# Acute cardiac dyspnea in the emergency department: diagnostic value of N-terminal prohormone of brain natriuretic peptide and galectin-3

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## Abstract

**Objective:** This study was performed to determine whether a dual-biomarker approach using N-terminal prohormone of brain natriuretic peptide (NT-proBNP) and galectin-3 optimizes the diagnosis and risk stratification of acute cardiac dyspnea. Atypical clinical manifestations and overlapping pathologies require objective and effective diagnostic methods to avoid treatment delays.

**Methods:** This prospective observational study included 208 patients who presented to the emergency department for acute dyspnea. NT-proBNP and galectin-3 were measured upon admission. The patients were divided into two groups according to the etiology of their clinical manifestations: cardiac and non-cardiac dyspnea. The patients' New York Heart Association functional class, left ventricular ejection fraction, and discharge status were assessed.

**Results:** Diagnostic criteria for acute heart failure were fulfilled in 61.1% of the patients. NT-proBNP and galectin-3 were strongly and significantly correlated. Receiver operating

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characteristic analysis revealed similar areas under the curve for both markers in the entire group of patients as well as in the high-risk subsets of patients.

**Conclusions:** The diagnostic performance of NT-proBNP and galectin-3 is comparable for both the total population and high-risk subsets. Galectin-3 adds diagnostic value to the conventional NT-proBNP in patients with acute cardiac dyspnea, and its utility is of major interest in uncertain clinical situations.

## Introduction

The large spectrum of subjective symptoms such as dyspnea, palpitations, and chest pain often makes the clinical diagnosis of acute heart failure misleading. In emergency settings, patients can overestimate their symptoms because of panic and anxiety; additionally, life-threatening conditions may have an indolent presentation. Population categories at risk of misdiagnosis are young adults with less specific clinical manifestations and patients with comorbidities or chronic treatment for heart failure; such conditions lead to difficult estimation of physical examination findings. Noninvasive paraclinical investigations such as standard 12-lead electrocardiography and chest radiography are needed for further assessment. In most cases, these techniques provide sufficient information to determine a cardiac etiology. Nevertheless, transthoracic echocardiography is indispensable for proper evaluation of patients suspected to have acute heart failure, but it is often unavailable in the emergency department (ED) and is highly operator-dependent.

Approximately 64% to 78% of patients with acute heart failure are admitted through the ED portal.[1–3] Premature ED discharge of a patient with acute or decompensated heart failure can have severe consequences. The assessment of patients with acute heart failure in the ED is burdened by the increased number of presentations, prolonged waiting time, and deficit of medical staff. Even when facing non-urgent and possible avoidable ED services, the progressive tendency toward defensive medicine and the continuous increase in patients' expectations and demands necessitate objective methods of evaluation before discharge.

Biomarkers are strongly objective when making medical decisions. The diagnostic and prognostic performance of natriuretic peptides [brain natriuretic peptide (BNP) and N-terminal prohormone of brain natriuretic peptide (NT-proBNP)] when assessing patients with heart failure has achieved worldwide agreement. The main limitation of these biomarkers is the different cut-off values established for the acute and chronic manifestations of heart failure. Additionally, parameters such as age, sex, body mass index (BMI), high-output states (e.g., cirrhosis, sepsis), and renal function interfere with their diagnostic abilities. Novel therapies in acute heart failure (e.g., neutral endopeptidase inhibitors) even further modify the natriuretic peptide levels, creating a divergent pattern: increased

levels of BNP and decreased levels of NT-proBNP.[4–6]

Several biomarkers that reflect different physiopathological pathways have been proposed for the diagnosis, prognosis, and risk stratification of patients with acute heart failure when natriuretic peptide levels are inconclusive.

Galectin-3, a member of the lectin family, is secreted by activated macrophages and is involved in biological processes such as inflammation, cardiac remodeling, and myofibroblast proliferation. Galectin-3 was recently approved by the Food and Drug Administration for its prognosis utility in acute heart failure, fulfilling important criteria that make it a possible ideal biomarker (early recognition of hypertrophic and fibrotic cardiac injuries, risk stratification, and potential therapeutic target as proven by experimental studies).[6–9]

The present study was performed to prospectively investigate whether a dual-biomarker approach using NT-proBNP and galectin-3 optimizes the diagnosis and risk stratification of acute cardiac dyspnea with a major impact on atypical clinical manifestations and overlapping pathologies.

