and for monitoring response to treatment. It is a cost-effective tool, and, since its introduction two decades ago, its use has been expanding. However, it is important to underscore that they should always be used in conjunction with clinical examination, and they have the limitation of reduced accuracy in some subgroups, due to the influence of some clinical variables, such as age,

Table 1 – Main cost-effectiveness studies on the diagnostic role of natriuretic peptides in the emergency room

Study	Study type	n	Main findings
Mueller C et al.[26]	Prospective, randomized, controlled, single-blind, single-center (Basel, Switzerland)	452	Savings of USD 1854 per patient; less need for hospitalization and use of intensive care; reduced length of hospital stay
Siebert et al.[27]	Prospective, blind, single-center; subanalysis of the PRIDE study (Boston, USA)	599	9.4% reduction in costs, with savings of $474 per patient
Moe et al.[28]	Prospective, randomized, controlled, double-blind, multicenter (Canada)	500	Savings of USD 949 per patient; reduced length of emergency room stay; reduced direct medical costs in the emergency room; reduced hospitalizations; reduced costs of outpatient services within 60 days of inclusion
Araújo et al.[29]	Analytical decision model, designed for the Brazilian Unified Health System, using the algorithm from the PRIDE[12] study (Brazil)	Not applicable	The costs per patient in the BNP group and the group with clinical diagnosis alone were BRL 652.04 and BRL 659.53, respectively; potential to reduce the need for echocardiogram exams by 58% and hospitalizations by 12%
Ontario Health[30]	Systematic review, with economic analysis of 12 studies	Not applicable	Reduced length of hospital stay by at least 1 day; highly cost-effective
Brazilian Ministry of Health[31,32]	Technical opinion	Not applicable	Natriuretic peptides are useful in ruling out acute HF in patients with dyspnea in the emergency room, and they are cost-effective in the Brazilian Unified Health System

BNP: B-type natriuretic peptide; HF: heart failure.

renal function, atrial fibrillation, and obesity. The use of cutoff values stratified by age group and machine learning techniques minimize the influence of confounding factors.

Author Contributions

Conception and design of the research and Writing of the manuscript: Villacorta H.

Potential conflict of interest

Speaker fees and study support from Roche Diagnostics

Sources of funding

There were no external funding sources for this study.

Study association

This study is not associated with any thesis or dissertation work.

Ethics approval and consent to participate

This article does not contain any studies with human participants or animals performed by any of the authors.

