JEIMP
The Journal of European Internal Medicine Professionals

Original Article

Relation Between nt-ProBNP and Serum Sodium Based on Glomerular Filtration Rate

Author(s)
[1]Muhammed Emir İnce, [2]Semahat Karahisar Şirali, [2]Mehmet Fatih Bulucu, [1]Ahmet Çorakcı

J Eur Int Prof. Year; 2025, Volume: 3, Issue: 1
Submitted at: 16.11.2024 Accepted at: 31.12.2024 Published at: 31.01.2025
doi 10.5281/zenodo.14692905

Affiliation(s)
[1]Ufuk University Medical School, Department of Internal Medicine, Ankara, Turkiye
[2]Ufuk University Medical School, Department of Nephrology, Ankara, Turkiye

Corresponding Author: Semahat Karahisar Şirali, M.D., Ufuk University Medical School, Department of Nephrology, Ankara, Turkiye.
E-mail: drsemahat@hotmail.com

Abstract

Background: Electrolyte imbalance and volume overload are common in chronic kidney disease and heart failure. We aimed to evaluate the relationship between serum sodium and N terminal pro-brain natriuretic peptide (NT-proBnp) based on estimated glomerular filtration rates in heart failure (HF) patients with low ejection fraction.

Methods: A total of 389 patients aged 18-80 years who presented to our hospital with symptoms of heart failure were included in the study. Demographic, laboratory, and echocardiography findings were recorded. The study group consisted of patients with ejection fraction (EF) less than 55% and estimated glomerular filtration rate (eGFR) less than 90mL/min, and subgroups were formed according to eGFR, ejection fraction and NT-proBnp level.

Results: Of the total group, 54.5% were female, and the median age was 64 (IQR18) years. Age, NT-ProBnp, creatinine, BUN, and CRP were significantly ($p<.05$) higher in the study group compared to the control group. When subgroups were compared according to eGFR, age, creatinine, NT-proBnp, BUN, and CRP were significantly ($p<.05$) higher in the group with eGFR<45mL/min compared to the group with eGFR=45-89mL/min. In the group with NT-proBNP above 6000, it was seen that eGFR, EF, sodium, albumin, and hematocrit were effective at a rate of 38.4% in the multivariate logistic regression model.

Conclusion: In HF and low eGFR, NT-proBnp increases with volume increase. In light of the data that NT-proBnp, which is known to be released from stress-induced cardiomyocytes, is excreted and metabolized via the renal route, renal function should be taken into consideration in the interpretation of NT-proBnp elevated levels.

Keywords: Heart Failure, Chronic Kidney Disease, Natriuretic Agents, Sodium

INTRODUCTION

The Heart failure is defined as the inability of the heart to deliver enough oxygen to tissues to meet its metabolic needs and structural or functional impairment of the heart. It is a life-threatening chronic health problem and is among the most common causes of hospitalization in the elderly. Early diagnosis not only slows the course of the disease but also reduces the number of hospitalizations, deaths, and costs. In patients with complaints of heart failure, natriuretic peptides play a key role in the diagnosis and have a high negative predictive value and exclude the diagnosis (1). Studies have revealed a significant increase in natriuretic peptide levels in chronic kidney disease and heart failure with low ejection fraction (2-5).

In both heart failure and chronic kidney disease (CKD), volume overload is an expected finding, especially in advanced stages (6). In addition to volume overload, salt restriction also predisposes to dilutional hyponatremia. In chronic kidney disease, impaired concentration and dilution ability of the kidney make patients even more prone to hyponatremia (7,8). In a study conducted in patients with hyponatremia, NT-proBnp levels were

used to assess volume status (9). Another study showed a negative correlation between serum sodium and NT-proBNP in venous congestion in heart failure patients (10). Sodium is the main cation of the extracellular fluid and a serum sodium level <135 meq/L is defined as hyponatremia. It is the most common electrolyte disturbance encountered in clinical practice and is estimated to be present in 10% to 30% of hospitalized patients. The presence of hyponatremia, regardless of etiology, is associated with increased morbidity and mortality in outpatients and hospitalized patients and is considered an important marker of serious illness (11).