## Patients and methods

### Study design and patient population

We prospectively evaluated patients who presented to the ED of a tertiary medical center with sudden-onset or aggravated dyspnea requiring admission in the Department of Internal Medicine. The study was conducted from November 2016 to March 2018. All possible cardiac etiologies of acute dyspnea were accepted as inclusion criteria. Patients were excluded if they required admission to the cardiac intensive care unit or had associated active neoplasia, active liver disease (alanine aminotransferase level of >5 times the upper limit of normal), fibrotic pathologies (e.g., pulmonary fibrosis,

collagenosis), or laboratory-based limitations for measurement of galectin-3 according to the manufacturer's instructions (serum cholesterol level of $\geq 500$ mg/dL or serum creatinine level of >5 mg/dL). All procedures for obtaining and documenting written informed consent complied with the Good Clinical Practice and ethical principles for medical research involving human subjects stated in the Declaration of Helsinki. The study was approved by the Ethics Committee of 'Sf. Spiridon' Emergency Hospital, Iasi, Romania and 'Gr. T. Popa' University of Medicine and Pharmacy, Iasi, Romania.

After completion of a standard evaluation (anamnesis, physical examination, laboratory tests, 12-lead electrocardiography, and chest radiography), additional investigations were performed as deemed necessary (abdominal ultrasound, vascular Doppler ultrasound, and computed tomography pulmonary angiography). The NT-proBNP and galectin-3 levels were measured upon admission. The galectin-3 level was determined from serum samples using a chemiluminescent microparticle immunoassay compatible with the ARCHITECT $i$ System (Abbott Laboratories, Chicago, IL, USA).

The specificity and sensitivity of NT-proBNP are considered optimal when using age-related cut-offs. Hence, the following cut-off values were used for the study: 450 pg/mL for patients aged <50 years, 900 pg/mL for patients aged 50 to 75 years, and 1800 pg/mL for patients aged >75 years.[6,10] Measurements above these values were defined as elevated values of NT-proBNP. Plasma galectin-3 levels were divided according to data obtained from clinical studies: low risk, <17.8 ng/mL; moderate risk, 17.8 to 25.9 ng/mL; high risk, >25.9 ng/mL.[11–13]

The following variables were recorded: age, sex, BMI, smoking habit, alcohol consumption, pathological antecedents, vital

parameters, standard laboratory values, New York Heart Association (NYHA) functional class, glomerular filtration rate (GFR) calculated using the Modification of Diet in Renal Disease Equation, concomitant medication, length of hospital stay, and discharge status. Transthoracic echocardiography was routinely performed at patient admission to evaluate the systolic and diastolic function of the left ventricle using a Fukuda Denshi Full Digital Ultrasound System UF-850XTD (Fukuda Denshi Co., Ltd., Tokyo, Japan).

Left ventricular systolic function was evaluated based on the following classification of the left ventricular ejection fraction (LVEF): reduced (LVEF of <40%), mid-range (LVEF of 40%–50%), preserved (LVEF of 50%–60%), or normal (LVEF of >60%).

The patients were divided into two groups according to the etiology of dyspnea: cardiac and non-cardiac. A team of two physicians (A.S. and O.S.) evaluated each patient's medical record.

## Statistical analysis

Continuous variables were tested for normal distribution using the Kolmogorov–Smirnov test and are presented either as mean ± standard deviation or median with 25th and 75th percentiles. Means between groups were compared using parametric tests (independent-sample t test, analysis of variance followed by the Bonferroni post-hoc test for multiple comparisons) or non-parametric tests (Kruskal–Wallis test, Mann–Whitney U test) as appropriate. In certain cases, logarithmic transformation of data was performed.[14]

Analysis of covariance (ANCOVA) was used to control for the effects that continuous variables such as age or GFR may have on the marker's output between patients with acute cardiac dyspnea and those with non-cardiac dyspnea.

For correlations between variables, Pearson's test was used after logarithmic transformation. Measures of associations were studied using phi or Cramer's V (nominal by nominal) and eta (nominal by interval) coefficients.

Receiver operating characteristic (ROC) analysis was used to ascertain the diagnostic performance of biomarker levels, and the areas under the curve (AUCs) were compared.[15]

The diagnostic performance of NT-proBNP and galectin-3 was ascertained for the entire group as well as for certain high-risk subsets such as patients with kidney failure (GFR of <60 mL/minute/1.73 m$^2$), age of >60 years, obesity (BMI of >30 kg/m$^2$), rhythm disorders (atrial fibrillation/flutter), LVEF of <40%, arterial hypertension, and type 2 diabetes mellitus.

ROC-optimized cut-off values as well as sensitivities and specificities were calculated.[16] Data analysis was performed using IBM SPSS Statistics for Windows, version 19.0 (IBM Corp., Armonk, NY, USA) and MedCalc version 18.2.1 (MedCalc Software bvba, Ostend, Belgium). All tests were two-tailed, and a p-value of <0.05 was considered statistically significant.

## Results

This study included 208 patients ranging in age from 41 to 94 years and with a female:male ratio of 1.44. The patients' NT-proBNP level ranged from 12 to 30,000 pg/mL, and their galectin-3 level ranged from 7.5 to 86.6 ng/mL.

