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B-type natriuretic peptide/ferritin ratio as a predictor of the risk of developing acute renal injury in acute decompensated heart failure

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Abstract:

OBJECTIVES: Acute decompensated heart failure (ADHF) is a clinical condition that requires urgent diagnosis and treatment. Patients present with pulmonary capillary wedge pressure, pulmonary arterial pressure, and venous pressure elevation. Along with the progressive deterioration observed in the clinical picture, impairment or deterioration of kidney function may also occur. In this study, we evaluated the B-type natriuretic peptide (BNP)/ferritin ratio as a predictor of the risk of developing acute renal injury (ARI) in ADHF.

METHODS: A total of 157 patients with a diagnosis of ischemic dilated cardiomyopathy for more than 6 months that presented to our clinic with ADHF were included in this cohort study. After the treatment protocol was applied, the sample was divided into two groups as patients with and without ARI. The BNP and ferritin levels were examined along with the routine blood parameters (BNP), and the BNP, ferritin, and BNP/ferritin values were compared between the groups.

RESULTS: ARI was present in 34.3% (n = 54) of the patients, who were also found to have higher BNP (892.76 vs. 817.54), lower ferritin (86.78 ± 57.2 vs. 105.46 ± 38.3), and higher BNP/ferritin (10.48 ± 2.14 vs. 7.89 ± 1.89). The multivariate logistic regression analysis revealed the BNP/ferritin ratio as an independent risk factor for ARI (odds ratio = 3.19; 95% CI, 1.92-6.54; P = 0.001). Using the receiver operating characteristic curve, a cutoff value of 9.32 for BNP/ferritin ratio had a sensitivity of 81.8% and a specificity of 93.5% (area under the curve 0.842, P < 0.001) for the prediction of ARI.

CONCLUSION: The BNP/ferritin ratio is a new parameter that can be used to draw attention to the severity of the treatment and renal function in ADHF cases in emergency situations.

Keywords:

B-type natriuretic peptide/ferritin ratio, heart failure, renal injury

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Introduction

Acute decompensated heart failure (ADHF) can manifest with a wide range of clinical signs from mild pulmonary edema to cardiogenic shock. After discharge from the hospital, 20% of patients require hospitalization again within the 1st month and 50% within the first 6 months, and the 2-month mortality is reported as 20%.[1,2] While diuretics are known to have positive effects in short and medium terms, mortality and morbidity outcomes related

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Box-ED Section

What is already known on the study topic?

BNP is a diagnostic and prognostic marker for acute heart failure. It is known that ferritin is associated with mortality in heart failure.

What is the conflict on the issue? Has it importance for readers?

Patients with a diagnosis of chronic heart failure may present to the emergency department with acute decompensation. One of the main goals in the treatment is to relieve the volume burden. The diuretic therapy given can sometimes impair renal function. In this sense, we determined the BNP/ferritin ratio as a parameter that has never been investigated before as a predictor of renal dysfunction in patients with acute decompensated heart failure.

How is this study structured?

This was a single-center, retrospective, observational study includes data from a total of 157 patients.

What does this study tell us?

This article supports the conclusion that the BNP/ferritin ratio is a new parameter that can be used in emergency situations to draw attention to the severity of treatment and renal function in ADHF cases. For this, we thought it was suitable for Turkish Journal of Emergency Medicine Journal.

to their long-term use have not yet been clarified. It has been recommended that BUN and creatinine values be monitored every 1–2 days during hospitalization, regardless of clinical condition.[3] In addition, the previously used renin-angiotensin-aldosterone system (RAAS) blockers prepare a sensitive environment for renal damage. As the risk of developing renal failure increases, in-hospital mortality significantly increases.[4]

B-type natriuretic peptide (BNP) is a heart hormone secreted by cardiac myocytes in the ventricles in response to pressure changes that occur when heart failure develops or worsens. BNP levels are associated with the severity and prognosis of heart failure.[5]

Anemia in heart failure, despite having a multifactorial etiology, is considered to be caused by complex interactions between poor renal function and bone marrow response and is associated with worse symptoms and higher mortality.[6,7] It has been shown that anemia has higher prevalence in patients with congestive heart failure, it is associated with rehospitalization due to decompensation and cardiac mortality, and it is related to poorer survival in the short term in cases of acute heart failure.[8,9] The correlation of mortality in heart failure with renal function, BNP, and ferritin that is an indicator of anemia also suggests the presence of a relationship between renal functions and BNP and ferritin. Thus, in this study, in patients with acute heart failure, we examined the relationship between acute renal injury (ARI) risk and BNP and ferritin, and a third combined parameter, i.e., the ratio of BNP/ferritin, which, to our knowledge, has not been previously investigated in the literature.