References

1. Marcondes-Braga FG, Moura LAZ, Issa VS, Vieira JL, Rohde LE, Simões MV, et al. Emerging Topics Update of the Brazilian Heart Failure Guideline - 2021. Arq Bras Cardiol. 2021;116(6):1174-212. doi: 10.36660/abc.20210367.
2. McCullough PA, Nowak RM, McCord J, Hollander JE, Herrmann HC, Steg PG, et al. B-type Natriuretic Peptide and Clinical Judgment in Emergency Diagnosis of Heart Failure: Analysis from Breathing Not Properly (BNP) Multinational Study. Circulation. 2002;106(4):416-22. doi: 10.1161/01.cir.0000025242.79963.4c.
3. Zwaan L, Thijs A, Wagner C, Timmermans DR. Does Inappropriate Selectivity in Information Use Relate to Diagnostic Errors and Patient Harm? The Diagnosis of Patients with Dyspnea. Soc Sci Med. 2013;91:32-8. doi: 10.1016/j.socscimed.2013.05.001.
4. Bozkurt B, Coats A, Tsutsui H. Universal Definition and Classification of Heart Failure. J Card Fail. 2021:1071-9164(21)00050-6. doi: 10.1016/j.cardfail.2021.01.022.
5. Bayes-Genis A, Docherty KF, Petrie MC, Januzzi JL, Mueller C, Anderson L, et al. Practical Algorithms for Early Diagnosis of Heart Failure and Heart Stress Using NT-proBNP: A Clinical Consensus Statement from the Heart Failure Association of the ESC. Eur J Heart Fail. 2023;25(11):1891-8. doi: 10.1002/ejhf.3036.
6. McMurray JJ, Pfeffer MA. Heart Failure. Lancet. 2005;365(9474):1877-89. doi: 10.1016/S0140-6736(05)66621-4.
7. Kuwahara K. The Natriuretic Peptide System in Heart Failure: Diagnostic and Therapeutic Implications. Pharmacol Ther. 2021;227:107863. doi: 10.1016/j.pharmthera.2021.107863.
8. Della Corte V, Pacinella G, Todaro F, Pecoraro R, Tuttolomondo A. The Natriuretic Peptide System: A Single Entity, Pleiotropic Effects. Int J Mol Sci. 2023;24(11):9642. doi: 10.3390/ijms24119642.
9. Dao Q, Krishnaswamy P, Kazanegra R, Harrison A, Amirnovin R, Lenert L, et al. Utility of B-type Natriuretic Peptide in the Diagnosis of Congestive Heart Failure in an Urgent-care Setting. J Am Coll Cardiol. 2001;37(2):379-85. doi: 10.1016/s0735-1097(00)01156-6.
10. Villacorta H, Duarte A, Duarte NM, Carrano A, Mesquita ET, Dohmann HJ, 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. doi: 10.1590/s0066-782x2002001500002.
11. Maisel AS, Krishnaswamy P, Nowak RM, McCord J, Hollander JE, Duc P, et al. Rapid Measurement of B-type natriuretic Peptide in the Emergency Diagnosis of Heart Failure. N Engl J Med. 2002;347(3):161-7. doi: 10.1056/NEJMoa020233.
12. Januzzi JL Jr, Camargo CA, Anwaruddin S, Baggish AL, Chen AA, Krauser DG, et al. The N-terminal Pro-BNP Investigation of Dyspnea in the Emergency Department (PRIDE) Study. Am J Cardiol. 2005;95(8):948-54. doi: 10.1016/j.amjcard.2004.12.032.
13. Januzzi JL, van Kimmenade R, Lainchbury J, Bayes-Genis A, Ordonez-Llanos J, Santalo-Bel M, et al. NT-proBNP Testing for Diagnosis and Short-term Prognosis in Acute Destabilized Heart Failure: An International Pooled Analysis of 1256 Patients: The International Collaborative of NT-proBNP Study. Eur Heart J. 2006;27(3):330-7. doi: 10.1093/eurheartj/ehi631.
14. Januzzi JL Jr, Chen-Tournoux AA, Christenson RH, Doros G, Hollander JE, Levy PD, et al. N-Terminal Pro-B-Type Natriuretic Peptide in the Emergency Department: The ICON-RELOADED Study. J Am Coll Cardiol. 2018;71(11):1191-200. doi: 10.1016/j.jacc.2018.01.021.
15. Clerico A, Fontana M, Zyw L, Passino C, Emdin M. Comparison of the Diagnostic Accuracy of Brain Natriuretic Peptide (BNP) and the N-terminal Part of the Propeptide of BNP Immunoassays in Chronic and Acute Heart Failure: A Systematic Review. Clin Chem. 2007;53(5):813-22. doi: 10.1373/clinchem.2006.075713.
16. Worster A, Balion CM, Hill SA, Santaguida P, Ismaila A, McKelvie R, et al. Diagnostic Accuracy of BNP and NT-proBNP in Patients Presenting to Acute Care Settings with Dyspnea: A Systematic Review. Clin Biochem. 2008;41(4-5):250-9. doi: 10.1016/j.clinbiochem.2007.08.008.
17. Mastandrea P. The Diagnostic Utility of Brain Natriuretic Peptide in Heart Failure Patients Presenting with Acute Dyspnea: A Meta-Analysis. Clin Chem Lab Med. 2013;51(6):1155-65. doi: 10.1515/cclm-2012-0503.
18. Martindale JL, Wakai A, Collins SP, Levy PD, Diercks D, Hiestand BC, et al. Diagnosing Acute Heart Failure in the Emergency Department: A Systematic Review and Meta-analysis. Acad Emerg Med. 2016;23(3):223-42. doi: 10.1111/acem.12878.
19. McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, Böhm M, et al. 2021 ESC Guidelines for the Diagnosis and Treatment of Acute and Chronic Heart Failure. Eur Heart J. 2021;42(36):3599-726. doi: 10.1093/eurheartj/ehab368.
20. Heidenreich PA, Bozkurt B, Aguilar D, Allen LA, Byun JJ, Colvin MM, et al. 2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. J Am Coll Cardiol. 2022;79(17):263-421. doi: 10.1016/j.jacc.2021.12.012.
21. Nishikimi T, Nakagawa Y. Potential Pitfalls When Interpreting Plasma BNP Levels in Heart Failure Practice. J Cardiol. 2021;78(4):269-74. doi: 10.1016/j.jjcc.2021.05.003.
22. Ibrahim NE, McCarthy CP, Shrestha S, Gaggin HK, Mukai R, Szymonifka J, et al. Effect of Neprilysin Inhibition on Various Natriuretic Peptide Assays. J Am Coll Cardiol. 2019;73(11):1273-84. doi: 10.1016/j.jacc.2018.12.063.
23. Kozhuharov N, Martin J, Wussler D, Lopez-Ayala P, Belkin M, Strebel I, et al. Clinical Effect of Obesity on N-terminal pro-B-type Natriuretic Peptide Cut-off Concentrations for the Diagnosis of Acute Heart Failure. Eur J Heart Fail. 2022;24(9):1545-54. doi: 10.1002/ejhf.2618.