The diagnostic criteria for acute cardiac dyspnea were fulfilled in 61.1% of the patients. The cardiac profile of the patients at the time of ED presentation showed that 76.0% were hypertensive and more than half (55.8%) had supraventricular rhythm disorders such as atrial fibrillation or atrial flutter. Chronic myocardial infarction
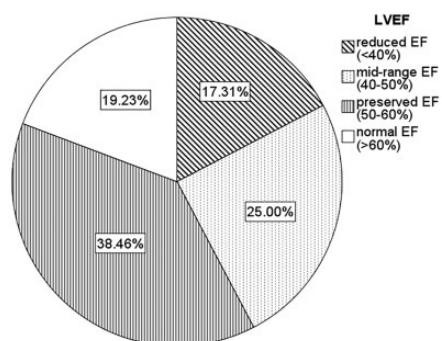
**Figure 1.** Distribution of patients according to the LVEF. LVEF, left ventricular ejection fraction.

was present in 5.3% of patients. Preserved left ventricular systolic function (50%–60%) defined the largest proportion of patients (38.46%) (Figure 1).

Clinical manifestations compatible with NYHA functional class III to IV heart failure presented a balanced distribution when compared with the subgroup of patients with mild dyspnea (NYHA class I–II) (49.6% vs. 50.4%, respectively).

One-third of the patients (30.3%) had associated acute bronchopulmonary manifestations, either community-acquired acute respiratory illness or an exacerbation of a previous chronic bronchopulmonary condition (chronic obstructive pulmonary disease or bronchial asthma).

Anemia, chest wall syndromes (costochondritis, musculoskeletal pain), diseases of the digestive system (gastroesophageal reflux), and anxiety were encountered among other non-cardiac etiologies of acute dyspnea.

Other comorbidities were obesity (BMI of >30 kg/m$^2$; 30.3%), type 2 diabetes mellitus (28.4%), chronic stroke (18.6%), chronic kidney disease (15.4%), lower extremity peripheral arterial disease grade II to IV (14.4%), and chronic bronchopulmonary pathology (10.1%).

Commonly associated medications at admission included beta-blockers (49.5%), diuretics (42.3%), platelet anti-aggregants (32.7%), and angiotensin-converting enzyme inhibitors (27.4%).

Alcohol consumption was classified as "yes," "no," and "former." Chronic alcohol consumption was present in 12.5% of the study group (n = 26) and was linked to an altered LVEF (consumer, 44.19% ± 10.64%; non-consumer, 51.39% ± 9.47%; former consumer, 49.69% ± 7.38%; p = 0.005), an increased alanine aminotransferase level as an indicator of impaired hepatic function (consumer, 37.96 ± 27.64 U/L; non-consumer, 25.49 ± 16.39 U/L; p = 0.012), and a proinflammatory status as reflected by the serum C-reactive protein level (consumer, 6.83 ± 11.81 mg/dL; non-consumer, 2.47 ± 4.75 mg/dL; p = 0.027). Additionally, higher estimated GFRs were noted in the subgroup of chronic alcohol consumers (consumer, 77.23 ± 28.8 mL/minute/1.73 m$^2$; non-consumer, 71.73 ± 25.01 mL/minute/1.73 m$^2$; p = 0.042).

Smoking habits were found in 20.2% (n = 42) of the patients but did not lead to any significant differences in the biomarker levels or LVEF between the cardiac and non-cardiac dyspnea groups.

Patients with acute cardiac dyspnea were significantly older (p = 0.000) and had a significantly longer in-hospital stay (p = 0.032). The heart rate was higher (p = 0.000) and the LVEF was lower (p = 0.000) in the cardiac than non-cardiac dyspnea group. Biochemical characteristics of the patients with acute cardiac dyspnea included increased serum levels of urea and uric acid (p = 0.000 for both) and significantly lower GFRs (p = 0.009) compared with the patients with non-cardiac dyspnea (p < 0.05) (Table 1).

Both biomarkers followed in this study, NT-proBNP and galectin-3, were significantly higher in the patients with acute cardiac dyspnea than in those with acute non-cardiac dyspnea (p = 0.000) (Figure 2).