Assessment of volume status is very difficult and of critical importance. Brain natriuretic peptide (BNP) is synthesized in the ventricles in response to myocyte stretch and/or pressure overload. Pro-BNP consists of 108 amino acids and proteolysis of pro-BNP results in active BNP with 32 amino acids and an inactive amino-terminal fragment with 76 amino acids (12). In the kidneys, BNP increases glomerular filtration rate and blood flow by increasing efferent arterial tone and decreasing afferent arterial tone. It also decreases renin release and sodium reabsorption, leading to diuresis and natriuresis. BNP is used in the diagnosis of congestive heart failure and to differentiate whether dyspnea is of cardiac or pulmonary origin (12). Clearance from plasma has been associated with renal excretion (13).

Chronic kidney disease is defined as the presence of kidney damage, glomerular filtration rate of less than 60 milliliters per minute, and this condition lasting longer than three months, regardless of the cause (14). It is one of the world's most common chronic non-communicable diseases. The World Health Organization predicts that by 2040, chronic kidney disease will be the fifth most common chronic disease (15).

Electrolyte changes may occur in chronic kidney disease and heart failure (16,17). The frequency of hypervolemic hyponatremia increases in heart failure (18). This study aimed to evaluate the relationship between sodium and NT-proBnp at different estimated glomerular filtration rates in heart failure patients with low ejection fraction. We investigated how different glomerular filtration rate levels affect NT-proBnp and serum sodium levels, which provide insight into volume overload. Since the effect of increased natriuretic peptides on mortality has been shown in previous studies, the relationship between NT-proBnp levels and other findings and parameters (volume status, sodium, potassium, eGFR, hematocrit, CRP, albumin, BUN, creatinine and EF%) without natriuretic peptide levels (19).

METHODS

Between January 1, 2018, and November 30, 2023, 389 patients admitted to our hospital with known heart failure or with a medical condition suspicious of heart failure were included in the study. Exclusion criteria were being under 18 years of age and over 80 years of age, having myxoma and mural thrombus in the heart on echocardiography, septic shock, pregnancy, acute coronary syndrome, known malignancy, acute kidney injury (anuria, increase in basal creatinine by more than 30% in the last 24 hours), peritoneal dialysis and being on hemodialysis program. A total of 176 patients fulfilling these criteria were excluded from the study. Two hundred thirteen patients were divided into study and control groups. The study group consisted of patients with EF less than 55% and eGFR less than 90 ml/min/1.73 m2, while the control group consisted of patients with EF greater than 55% and eGFR greater than 90 ml/min/1.73 m2. The study group was divided into subgroups according to progression risk assessment as Stage 3b below (<44 ml/min/1.73m2) and Stage 3a above (45-89 ml/min/1.73m2) eGFR, low (40%) and preserved (41-54%) EF and NT-ProBnp >6000 pg/mL and above with increased mortality risk. Demographic data including age and gender, laboratory data including NT-proBNP, eGFR, sodium, potassium, albumin, creatinine, blood urea nitrogen (BUN), C reactive protein (CRP), hematocrit and ejection fraction (EF%) measured by echocardiography were recorded from the database.

The study group was subdivided into EF≤40% and EF 41-54%, eGFR <45 ml/min/1.73m2 and eGFR 45-89 ml/min/1.73m2, NT-ProBnp <6000pg/mL, NT-ProBnp ≥6000pg/dL.

Laboratory tests, including BUN, creatinine, albumin, CRP, sodium, potassium, and hematocrit levels, were measured with a clinical biochemistry auto analyzer Abbott Architect c8000 (Abbott Diagnostics, Illinois, USA). Echocardiography was performed with a Vivid S70N Version 202 device.

STATISTICAL ANALYSIS

Statistical analyses were performed using SPSS version 29.0 (SPSS Inc., Chicago, IL, USA, 2023). Categorical variables were summarized as frequencies (n) and percentages (%). The normality of continuous variables was assessed using the Kolmogorov-Smirnov test. Continuous variables were described using arithmetic mean, standard deviation, median, minimum, and maximum values.