Methods

The study was conducted following the ethical guidelines of the declaration of Helsinki after receiving approval from the Institutional Ethics Committee. Ethical approval for the present study was obtained from Atatürk University Medical Faculty Clinical Research Ethics Committee (No: 07/25) Date: June 26, 2020. Data were obtained from the patients who were evaluated in the emergency service of our institution, where 100–150 patients applied daily. Patients who presented to the emergency department of our center with ADHF between November 2019 and June 2020 were included in the study. The diagnoses of the patients were determined in the emergency department by a cardiologist or specialist emergency physician experienced in echocardiography. These patients were observed in the cardiology intensive care unit after their first treatment in the emergency department. Patients with end-stage renal failure (estimated glomerular filtration rate (eGFR) <15 ml/min/1.73 m^2), those receiving iron supplements, pregnant and lactating women, those with malignant cancer, hematological problems, or acute coronary syndrome, with cardiac arrest and hemodynamic impairment, those with a left ventricular ejection fraction of >40%, or right heart failure, obese patients (body mass index >30), patients aged >75, and those with liver dysfunction were excluded. Patients with a diagnosis of ischemic dilated cardiomyopathy for more than 6 months that presented to our clinic with ADHF were included in our study. As a result, 157 patients were divided into two groups as those with and without ARI risk according to the rifle criteria. In the Rifle criteria, the risk of ARI is defined as a 50% increase in the serum creatinine level and a consequent 25% decrease in GFR or urine excretion decreasing below 0.5 mL kg/h for more than 6 h.[10] To identify renal dysfunction, the changes in the highest renal parameters of patients observed during a hospitalization period of at least 3 days were taken into consideration. An echocardiographic evaluation was performed in the left lateral decubitus position with a 3.5 MHz transducer using the cardiovascular ultrasound system. Ejection fraction was calculated using the modified Simpson method.

Serum glucose, creatinine, and lipid profile were determined by the standard methods. Complete blood counts were obtained with an automated blood cell counter. Blood urea nitrogen, total protein, and albumin

values were analyzed using test kits according to the manufacturer's instructions.

The Statistical Package for the Social Sciences software version 20 for Windows was used for the statistical analysis of all data (SPSS, Inc.,Chicago, IL). Categorical variables were expressed as percentages, and the Chi-square test and Fisher's exact test were used for comparisons. Continuous variables were calculated as mean value ± standard deviation, and the Shapiro–Wilk test was conducted to check the normality of the distribution of variables. Student's *t*-test was used to compare the continuous variables with normal distribution, and the Mann–Whitney U-test to compare those that did not show normal distribution. Relationships of two different variables with each other were made using Spearman or Pearson correlation analysis. Spearman rank test was performed to define the correlation of ARI with BNP, ferritin and BNP/ferritin ratio. Calibration was evaluated through the Hosmer-Lemeshow goodness-of-fit test with groups (P = 0.32). Univariate and multivariate logistic regression analyses were performed to calculate the odds ratio (OR) of the ARI risk factors. The variables found significant in the univariate analysis ($P < 0.05$) and several variables confirmed to be significant in clinical practice were included in the multiple logistic regression analysis (model summary; Nagelkerke R^2: %53). The ability of the model to distinguish between patients with and without the risk of ARI was also analyzed based on the receiver operating characteristic (ROC) curve.

Results

A total of 157 ADHF patients with ischemic etiology were included in this study. The basic clinical and laboratory features of the patients are given in Table 1. Kidney damage consistent with ARI was detected in 54 (34.3%) patients. The ARI group was older, and their hypertension rate was higher. Heart failure duration was similar between the ARI and non-ARI groups. There was no significant difference between the groups in terms of vital signs. The basal creatinine value was higher in the group with ARI but not at a statistically significant level, while eGFR was significantly lower in the same group. In addition, in the group with ARI, troponin I, BNP, and BNP/ferritin ratio were high, and the ferritin value was lower compared to the non-ARI group.

The univariate logistic regression revealed that age, hypertension, eGFR, troponin I, BNP, ferritin, and BNP/ferritin ratio were associated with ARI ($P < 0.05$ for all). In the multivariate analysis, the BNP/ferritin ratio (OR = 3.19; 95% confidence interval [CI], 1.92–6.54; P = 0.001), ferritin (OR = 0.72; 95% CI, 0.89–0.53; P = 0.028), BNP (OR = 1.13; 95% CI, 1.01—1.73; P = 0.043), and age (OR = 3.02; 95% CI, 1.83–9.62; P = 0.001) remained significant predictors for the development of ARI in patients after ADHF [Table 2]. Furthermore, ARI had a positive correlation with age (r = 0.384, $P < 0.001$) and hypertension (r = 0.424, $P < 0.001$).