**Table 1.** Comparison between cardiac and non-cardiac dyspnea groups.

| | All patients | Acute cardiac dyspnea | Acute non-cardiac dyspnea | p-value |
|---|---|---|---|---|
| Age, years | $72.96 \pm 11.11$ | $75.96 \pm 10.18$ | $69.14 \pm 11.49$ | 0.000* |
| Hospitalization, days | $7.27 \pm 3.45$ | $7.61 \pm 3.42$ | $6.74 \pm 3.46$ | 0.032* |
| HR, beats/minute | $91.99 \pm 25.78$ | $98.06 \pm 27.68$ | $82.46 \pm 19.06$ | 0.000* |
| GFR, mL/minute/1.73 m$^2$ | $72.69 \pm 25.68$ | $67.50 \pm 26.93$ | $80.82 \pm 21.33$ | 0.009* |
| Serum level of urea, mg/dL | $50.47 \pm 26.94$ | $56.70 \pm 30.71$ | $40.71 \pm 15.28$ | 0.000* |
| Serum level of uric acid, mg/dL | $5.89 \pm 2.66$ | $6.26 \pm 2.92$ | $5.30 \pm 2.07$ | 0.000* |
| LVEF, % | $50.38 \pm 9.76$ | $46.60 \pm 9.43$ | $56.32 \pm 6.95$ | 0.000* |

Data are presented as mean $\pm$ standard deviation. HR, heart rate; GFR, glomerular filtration rate; LVEF, left ventricular ejection fraction. *$p < 0.05$.
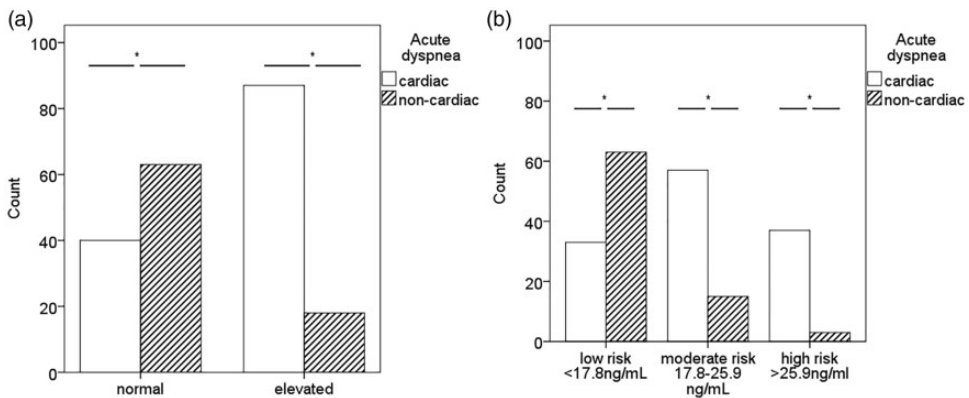


**Figure 2.** NT-proBNP and galectin-3 levels based upon acute dyspnea groups. (a) NT-proBNP. (b) Galectin-3. *$p < 0.05$. NT-proBNP, N-terminal prohormone of brain natriuretic peptide.

Several parameters showed a significant association with the etiology of acute dyspnea: age, elevated systolic blood pressure, LVEF, presence of atrial fibrillation/flutter, and GFR. Additionally, both biomarkers had a strong and significant connection with the etiology of dyspnea (p = 0.000 for both) (Table 2).

The serum concentrations of both NT-proBNP and galectin-3 were significantly higher in patients with acute cardiac dyspnea than in those with non-cardiac dyspnea (p = 0.000 for both) (Table 3).

ANCOVA was performed to determine whether the differences observed in the NT-proBNP and galectin-3 levels between patients with cardiac and non-cardiac dyspnea were indeed due to the type of dyspnea and not solely to the influences that factors such as older age or impaired GFR may exert on these markers. After controlling for the differences between patients with cardiac and non-cardiac dyspnea with respect to age (higher in patients with cardiac dyspnea) and GFR (impaired in patients with cardiac dyspnea), ANCOVA was performed to assess whether patients with cardiac dyspnea still had higher levels of NT-proBNP than patients with non-cardiac dyspnea. The same analysis was performed for the second marker evaluated in this study (galectin-3).

**Table 2.** Profile of acute cardiac and non-cardiac dyspnea groups.

| Parameter | All patients (n) | Cardiac (n) | Non-cardiac (n) | Coefficient | p-value |
|---|---|---|---|---|---|
| | | **Dyspnea etiology groups** | | **Measures of association with dyspnea etiology groups** | |
| Total number of patients | 208 | 127 | 81 | | |
| Age of >60 years | 181 | 115 | 66 | 0.193 | 0.021* |
| Male sex | 85 | 55 | 30 | 0.062 | 0.370 |
| Smoking | 20 | 11 | 9 | 0.61 | 0.677 |
| Elevated NT-proBNP, pg/mL | 105 | 87 | 18 | 0.451 | 0.000* |
| Elevated galectin-3, >17.8 ng/mL | 112 | 94 | 18 | 0.516 | 0.000* |
| GFR of <60 mL/minute/1.73 m$^2$ | 66 | 52 | 14 | 0.267 | 0.005* |
| SBP of >140 mmHg | 115 | 60 | 55 | 0.228 | 0.029* |
| LVEF of <40% | 36 | 33 | 3 | 0.512 | 0.000* |
| Rhythm disorders (atrial fibrillation/flutter) | 116 | 97 | 19 | 0.520 | 0.000* |
| Type 2 diabetes mellitus | 59 | 37 | 22 | 0.021 | 0.758 |
| Obesity (BMI of >30 kg/m$^2$) | 63 | 39 | 24 | 0.095 | 0.598 |

NT-proBNP, N-terminal prohormone of brain natriuretic peptide; GFR, glomerular filtration rate; SBP, systolic blood pressure; LVEF, left ventricular ejection fraction; BMI, body mass index.