For quantitative independent data, the Kruskal-Wallis and Mann-Whitney U tests were employed, while qualitative independent data were analyzed using the chi-square test. Relationships between variables were examined using Pearson's and Spearman's correlation coefficients, depending on data distribution. The effect sizes of variables that did not follow a normal distribution

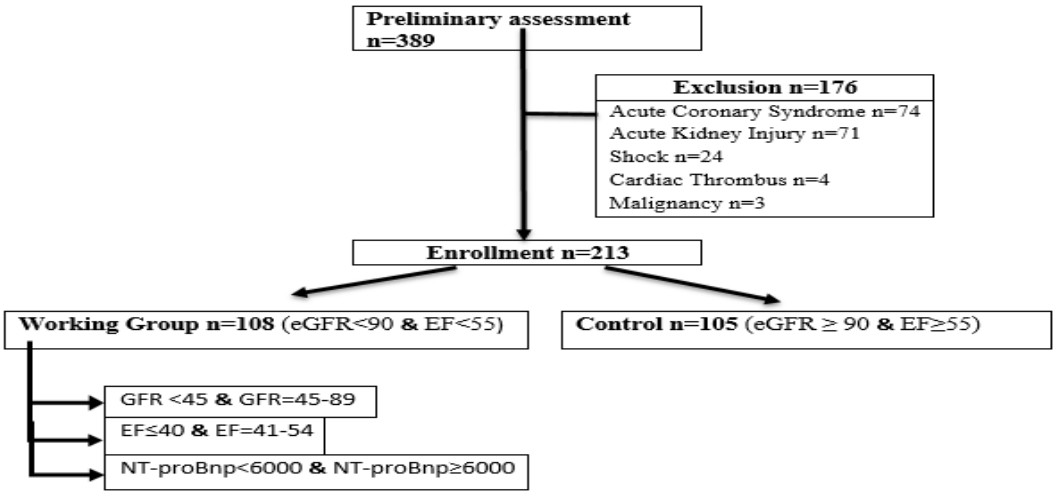

Figure 1. Flow diagram demonstrates the study design

were evaluated using univariate and multivariate logistic regression models. A significance level of p < .05 was considered statistically significant.

RESULTS

A total of 389 patients, both male and female, aged 18-80 years, who presented to our hospital with symptoms of heart failure were included in the study. After excluding 176 patients who did not meet the inclusion criteria, 213 patients were included in the study. Two main groups were formed: study and control groups. The study group was divided into subgroups according to eGFR EF and NT-ProBnp (**Figure 1**).

Of the total group, 54.5% were female, and the median age was 64 (IQR18) years. There was no significant difference between the study and control groups in gender, sodium, and potassium (p>.05). Age, NT-ProBnp, creatinine, BUN, and CRP were significantly higher in the study group compared to the control group (p<.05). Hematocrit, albumin, EF and eGFR were significantly higher in the control group than in the study group (p<.05) (**Table 1**).

When subgroups were compared according to eGFR, no significant difference was found between gender, EF, sodium, and potassium (p>.05). Age, NT-ProBnp, creatinine, BUN, CRP were significantly (p<.05) higher in the group with eGFR<45mL/min compared to the group with eGFR 45-89ml/min. Serum albumin and hematocrit were significantly (p<.05) higher in the group with eGFR 45-89mL/min (**Table 2**).

When subgroups were compared according to EF, no significant difference was found in gender, NT-ProBnp, sodium, potassium, albumin, creatinine, BUN, CRP, and hematocrit (p>.05). Age was significantly(p<.05) higher in the subgroup with EF between 40-54% (**Table 3**).

When the subgroups were compared according to NT-ProBnp, eGFR, sodium, albumin, and hematocrit were

Table 1. Demographic characteristic of the group and laboratory results

Parameter		Total group n=213	Working group n=108	Control group n=105	x^2,t,z	p
Gender	**F:** **M:**	117 (%54.5) 96 (%45.5)	64 (%59) 44 (%41)	53 (%51) 52 (%49)	-1.43	.155
Age (year)		64 (18)	71 (11)	55 (20)	-8,8	<.001
EF %		54 (35)	31(20)	65 (2)	-12.70	<.001
eGFR(ml/min/1.73m²)		88 (46)	53.5 (36)	98 (11)	-12.42	<.001
NT-ProBnp(pg/mL)		984 (5613)	5577 (9017)	100 (133)	-12.59	<.001
Sodium(mmol/L)		139(4)	139 (5)	139 (3)	-1.37	.169
Potassium(mmol/L)		4.2 (0.6)	4,1 (0,8)	4.2 (0.5)	-1.80	.071
Albumin(g/L)		37 (8)	34 (7.4)	39 (4.7)	-6.62	<.001
Creatinine(mg/dL)		0.91 (0.48)	1.17 (0.61)	0.7 (0.16)	-11.07	<.001
BUN (mg/dL)		17 (13)	26 (16)	13 (5)	-10.48	<.001
CRP (mg/L)		5 (19.4)	7.2 (25.4)	3.1 (13.5)	-3.30	<.001
Hematocrit(%)*		41.24 ± 6.32	39.09 ± 6.18	43.44 ± 5.69	-5.33	<.001