According to the ROC analysis of the ability of the investigated parameter to predict ARI risk, the sensitivity and specificity values were calculated as 73.2 and 86.4%, respectively, for BNP at the optimal cutoff value of 624.84; 71.2 and 79.5%, respectively, for ferritin at the optimal cutoff value of 53.48 and 81.8 and 93.5%, respectively, for the BNP/ferritin ratio at the optimal cutoff value of 9.32. The area under the curve value was found to be 0.779 for BNP, 0.754 for ferritin, and 0.842 for the BNP/ferritin ratio [Figure 1].

Discussion

Deterioration of renal function is directly linked to poor prognosis in patients with ADHF. The underlying causes of renal function deterioration are multifactorial, and some are associated with the cardiological effects of aggressive diuretic therapy to resolve congestion and with tubular damage caused by reduced ejection fraction. Early detection of deterioration of renal function is important for detecting end-organ damage.[11] Aghel *et al*., evaluating ADHF cases, found that the number of presentations to the hospital was higher among the patients with worsening renal function than in those with normal renal function.[12] Other researchers indicated the need for investigating markers to determine kidney damage in an early and sensitive manner due to heterogeneity of the group of patients with renal dysfunction.[13,14] In other studies, various biomarkers, such as cystatin C,

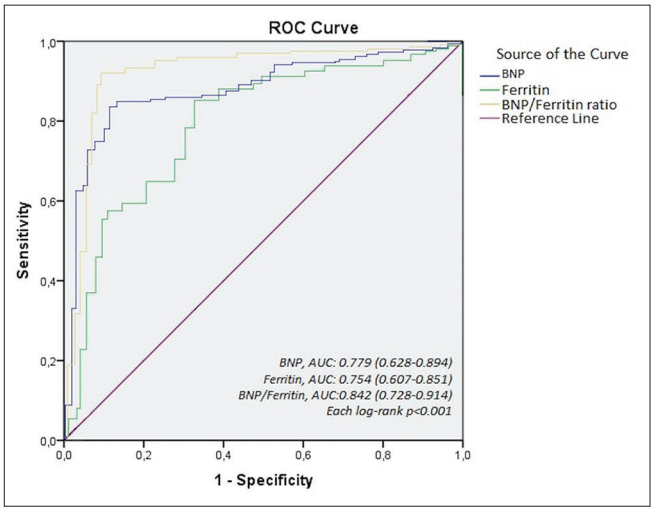

Figure 1: Receiver operating characteristic curves for B-type natriuretic peptide, ferritin and B-type natriuretic peptide/ferritin ratio in predicting the risk of acute renal injury development

Table 1: Baseline characteristics and laboratory findings of the study population

	ARI-R (–) (*n*=103), *n* (%)	ARI-R (+) (*n*=54), *n* (%)	*P*
Age (years)	61.40±9.08	66.34±8.16	<0.001
Female	59 (57.2)	31 (57.4)	0.816
Hypertension	48 (46.6)	32 (59.2)	<0.001
Diabetes mellitus	46 (44.6)	25 (46.2)	0.196
Current smoking	39 (37.8)	23 (42.6)	0.067
LVEF (%)	28.91±8.42	30.63±7.86	0.089
Heart rate (bpm)	94.4±14.2	103.6±10.1	0.082
SBP (mmHg)	145.5±24.6	152.5±34.6	0.052
DBP (mmHg)	93.8±16.2	98.4±20.1	0.091
Respiratory rate (rpm)	29.3±4.3	30.1±5.1	0.610
SaO_2 (%)	92.2±6.4	89.4±7.2	0.341
Duration of HF (years)	1.43±0.2	1.52±0.3	0.078
BMI (kg/m^2)	25.42±1.40	27.12±2.82	0.217
Hemoglobin (g/dl)	12.61±2.42	13.04±1.082	0.144
Lymphocytes (10^3/µl)	2.31±0.7	2.59±1.12	0.358
Neutrophils (10^3/µl)	3.70±0.80	4.30±1.40	0.457
Platelet (10^3/mm^3)	288.72±83.01	262.92±73.00	0.348
Basal creatinine (mg/dl), median (IQR)	1.4 (0.9-2.4)	1.5 (1.1-2.6)	0.053
eGFR (mL/min/1.73m^2)	58.53±13.8	45.24±21.8	0.041
Total cholesterol (mg/dL)	183.54±33.4	197.27±47.8	0.314
Urea (mg/dL)	21.14±6.05	20.22±7.53	0.345
Glucose (mg/dL)	162.9±73.7	172.2±74.2	0.218
Sodium (mmol/L)	136.80±3.92	135.90±4.13	0.278
Potassium (mmol/L)	4.34±0.65	4.22±0.54	0.314
Troponin I (ng/L), median (IQR)	170.2 (32.3-1094.8)	211.5 (42.5-1648.2)	0.013
BNP (pg/mL), median (IQR)	817.54 (486.42-1447.32)	892.76 (512.80-1528.47)	0.005
Albumin (mg/dL)	4.1±0.4	3.7±0.3	0.645
Ferritin (ng/mL)	105.46±38.3	86.78±57.2	0.008
Transferrin saturation (%)	25.53±8.9	22.44±11.7	0.064
Length of stay in hospital	6.5±2.3	6.6±1.9	0.372
BNP/ferritin ratio	7.89±1.89	10.48±2.14	0.002
Medication			
β-Blocker	101 (98.0)	52 (96.2)	0.258
ACE-I or ARB	85 (82.5)	46 (85.1)	0.165
ASA	94 (91.2)	47 (87.0)	0.345
Statin	61 (59.2)	33 (61.1)	0.489
Digoxin	20 (19.4)	11 (20.3)	0.647
Ivabradine	14 (13.6)	8 (14.8)	0.687
ICD implantation	24 (23.3)	10 (18.5)	0.098
CRT implantation	18 (17.4)	8 (14.8)	0.061