**Table 3.** NT-proBNP and galectin-3 in subgroups of patients with associated risks.

| Subgroups | NT-proBNP (pg/mL) | | | Galectin-3 (ng/mL) | | |
|---|---|---|---|---|---|---|
| | Cardiac | Non-cardiac | p-value | Cardiac | Non-cardiac | p-value |
| All patients | 3137 (829–7933) | 543 (166–1065.5) | 0.00** | 22.3 (17.5–28.4) | 15.7 (12.6–17.8) | 0.00** |
| Age of >60 years | 3508 (829–9261) | 613.5 (212.8–1203.5) | 0.00** | 22.4 (18.6–29.2) | 15.7 (12.3–17.8) | 0.00** |
| Obesity (BMI of >30 kg/m$^2$) | 2325 (736–4570) | 344 (89.7–744.8) | 0.00** | 22.8 (19.2–29.2) | 16.05 (14.5–17.9) | 0.00** |
| GFR of <60 mL/minute/1.73 m$^2$ | 4246.5 (1301–10592.3) | 1254.5 (530–4783) | 0.00** | 24.65 (19.9–34.6) | 15.95 (13.3–19.3) | 0.00** |
| LVEF of <40% | 5810 (3230–10131) | 173 (139.5–1119) | 0.011* | 22.8 (19.6–28.5) | 17.9 (14.8–18.7) | 0.045* |
| Rhythm disorders (atrial fibrillation/flutter) | 3508 (893.5–7829) | 1081 (390–2706) | 0.00** | 22 (17.1–26.2) | 14.8 (11.7–15.9) | 0.00** |
| Type 2 diabetes mellitus | 2567 (882–8033.5) | 326.5 (104.3–816.8) | 0.00** | 22 (18.6–31.8) | 16.65 (14.6–18.1) | 0.00** |
| Arterial hypertension (SBP of >140 mmHg) | 2909.5 (696.25–9291.25) | 556 (194–1167) | 0.00** | 22 (17.4–30.9) | 15.8 (13.4–17.6) | 0.00** |

Data are presented as median and interquartile range (25th–75th percentile).
NT-proBNP, N-terminal prohormone of brain natriuretic peptide; BMI, body mass index; GFR, glomerular filtration rate; LVEF, left ventricular ejection fraction; SBP, systolic blood pressure.
*p < 0.05, **p < 0.001.

The results indicated that after controlling for the differences in age and GFR between patients with cardiac and non-cardiac dyspnea, the differences in NT-proBNP (F = 16.81(1,204), p = 0.000) and galectin-3 (F = 22.45(1,204), p = 0.000) between the two groups remained significant. The adjusted group means and variability (standard error) after controlling for differences in age and GFR as covariates were as follows: cardiac acute dyspnea: NT-proBNP, 5002.977 ± 450.4 pg/mL and galectin-3, 23.785 ± 0.823 ng/mL; non-cardiac acute dyspnea: NT-proBNP, 2020.745 ± 551.913 pg/mL and galectin-3, 17.485 ± 1.009 ng/mL. These findings indicate that the type of dyspnea significantly influences the levels of NT-proBNP and galectin-3.

Among all patients enrolled in this study, 4.3% (n = 9) died before discharge from the hospital and 2.9% required transfer to the coronarography unit for acute coronary syndrome and revascularization procedures. In the subgroup of patients who died of cardiac causes (n = 8), the serum galectin-3 levels were significantly higher and ranged from 17.8 to 63.4 ng/mL [cardiac median, 29.2 ng/mL; interquartile range (IQR), 24.7–36.5 ng/mL and non-cardiac median, 20.1 ng/mL; IQR, 11.7–28.5 ng/mL; p = 0.038]. For NT-proBNP, these values ranged from 897 to and 30000 pg/mL (p = 0.003).

The patients were divided into three subgroups according to their outcome at discharge: deceased, aggravated, and improved. Both NT-proBNP and galectin-3 showed significant differences among these subgroups. The differences were very significant between the deceased subgroup [median galectin-3, 28.5 ng/mL (IQR, 21.05–36.55 ng/mL); median NT-proBNP, 9599 pg/mL (IQR, 4284–16235 pg/mL)] and improved subgroup [median galectin-3, 18.6 ng/mL (IQR, 15.2–23 ng/mL); median NT-proBNP, 1132 pg/mL (IQR, 432.5–4184.5 pg/mL)] (NT-proBNP, p = 0.001; galectin-3, p = 0.012).