EF; ejection fraction, eGFR; estimated glomerular filtration rate, NT-ProBNP; N-terminal pro-brain natriuretic peptide, BUN; blood urea nitrogen, CRP; C-reactive protein. P<.001 was considered significant. x2: Fisher's exact test. *Data are presented as median(IQR) excluding Htc.

Table 2. Comparison of subgroups according to estimated glomerular filtration

Parameter		eGFR<45 n=38	eGFR=45-89 n=70	x^2, t, z	p
Gender	**F:** **M:**	23 (%61) 15 (%39)	41 (%59) 29 (%41)	-.039	.505
Age (year)		73 (9)	69 (13)	-2.19	.028
EF %		35 (22)	30(15)	-1.43	.152
NT-ProBnp		9005 (15873)	4077 (5169)	-3.64	<.001
Sodium		138 (4)	139 (4)	-1.79	.073
Potassium		4.20 (0.9)	4.05 (0.7)	-1.10	.270
Albumin		32.4 (6.3)	35.3 (7.8)	-2.02	.043
Creatinine		1.85 (1.09)	1.01 (0.27)	-7.68	<.001
BUN		39.5 (30)	21.0 (9)	-6.73	<.001
CRP		15.8 (32.2)	6.6(15)	-2.10	.035
Hematocrit		36.3 ± 5.4	40.5 ± 6.0	3.56	<.001

x2: Fisher's exact test. *Data are presented as median(IQR) excluding Htc.

significantly (p<.05) higher in the subgroup with NT-ProBnp<6000 pg/ml compared to the subgroup with NT-ProBnp≥6000 pg/ml. At the same time, no significant difference was found in gender, age, potassium, EF, and CRP (p>.05). BUN and creatinine were significantly (p<.05) higher in the group with ProBnp ≥6000 compared to the NT-ProBnp<6000 pg/ml subgroup (**Table 4**).

In the study group, there was a low negative correlation between age and eGFR and hematocrit and a moderate positive correlation between Age and EF. There was a low negative correlation between EF and NT-ProBnp. There was a low positive correlation between eGFR and sodium and albumin, a low negative correlation between potassium and CRP, a low negative correlation between NT-ProBnp, and a moderate positive correlation between eGFR and hematocrit. NT-ProBnp had a low positive correlation with CRP, a low positive correlation with creatinine, and a low negative correlation with sodium, albumin, and hematocrit.There was a low negative correlation between sodium and creatinine and a moderate positive correlation between creatinine and hematocrit. There was a low negative correlation between creatinine and hematocrit and a low positive correlation between creatinine and CRP.

In accordance with the study that found that 90-day survival after hospital discharge was higher in patients with NT-ProBnp below 6000 pg/mL, we created two subgroups by taking 6000 pq/mL as a threshold value in our study.15 In the group with NT-proBNP above 6000pg/mL, eGFR was 22.4% (95% CI [.936-.977], p<.001), EF 4.5% (%95 CI [.932-1.001], p=.05), sodium 7.7% (%95 CI[.800-.983], p=.022), hematocrit 7.5% (%95 CI [.859-.986], p=.018), and albumin 5.8% (%95 CI [.856-.994], p=.033) effective in the univariate model in logistic regression (Table 5). In the univariate model, eGFR, sodium, albumin, and hematocrit were significantly effective in differentiating the groups with NT-proBnp<6000 and ≥6000. EF was found to be borderline statistically effective but not significant.