LVEF=Left ventricular ejection fraction, bpm=Beats per minute, SBP=Systolic blood pressure, DBP=Diastolic blood pressure, rpm=Respiration per minute, SaO_2=Oxygen saturation, HF=Heart failure, BMI=Body mass index, eGFR=Estimated glomerular filtration rate, BNP=Brain natriuretic peptide, ACE=Angiotensin-converting enzyme, ARB=Angiotensin receptor blocker, ASA=Acetylsalicylic acid, ICD=Implantable cardioverter defibrillator, CRT=Cardiac resynchronization therapy

Table 2: Univariate and multivariate logistic regression analyses for the risk of developing acute renal injury

Risk factors	Univariate logistic regression			Multivariate logistic regression		
	OR	95% CI	*P*	OR	95% CI	*P*
Age (years)	1.06	1.03-1.11	<0.001	1.02	1.01-1.09	0.001
Hypertension	2.46	1.64-3.98	0.001	1.58	1.16-2.66	0.003
eGFR	0.72	0.64-0.91	0.034	0.93	0.76-1.19	0.219
Troponin I (ng/L)	1.18	1.07-2.03	0.025	1.06	0.93-1.96	0.078
BNP/ferritin ratio	6.42	2.32-18.41	<0.001	3.19	1.92-6.54	0.001

eGFR=Estimated glomerular filtration rate, BNP=Brain natriuretic peptide, CI=Confidence interval, OR=Odds ratio

neutrophil gelatinase-associated lipocalin, and kidney injury molecule 1 were reported to be prognostic indicators of early-stage renal damage in ADHF.[15-17] An absolute increase in creatinine in approximately

20% of individuals hospitalized with ADHF also suggests that renal failure is a common morbidity in this patient population.[18,19]

In the ADHERE registry, a linear relationship was found between BNP concentrations and the in-hospital mortality of ADHF patients.[20] The efficacy of predicting outcomes in patients with chronic renal failure has been evaluated in several studies, and a positive correlation has been found between high-serum BNP levels and mortality and renal disease progression in most cases.[21] Similarly, in our study, the relationship of BNP with cardiac and renal dysfunction was observed to be an indicator of the risk of renal dysfunction in ADHF.

The anemia and iron deficiency have been shown to be independent predictors for poor prognosis in heart failure, decrease the quality of life, and increase the risk of mortality and hospitalization.[3] Iron deficiency etiopathogenesis is considered to be complex and multifactorial, with the most discussed causes being inflammatory activation, malnutrition, intestinal edema, renal dysfunction, hemodilution, diabetes, impaired bone marrow function, use of RAAS inhibitors, and occult gastrointestinal bleeding.[22] In our study, similar to BNP, a low ferritin level was found to be an indicator of renal dysfunction in ADHF, which supports previous studies reporting the close relationship between ferritin and cardiac and renal functions.

Limitations

The main limitation of the study is that it is retrospective and single center. Our information about recurrent problems is limited because some patients do not come to follow-up.

Conclusions

We determined that elevated BNP and reduced ferritin could be evaluated in combination as the BNP/ferritin ratio to predict the risk of ARI in patients with ADHF in a stronger manner than either parameter alone.

Author contributions statement

Küçüksu Z. and Öztürk M. performed the measurements, Ceyhun G. and Aydın Ş.S. were involved in planning and supervised the work, Ceyhun G. processed the experimental data, performed the analysis, drafted the manuscript and designed the figures. Özkoç M., Altınkaya O., Ateş A., aided in interpreting the results and worked on the manuscript. All authors provided critical feedback and helped shape the research, analysis and manuscript.

Conflicts of interest

None Declared.

Ethical approval

Institutional review board approval was obtained from the Atatürk University Board of Ethics on Clinical Studies Ethics Committee (Date: June 26, 2020, Number: 07/25).

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