Statistically significant differences between the deceased and survivors (improved or aggravated) subgroups were observed for age (improved, 72.5 ± 11.20 years; deceased, 79.78 ± 10.09 years; p = 0.043), the serum C-reactive protein level (improved, 2.39 ± 5.3 mg/dL; deceased, 11.72 ± 10.01 mg/dL; p = 0.000), and hyponatremia (serum sodium level of <135 mmol/L) (improved, 138.65 ± 4.89 mmol/L; deceased, 134.44 ± 5.22 mmol/L; p = 0.031).

Inclusion in a certain NYHA functional class weightly influenced the outcome at discharge as shown by significant differences in the categorization in different NYHA classes between the deceased and survivor groups (p = 0.020).

The correlation between the NT-proBNP and galectin-3 levels was direct, moderate to strong (r = 0.477), and significant (p = 0.000) (Figure 3).

The diagnostic performance of both biomarkers was tested in all patients as well as in the subsets of patients with high risk and a potential for unclear interpretation of NT-proBNP and galectin-3. These subsets of patients were those with kidney failure
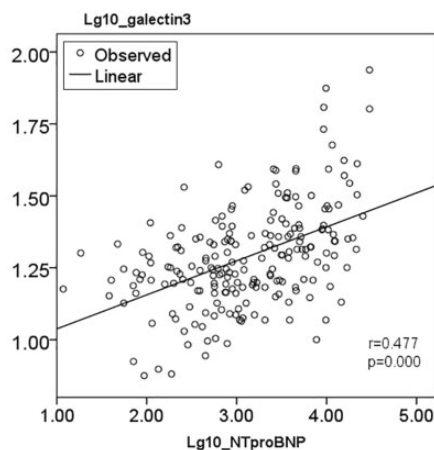


**Figure 3.** Pearson correlation between galectin-3 and NT-proBNP. A base-10 log scale is used for the x- and y-axes. NT-proBNP, N-terminal prohormone of brain natriuretic peptide.

(GFR of $<60$ mL/minute/1.73 m$^2$), age of $>60$ years, obesity (BMI of $>30$ kg/m$^2$), rhythm disorders (atrial fibrillation/flutter), LVEF of $<40\%$, arterial hypertension, and type 2 diabetes mellitus. Patients with acute cardiac dyspnea showed significantly higher serum concentrations of both NT-proBNP and galectin-3, both overall and in each particular subset of patients with these associated conditions (p $<$ 0.05 for all) (Table 3).

To test the diagnostic performance of NT-proBNP and galectin-3 for acute cardiac dyspnea, comparative accuracy was evaluated using ROC analysis. Both biomarkers showed similar diagnostic abilities as indicated by the lack of statistically significant differences between the AUCs (Table 4).

Dimension reduction through principal component analysis was used to ascertain whether the component summarizing both NT-proBNP and galectin-3 into a single latent variable may be of use in diagnostic prediction. Better predicting accuracy was found when using the component latent variable (AUC $=$ 0.859, p $=$ 0.000) than when using the two biomarkers independently (NT-proBNP: AUC $=$ 0.807, p $=$ 0.000; galectin-3: AUC $=$ 0.815, p $=$ 0.000) (Figure 4).

The diagnostic performance of the two biomarkers was also studied in subsets of particular interest, given the increased cardiovascular morbidity/mortality in the general population (age of $>60$ years, GFR of $<60$ mL/minute/1.73 m$^2$, obesity as defined by a BMI of $>30$ kg/m$^2$, impaired left ventricular function as defined by an LVEF of $<40\%$, type 2 diabetes mellitus, and rhythm disorders). There were no statistically significant differences between the AUCs for galectin-3 and NT-proBNP in any of the high-risk subsets (Table 4).

ROC analysis also indicated that the optimal diagnostic cut-offs values were higher in certain high-risk subsets of patients such as those with impaired renal function, impaired cardiac function (reduced LVEF), rhythm disorders, and diabetes than in the overall study group (Table 4).

## Discussion

Current guidelines recommend an active and rapid approach to establishing the diagnosis of acute heart failure; specific treatment should be promptly initiated within an optimal time frame of 30 to 60 minutes after admission.[17–20] In a "real life" context, patients with acute dyspnea and/or atypical manifestations of heart failure often require multidisciplinary evaluation by a cardiologist, pulmonologist, and internist, which is time-consuming and technically demanding, requiring chest X-ray and transthoracic echocardiography $\pm$ computed tomography pulmonary angiography.