In the multivariate model, significant (p<.05) efficacy of eGFR and EF was observed in separating groups with NT-proBnp<6000pg/mL and ≥6000pg/mL. Sodium efficacy was borderline but not statistically significant. In the multivariate logistic regression model on NT-proBNP ≥6000, eGFR, EF, sodium, albumin, and

Table 3. Comparison of groups according to ejection fraction.

Parameter		EF<40 n=70	EF=40-54 n=38	x^2,t,z	p
Gender	**F :** **M:**	44 (%63) 26 (%37)	20 (%53) 18 (%47)	1.06	.204
Age (year)		69.5 (12)	72.5 (9)	-2.11	.034
eGFR		63 (35)	46.5 (24)	-2.36	.018
NT-ProBnp		6264 (11112)	4831 (6101)	-1.66	.078
Sodium		139 (4)	138 (4)	-1.17	.242
Potassium		4 (0.7)	4.3 (0.7)	-1.87	.061
Albumin		34 (7)	34.7 (7.9)	-0.28	.775
Creatinine		1.13 (0.57)	1.28 (0.74)	-1.39	.162
BUN		24.5 (15)	26 (24)	-0.79	.425
CRP		7.1 (25.5)	8.3 (27.5)	-0.25	.737
Hematocrit		39.8 ± 5.8	37.6 ± 6.5	-1.81	.290

Table 4. Comparison of subgroups according to NT-proBNP

Parameter	NT-ProBnp<6000 n=59	NT-ProBnp≥6000 n=49	x^2,t,z	p
Gender F : M:	37 (%63) 22 (%37)	27 (%55) 22 (%45)	1.06	.204
Age (year)	70 (11)	72 (10.4)	-0.76	.443
eGFR	62.63 ± 18.9	44.8 ± 20.3	4.70	<.001
EF %	35 (20)	30 (15)	-1.93	.053
Sodium	139 (3)	137 (5)	-3.03	.002
Potassium	4.2 (0.8)	4.0 (0.8)	-0.69	.490
Albumin	35.8 (7.9)	32.3 ± 5.5	-2.15	.031
Creatinine	1.04 (0.43)	1.44 (0.85)	-4.15	<.001
BUN	21 (11)	30 (22)	-4.74	<.001
CRP	5.9 (15)	13 (32,3)	-1.46	.144
Hematocrit	40.4 ± 6.4	37.5 ± 5.5	2.50	<.001

hematocrit had an effect of 38.4% (Table 5)

DISCUSSION

Heart failure is a life-threatening chronic health problem and a common cause of hospitalization in the elderly. Early diagnosis not only slows the course of the disease but also reduces the number of hospitalizations, mortality, and costs. Serum natriuretic peptide levels, which have a very high negative predictive value in heart failure, play a key role in the diagnosis. Knowing the NT-proBnp level has an important role in terms of survival and appropriate medical treatment (1).

In heart failure and chronic kidney disease, in addition to volume overload, potent diuretic use and salt restriction also lead to dilutional hyponatremia (6-8)

In this study, which aimed to evaluate the importance of natriuretic peptide levels in the diagnosis and follow-up of chronic kidney disease and heart failure with low ejection fraction, serum sodium was significantly lower in the group with NT-proBnp above 6000 pg/ml compared to the group with NT-proBnp below 6000 pg/ml (2,3).

Hall et al. pointed out that data suggest that NT-proBnp is renally excreted or metabolized (13). Although serum NT-proBnp is known to be affected by glomerular filtration rate, in their study of urinary NT-proBnp excretion in patients with heart failure, Linssen et al. found that it was associated with renal blood flow but not with estimated glomerular filtration rate [20]. Although NT-proBnp was not investigated in urine in our study, the association of NT-proBnp with renal function was shown in our study.