24. Lee KK, Doudesis D, Anwar M, Astengo F, Chenevier-Gobeaux C, Claessens YE, et al. Development and Validation of a Decision Support Tool for the Diagnosis of Acute Heart Failure: Systematic Review, Meta-analysis, and Modelling study. BMJ. 2022;377:e068424. doi: 10.1136/bmj-2021-068424.

25. Palazzuoli A, Ruocco G, Pellicori P, Gargani L, Coiro S, Lamiral Z, et al. Multimodality Assessment of Congestion in Acute Heart Failure: Associations with Left Ventricular Ejection Fraction and Prognosis. Curr Probl Cardiol. 2024;49(3):102374. doi: 10.1016/j.cpcardiol.2024.102374.

26. Mueller C, Scholer A, Laule-Kilian K, Martina B, Schindler C, Buser P, et al. Use of B-type Natriuretic Peptide in the Evaluation and Management of Acute Dyspnea. N Engl J Med. 2004;350(7):647-54. doi: 10.1056/NEJMoa031681.

27. Siebert U, Januzzi JL Jr, Beinfeld MT, Cameron R, Gazelle GS. Cost-effectiveness of Using N-terminal pro-brain Natriuretic Peptide to Guide the Diagnostic Assessment and Management of Dyspneic Patients in the Emergency Department. Am J Cardiol. 2006;98(6):800-5. doi: 10.1016/j.amjcard.2006.06.005.

28. Moe GW, Howlett J, Januzzi JL, Zowall H. N-terminal Pro-B-type Natriuretic Peptide Testing Improves the Management of Patients with Suspected Acute Heart Failure: Primary Results of the Canadian Prospective Randomized Multicenter IMPROVE-CHF Study. Circulation. 2007;115(24):3103-10. doi: 10.1161/CIRCULATIONAHA.106.666255.

29. Araújo DV, Souza CPR. Analysis of the Cost-effectiveness of B-type Natriuretic Peptide Compared to Clinical Judgment in Patients Presenting Acute Dyspnea Within the Context of Brazil's Unified Healthcare System (SUS). Rev SOCERJ 2008;21(4):217-25.

30. Ontario Health. Use of B-Type Natriuretic Peptide (BNP) and N-Terminal proBNP (NT-proBNP) as Diagnostic Tests in Adults With Suspected Heart Failure: A Health Technology Assessment. Ont Health Technol Assess Ser. 2021;21(2):1-125.

31. Brasil. Ministério da Saúde. Parecer Técnico-Científico: Uso dos Peptídeos Natriuréticos para o Diagnóstico de Insuficiência Cardíaca em Pacientes com Dispneia Aguda. Brasília: Ministério da Saúde; 2009.

32. Brasil. Ministério da Saúde. Comissão Nacional de Incorporação de Tecnologias no Sistema Único de Saúde. Relatório de Recomendação: Peptídeos Natriuréticos tipo B (BNP e NT-proBNP) para Pacientes de 18 a 44 anos com Insuficiência Cardíaca. Brasília: Ministério da Saúde; 2022.