This prospective observational study focused on the difficulties that confront the clinician when assessing dyspnea of acute onset. Furthermore, the heterogeneity of patients included in the present study with respect to the age range and different etiologies of heart failure as triggering factors of acute dyspnea reflect "real life" situations.

A small percentage of patients with NYHA class I heart failure were included in our study (5.28%). In fact, these patients presenting to the ED were younger, had a more atypical description of symptoms, and had more non-cardiac etiologies of dyspnea, mainly anxiety and panic disorders. Although easily manageable by the primary care physician, a significant number of similar presentations in the ED are related to hypochondria and anxiety.[21] Without an obvious organic pathology, more challenges arise from managing these patients, thus necessitating objective methods of diagnosis.

Although BNP and NT-proBNP have an established position regarding their diagnostic abilities in acute heart failure (Class I recommendation), multiple

**Table 4.** Diagnostic test performance of NT-proBNP and galectin-3 for acute cardiac dyspnea.

| Biomarker | AUC (95% CI) | p | Sensitivity (%) | Specificity (%) | Optimal cut-off | p |
|---|---|---|---|---|---|---|
| All patients | | | | | | |
| NT-proBNP (pg/mL) | 0.781 (0.718–0.835) | 0.55 | 66.13 | 82.14 | 1538 | 0.000** |
| Galectin-3 (ng/mL) | 0.803 (0.742–0.855) | | 72.6 | 84.52 | 18.8 | 0.000** |
| Age of >60 years | | | | | | |
| NT-proBNP (pg/mL) | 0.745 (0.675–0.807) | 0.13 | 66.7 | 77.9 | 1538 | 0.000** |
| Galectin-3 (ng/mL) | 0.811 (0.746–0.866) | | 75.7 | 83.8 | 18.8 | 0.000** |
| Obesity (BMI of >30 kg/m$^2$) | | | | | | |
| NT-proBNP (pg/mL) | 0.781 (0.659–0.875) | 0.44 | 58.97 | 87.5 | 1081 | 0.000** |
| Galectin-3 (ng/mL) | 0.841 (0.727–0.921) | | 74.36 | 91.67 | 19.5 | 0.000** |
| GFR of <60 mL/minute/1.73 m$^2$ | | | | | | |
| NT-proBNP (pg/mL) | 0.671 (0.545–0.781) | 0.28 | 75.0 | 60.0 | 1538 | 0.023* |
| Galectin-3 (ng/mL) | 0.769 (0.650–0.863) | | 80.77 | 73.33 | 18.6 | 0.006* |
| LVEF of <40% | | | | | | |
| NT-proBNP (pg/mL) | 0.792 (0.597–0.921) | 0.23 | 83.33 | 75 | 2065 | 0.071 |
| Galectin-3 (ng/mL) | 0.651 (0.449–0.820) | | 75 | 75 | 19.5 | 0.481 |
| Rhythm disorder (atrial fibrillation/flutter) | | | | | | |
| NT-proBNP (pg/mL) | 0.697 (0.605–0.779) | 0.07 | 51.06 | 86.36 | 3228 | 0.0007* |
| Galectin-3 (ng/mL) | 0.825 (0.743–0.889) | | 71.28 | 90.91 | 17.9 | 0.000** |
| Type 2 diabetes mellitus | | | | | | |
| NT-proBNP (pg/mL) | 0.838 (0.719–0.921) | 0.64 | 67.57 | 90.91 | 1648 | 0.000** |
| Galectin-3 (ng/mL) | 0.803 (0.679–0.895) | | 75.68 | 81.82 | 18.5 | 0.000** |

NT-proBNP, N-terminal prohormone of brain natriuretic peptide; AUC, area under the curve; CI, confidence interval; BMI, body mass index; GFR, glomerular filtration rate; LVEF, left ventricular ejection fraction.
*$p < 0.05$, **$p < 0.0001$.

interferences with different pathologies limit the utility of these biomarkers in emergency situations.[4,22]

A significant proportion of the study group presented to the ED for aggravated dyspnea, which is an expression of decompensated chronic heart failure, despite adherence to a chronic cardiovascular medication. In fact, this category of patients represents a major concern regarding a
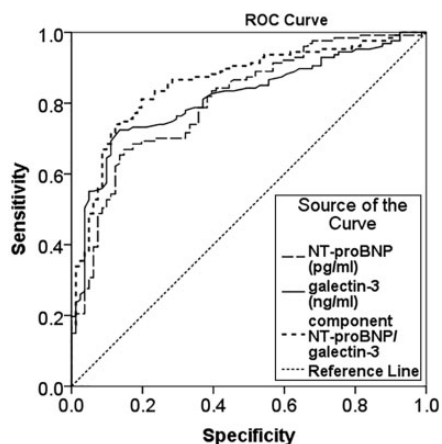
**Figure 4.** ROC curves for the diagnosis of acute cardiac dyspnea for NT-proBNP, galectin-3, and the component of the two markers. NT-proBNP, N-terminal prohormone of brain natriuretic peptide; ROC, receiver operating characteristic.

clinician's diagnostic abilities because chronic therapy tends to mask the signs and symptoms characteristic of acute heart failure. The most common coexistent cardiometabolic diseases on admission were arterial hypertension, supraventricular rhythm disorders (atrial fibrillation/atrial flutter), obesity, diabetes mellitus, chronic myocardial infarction, and lower extremity peripheral arterial disease.