Belagavi et al. investigated the relationship between NT-ProBnp and EF in patients admitted to the emergency department with dyspnea and showed a negative correlation between these two parameters (2). In our study group, a significant negative correlation was found between these parameters. However, no statistically significant correlation was found between these two parameters in our subgroups with low and

Table 5. Univariate and multivariate regresyon analysis of factors have impact on T-proBnp ≥6000 pg/mL

Univariate model in the group with NT-proBnp ≥6000 pg/mL					
Independent	R^2	B	OR	CI	p
eGFR	.224	-.044	.957	.936 – .977	<.001
EF	.045	-.034	.966	.932 – 1.001	.059
Sodium	.077	-.120	.887	.800 – .983	.022
Potassium	.001	-.090	.914	.456 –1.833	.800
Albumin	.058	-.081	.922	.856 – .994	.033
CRP	.001	.002	1.002	.991 – 1.013	.729
Hematocrit	.075	-.083	.920	.859 – .986	.018
Multivarite model in the group with NT-proBnp≥6000 pg/mL					
Independent	R^2	B	OR	CI	p
eGFR	.384	-.053	.948	.886 – .974	<.001
EF		-.074	.929	.923 – .974	.002
Sodium		-.114	.892	.795 – 1.001	.052
Albumin		-.036	.946	.886 – 1.051	.414
Hematocrit		-.025	.990	.898 – 1.060	.560

mildly reduced EF. This may be due to the small number of patients with mildly reduced EF and the older age group. Anemia from chronic kidney disease and reduced blood circulation in heart failure can cause hypoperfusion and hypoxia in tissue (1,21). These reasons suggest that in addition to the association of NT-proBNP with EF, other factors, such as hypoxia, may also contribute to the release of NT-proBNP from cardiomyocytes.

In the elderly population, Nerpin et al. demonstrated the early onset of left ventricular dysfunction before the development of symptomatic heart failure and CKD. Low eGFR was found to have an independent effect on left ventricular function decline (22). When our study subgroups were compared according to eGFR, no significant correlation was found with EF, whereas when our study subgroups were compared according to EF, it was observed that eGFR was higher in the subgroup with EF <40. This difference may be attributed to the small number of subgroups and the significant difference in age distribution. In addition, low eGFR and EF together increase mortality. This group was not used in the sample because the number of patients could not be reached, and those who started renal replacement therapy were not included in the inclusion criteria.

Arzhan et al. reported that CKD predisposes to dysnatremia, and the prevalence of hyponatremia and hypernatremia is higher than in the general population (23). Bianchi et al. also showed that hyperkalemia is the most common electrolyte disturbance in kidney disease and heart failure (24). We did not find a significant difference in serum sodium and potassium electrolytes between the control and study groups and between the eGFR subgroups. The reason may be that patients with chronic kidney disease are put on renal replacement therapy before electrolyte imbalance develops, the number of patients in the GFR<45% subgroup is less than in the GFR>45% group, and antihypertensive and diuretic treatments are adjusted by considering electrolyte levels in close follow-up of patients.

Portoles et al. reported that the prevalence of anemia in the predialysis phase of CKD was approximately 60% (21). As eGFR decreased, anemia became more common and severe. Analysis of cross-sectional data from the National Health and Nutrition Examination Survey (NHANES) also found that anemia was twice as common in CKD patients compared to the general population.48 In the study by Guglin et al., anemia was found in half of the patients with advanced systolic heart failure. In the same study, it was shown that the decrease in hematocrit in heart failure was due to overload and hemodilution (25). In our study group with heart failure, the decrease in hematocrit with decreasing eGFR was significant compared to the control group, and it was also significant in the subgroup with eGFR <45 ml/min/1.73 m2 compared to the eGFR 45-89 ml/min/1.73 m2 group. This result was similar to the results of other studies. Early diagnosis and treatment of anemia has positive effects on the prognosis of heart failure. Willis et al. investigated the effects of anemia on NT-proBnp in patients without heart failure or renal disease. NT-proBnp levels were significantly higher in those with anemia (26). In this study, NT-proBnp and hematocrit parameters were significantly negatively correlated between the control and study groups. In the subgroup comparison according to NT-proBnp, hematocrit was significantly lower in the NT-proBnp ≥6000 pg/ml subgroup. It was stated in the ESC 2021 Guideline that NT-proBnp may be affected not only by cardiac events but also by non-cardiac causes such as anemia (1). Our study also suggests that anemia, affects natriuretic peptides.

Limitations

Limitations of the study include the fact that it was a retrospective and cross-sectional study, the number of cases was limited in subgroups, the use of drugs effective on sodium in the patients, and the inability to access information on other factors affecting sodium. In order to evaluate the relationship between sodium and NT-proBnp in these patients, multicenter, prospective and large case numbers are needed.