There were no significant sex-related differences between the two groups. The patients with cardiac dyspnea were older and had more advanced renal function decline. Moreover, prolonged hospitalizations were required for the subgroups of patients with acute dyspnea of cardiac origin.

An additional finding of this study is the paradoxical relationship between alcohol consumption and renal function. Higher estimated GFRs have been associated with chronic alcohol consumption. This paradoxical relationship can be partially explained by the diuretic effects of alcohol consumption through inhibition of vasopressin, but this finding requires cautious

interpretation and judicious use in an adequate scientific context.[23]

In this study, the distribution of patients according to their LVEF showed that most patients had a preserved LVEF. This is also the category of patients that is more likely to receive an incorrect diagnosis.

Assessment of the serum concentrations of both NT-proBNP and galectin-3 showed significantly higher levels in patients with acute cardiac dyspnea, suggesting an ability to identify patients with increased cardiovascular risk. The same observation was true for subsets of patients with higher risk such as those with kidney failure, advanced age, obesity, rhythm disorders, impaired left ventricular function, arterial hypertension, and type 2 diabetes mellitus.

Concerns that the higher levels of NT-proBNP and galectin-3 in patients with acute cardiac dyspnea were due solely to the influence of factors such as older age or impaired GFR were alleviated by controlling for the impact of these covariates. While this does not completely exclude the impact that older age or impaired GFR may have on these markers, it was important to prove that the type of dyspnea significantly influenced the levels of NT-proBNP and galectin-3, making these markers useful indicators of the risk of acute cardiac dyspnea.

While the values for both markers were higher in the deceased group than in the improved outcome group, galectin-3 had a tighter range than NT-proBNP in the deceased group. This may imply that galectin-3 has the potential to serve as a more specific prognostic factor.

In patients expected to have a poor outcome, we found that more advanced age, an increased serum C-reactive protein level, and/or hyponatremia better identified patients with high cardiovascular risk. More advanced NYHA functional classes (III–IV) were also strong predictors of a negative outcome.

The present study findings confirm that a significant association exists not only between NT-proBNP and acute cardiac dyspnea but also between galectin-3 and acute cardiac dyspnea.

The existence of a strong correlation between NT-proBNP and galectin-3 (highlighted in Figure 3) lends credibility to the utility of a dual-biomarker approach to the diagnosis of acute cardiac dyspnea. This finding represented a good argument to further proceed with the ROC curve analysis in an effort to ascertain the diagnostic performance of both biomarkers.

High diagnostic accuracy for NT-proBNP and galectin-3 was demonstrated in the ROC analysis, indicating that both biomarkers are reliable tools for the prediction of acute cardiac dyspnea. The results were comparable when analyzing the entire study group as well as the subgroups of high-risk cardiovascular patients. The associated comorbidities led to higher optimal diagnostic cut-off values but did not impair the diagnostic accuracy of either marker.

After the independent analysis of the two biomarkers confirmed their diagnostic performance in identifying acute cardiac patients, a component variable was proven to have even better predictive diagnostic ability. This indicates that serum determination of galectin-3 enhances the diagnosis of acute cardiac dyspnea when used in conjunction with NT-proBNP.

## Study limitations

The patients came from a single tertiary center, and the population was representative of the northeastern region of Romania. Our study findings are not applicable to pediatric patients or non-Caucasian ethnic groups. Although the number of patients was limited, statistically significant

diagnostic accuracy of the two biomarkers in patients with acute cardiac dyspnea was demonstrated.

In conclusion, these findings indicate that dual-biomarker analysis (NT-proBNP and galectin-3) represents an important practical approach that leads to early recognition of atypical manifestations of acute heart failure in patients with acute dyspnea presenting to the ED. The combination of NT-proBNP and galectin-3 is superior to NT-proBNP alone. This may improve outcomes for patients in whom the determination of NT-proBNP does not reflect, for various reasons, the severity of the underlying cardiac condition. These results have immediate clinical applicability in identifying high-risk cardiovascular patients who require intensive care treatment. Furthermore, accurate triage and early cardiovascular risk stratification of patients with acute dyspnea in emergency settings reduces the economic impact of the disease and associated treatments.

## Declaration of conflicting interest

The authors declare that there is no conflict of interest.

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