CONCLUSION

In heart failure and low eGFR, NT-proBnp increases with increasing volume. In addition to the known negative correlation between NT-proBnp and sodium in chronic cardiorenal syndrome, we think that sodium level has a direct effect on NT-proBnp level. Strain-induced NT-proBnp is known to be released from cardiomyocytes. In light of the data indicating that excretion and metabolization are via the renal route, renal function should be taken into consideration in the interpretation of high NT-proBnp levels.

DECLERATIONS

Ethical Issues: The study was approved by the Ufuk University Non-Interventional Clinical Research Evaluation Ethics Committee with decision date: 14.12.2023 and IRB no: 12024861-77. This study was conducted in accordance with the principles of the Declaration of Helsinki, ensuring ethical standards for medical research involving human participants. As this research involved a retrospective review of existing data, it posed minimal risk to participants, and no additional interventions were performed. There were no ethical issues encountered during the conduct of this study.

Funding and Conflict of Interest: The authors declare that this research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors. There are no conflicts of interest to disclose related to this study.

Author Contributions: The design of the research,

data acquisition and analysis was done by M Emin Ince and Semahat Karahisar Sirali, the control and revision of the comments and the article were made by M Fatih Bulucu, and the version to be published was approved by M Fatih Bulucu and Ahmet Corakcı.

AI: No artificial intelligence was used at any stage of the article.

REFERENCES

1. McDonagh TA, Metra M, Adamo M, et al. Corrigendum to: 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: Developed by the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) With the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur Heart J.* 2021;42(48):4901. doi:10.1093/eurheartj/ehab670
2. Belagavi AC, Rao M, Pillai AY, Srihari US. Correlation between NT proBNP and left ventricular ejection fraction in elderly patients presenting to emergency department with dyspnoea. *Indian Heart J.* 2012;64(3):302-304. doi:10.1016/S0019-4832(12)60091-1
3. DeFilippi C, van Kimmenade RR, Pinto YM. Amino-terminal pro-B-type natriuretic peptide testing in renal disease. *Am J Cardiol.* 2008;101(3A):82-88. doi:10.1016/j.amjcard.2007.11.029
4. Tsai YC, Tsai HJ, Lee CS, et al. The interaction between N-terminal pro-brain natriuretic peptide and fluid status in adverse clinical outcomes of late stages of chronic kidney disease. **PLoS One.** 2018;13(8):e0202733. Published 2018 Aug 22. doi:10.1371/journal.pone.0202733
5. Arjamaa O. Physiology of natriuretic peptides: The volume overload hypothesis revisited. *World J Cardiol.* 2014;6(1):4-7. doi:10.4330/wjc.v6.i1.4
6. Novak JE, Ellison DH. Diuretics in States of Volume Overload: Core Curriculum 2022. *Am J Kidney Dis.* 2022;80(2):264-276. doi:10.1053/j.ajkd.2021.09.029
7. Adrogué HJ. *Hyponatremia in Heart Failure.* Methodist Debakey Cardiovasc J. 2017;13(1):40. doi:10.14797/mdcj-13-1-40
8. Lim LM, Tsai NC, Lin MY, et al. Hyponatremia is Associated with Fluid Imbalance and Adverse Renal Outcome in Chronic Kidney Disease Patients Treated with Diuretics. *Sci Rep.* 2016;6:36817. Published 2016 Nov 14. doi:10.1038/srep36817
9. Bunnag S, Pattanasombatsakul K. N-terminal-pro-brain natriuretic peptide for the differential diagnosis of hypovolemia vs. euvolemia in hyponatremic patients. *J Med Assoc Thai.* 2012;95 Suppl 3:S69-S74.
10. Caraba A, Iurciuc S, Munteanu A, Iurciuc M. Hyponatremia and Renal Venous Congestion in Heart Failure Patients. *Dis Markers.* 2021;2021:6499346. Published 2021 Aug 12. doi:10.1155/2021/6499346
11. Khan S, Floris M, Pani A, Rosner MH. Sodium and Volume Disorders in Advanced Chronic Kidney Disease. *Adv Chronic Kidney Dis.* 2016;23(4):240-246. doi:10.1053/j.ackd.2015.12.003
12. Maries L, Manitiu I. Diagnostic and prognostic values of B-type natriuretic peptides (BNP) and N-terminal fragment brain natriuretic peptides (NT-pro-BNP). *Cardiovasc J Afr.* 2013;24(7):286-289. doi:10.5830/CVJA-2013-055
13. Hall C. NT-ProBNP: the mechanism behind the marker. *J Card Fail.* 2005;11(5 Suppl):S81-S83. doi:10.1016/j.cardfail.2005.04.019
14. Levey AS, de Jong PE, Coresh J, et al. The definition, classification, and prognosis of chronic kidney disease: a KDIGO Controversies Conference report [published correction appears in Kidney Int. 2011 Nov;80(9):1000] [published correction appears in Kidney Int. 2011 Nov 1;80(9):1000. doi: 10.1038/ki.2011.310]. *Kidney Int.* 2011;80(1):17-28. doi:10.1038/ki.2010.483
15. Borg R, Carlson N, Søndergaard J, Persson F. The Growing Challenge of Chronic Kidney Disease: An Overview of Current Knowledge. *Int J Nephrol.* 2023;2023:9609266. Published 2023 Mar 1. doi:10.1155/2023/9609266
16. Dhondup T, Qian Q. Acid-Base and Electrolyte Disorders in Patients with and without Chronic Kidney Disease: An Update. *Kidney Dis (Basel).* 2017;3(4):136-148. doi:10.1159/000479968
17. Urso C, Brucculeri S, Caimi G. Acid-base and electrolyte abnormalities in heart failure: pathophysiology and implications. *Heart Fail Rev.* 2015;20(4):493-503. doi:10.1007/s10741-015-9482-y
18. Rodriguez M, Hernandez M, Cheungpasitporn W, et al. Hyponatremia in Heart Failure: Pathogenesis and Management. *Curr Cardiol Rev.* 2019;15(4):252-261. doi:10.2174/1573403X15666190306111812
19. Pereira-Barretto AC, de Oliveira MT Jr, Strunz CC, Del Carlo CH, Scipioni AR, Ramires JA. O nível sérico de NT-proBNP é um preditor prognóstico em pacientes com insuficiência cardíaca avançada [Serum NT-proBNP levels are a prognostic predictor in patients with advanced heart failure]. *Arq Bras Cardiol.* 2006;87(2):174-177. doi:10.1590/s0066-782x2006001500016
20. Linssen GC, Damman K, Hillege HL, Navis G, van Veldhuisen DJ, Voors AA. Urinary N-terminal prohormone brain natriuretic peptide excretion in patients with chronic heart failure. *Circulation.* 2009;120(1):35-41. doi:10.1161/CIRCULATIONAHA.108.824581
21. Portolés J, Martín L, Broseta JJ, Cases A. Anemia in Chronic Kidney Disease: From Pathophysiology and Current Treatments, to Future Agents. *Front Med (Lausanne).* 2021;8:642296. Published 2021 Mar 26. doi:10.3389/fmed.2021.642296
22. Nerpin E, Ingelsson E, Risérus U, et al. The association between glomerular filtration rate and left ventricular function in two independent community-based cohorts of elderly. *Nephrol Dial Transplant.* 2014;29(11):2069-2074. doi:10.1093/ndt/gfu199
23. Arzhan S, Lew SQ, Ing TS, Tzamaloukas AH, Unruh ML. Dysnatremias in Chronic Kidney Disease: Pathophysiology, Manifestations, and Treatment. *Front Med (Lausanne).* 2021;8:769287. Published 2021 Dec 6. doi:10.3389/fmed.2021.769287
24. Bianchi S, Aucella F, De Nicola L, Genovesi S, Paoletti E, Regolisti G. Management of hyperkalemia in patients with kidney disease: a position paper endorsed by the Italian Society of Nephrology. *J Nephrol.* 2019;32(4):499-516. doi:10.1007/s40620-019-00617-y
25. Guglin M, Darbinyan N. Relationship of hemoglobin and hematocrit to systolic function in advanced heart failure. *Cardiology.* 2012;122(3):187-194. doi:10.1159/000339536
26. Willis MS, Lee ES, Grenache DG. Effect of anemia on plasma concentrations of NT-proBNP. *Clin Chim Acta.* 2005;358(1-2):175-181. doi:10.1016/j.cccn.2005.03.009