Relationship between intrarenal renin-angiotensin activity and re-hospitalization in patients with heart failure with reduced ejection fraction

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Abstract

Objective: Heart failure (HF) is a clinical syndrome resulting from structural or functional damages. Although clinical trials have shown that the plasma renin–angiotensin system (RAS) activation decreases HF functional status and increases hospitalization for HF patients, the effect of intrarenal RAS activity is still unknown. In this study, we investigated the relationship between the New York Heart Association (NYHA) class, duration, and number of hospitalizations in the previous year and urinary angiotensinogen (UAGT) in patients with HF with reduced ejection fraction (HFrEF).

Methods: This study included 85 patients who had an ejection fraction of <40% and were receiving optimal medical treatment. Among these, 22 were excluded from the study for various reasons. Demographically and biochemically, the remaining 63 patients were compared according to the NYHA functional classes and re-hospitalization status.

Results: When the groups were compared in terms of N-terminal pro–B-type natriuretic peptide (NT-proBNP), UAGT, and high-sensitivity C-reactive protein (Hs-CRP), it was found that these parameters were significantly higher in patients who were hospitalized more than two times in the previous year [p<0.001; p=0.007; p<0.001, respectively]. There was a significant correlation between number of hospitalizations and NT-proBNP (r=0.507, p<0.001), Hs-CRP (r=0.511, p<0.001), hemoglobin (r=–0.419, p=0.001), serum sodium (r=–0.26, p=0.04), and systolic blood pressure (r=–0.283, p=0.02). When the independence of multiple correlations was assessed using multiple linear regression analysis, NT-proBNP, Hs-CRP, and hemoglobin levels were independent predictors of re-hospitalization, but this was not the same for UAGT.

Conclusion: Although UAGT levels are high in patients with poor NYHA functional class and repeated hospitalizations, this marker is not valuable for predicting repeated hospitalization in patients with HFrEF. *(Anatol J Cardiol 2018; 19: 205-12)*

Keywords: heart failure, plasma renin–angiotensin activity, intrarenal renin-angiotensin activity, urinary angiotensinogen

Introduction

Heart failure (HF) is a clinical syndrome accompanied by typical signs and symptoms that develop as a result of structural and/or functional defects (1). While the overall prevalence of HF is estimated to be 2%, it increases with age and affects more than 10% of individuals older than 65 years (2). Despite improvements in the survival of patients with HF achieved with current treatments, mortality and morbidity rates are still high. This results in a serious economic and health burden for the society (3, 4). In the natural course of HF, patients go through repeated re-hospitalizations, and acute decompensated HF (ADHF) is the leading cause of hospitalizations in the USA (5). Studies have shown that most re-hospitalizations related to HF occur in the early post-discharge period or in the period before death (6). As a result, new methods are increasingly being investigated to predict both short-and long-term re-hospitalization and death in patients with ADHF (7).

Although previous studies have shown that plasma renin–angiotensin system (RAS) activation increases the severity of HF and the number of hospitalizations due to HF (8, 9), the effect of intrarenal RAS activity is still unknown. Angiotensinogen (AGT), which is synthesized by the liver, released into the systemic circulation, and found in abundance in the plasma, is converted to angiotensin I by renin (10). Because of its high molecular weight, plasma AGT is unable to pass through the glomerular membrane. Thus, it is claimed that urinary AGT (UAGT) is synthesized by the kidneys and is an indicator of direct intrarenal RAS activation (11).

Therefore, different clinical responses to similar treatments and varying rates of re-hospitalization and mortality among pa-

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tients with HF may be because of the differences between in intrarenal RAS activation in patients. In the present study, we investigated the relationships between UAGT level and New York Heart Association (NYHA) class and number and duration of hospitalizations within the previous year in patients being followed up for HF with reduced ejection fraction (HFrEF).

Methods

This study included 85 patients who were admitted to the cardiology clinic between April and June 2017, had an ejection fraction (EF) of <40% on transthoracic echocardiography, and were receiving optimal medical treatment. Data regarding patients' demographic characteristics (age and gender), medical history [diabetes mellitus (DM), hypertension (HT), coronary artery disease, and coronary artery bypass graft surgery], medications used [beta-blockers, angiotensin-converting enzyme inhibitors (ACE-i), angiotensin receptor blockers (ARB), mineralocorticoid receptor antagonists (MRA), and ivabradine], device therapy (implantable cardioverter defibrillator and cardiac resynchronization therapy), and cardiac rhythm (sinus rhythm, atrial fibrillation, and pacemaker rhythm) were recorded. The NYHA functional class of each patient was determined. In order to avoid statistical errors that may arise from numerical differences, the patients were divided into two groups, NYHA I-II and NYHA III-IV, and an equal number of patients was recruited for each group. Re-hospitalization was defined as two or more occurrences of hospitalization due to HF in the previous year. The study was approved by the Local Clinical Research Ethics Committee.

Patients who were aged <18 years or >90 years; who had a history of acute coronary syndrome or primary coronary intervention within the past 6 months; and who had hypotension, pulmonary edema, or cardiogenic shock were excluded from the study. In addition, patients with stage 4-5 chronic kidney disease (CKD); those with an active focus of infection, neurological illness severe enough to affect biochemical and hematological results, chronic obstructive pulmonary disease (COPD), malignancy, or liver function impairment/liver failure; and those who did not consent to participate in the study were excluded from the study.

Six of the 85 patients included in the study later withdrew. After the evaluations, 13 patients were excluded from the study because they had non-cardiac diseases. Three of these patients had COPD, eight had stage 4-5 CKD, and two had malignancy. Three patients were excluded from the study because of incomplete data.

Echocardiographic imaging was performed for all participants using a GE Vivid E90 echocardiography device. Based on the guidelines of the American Society of Echocardiography, patients were evaluated in the left lateral decubitus position. Measurements were made using the two-dimensional, M-mode, and color Doppler methods with parasternal long-axis view, short-axis view, and apical four- and five-chamber views. At least three consecutive pulses were recorded by a blinded experienced operator, and the average was calculated. Left ventricular diameters, interventricular septum and posterior wall thicknesses, and ventricular EF were measured by placing an M-mode cursor just below the mitral valve leaflets in the parasternal long-axis view, as described in the guidelines of the American Society of Echocardiography (12).

Blood pressure was measured twice from the right arm with an interval of 2 min in the sitting position after at least 10 min of resting. The average of the two measurements was recorded as the blood pressure value. Body mass index (BMI) was calculated at the first examination using the following formula: height/weight^2.

Hemogram and biochemical analyses were performed using the Sysmex XN-1000 (Sysmex America, Inc. Lincolnshire, IL, USA) and Roche Cobas C501 (Roche Diagnostics GmbH, Penzberg, Germany) devices, and N-terminal pro–B-type natriuretic peptide (NT-proBNP) analyses were done using an Immulite 2000® immunoassay analyzer (Diagnostic Products Corporation, Los Angeles, CA, USA). Blood samples were obtained from the antecubital fossa veins in the sitting position after a 20-min rest following 12 h of fasting.

Urine samples for UAGT measurement were collected in sterile tubes and centrifuged at 3000 rpm for 20 min. The supernatants were carefully collected and stored at -70°C in a freezer for further analysis. UAGT measurement was done using the sandwich ELISA immunoassay method (YHB20.60901646, YH Biosearch Laboratory, Shanghai, China). The UAGT concentration was normalized to the urine creatinine value measured from the same urine sample (UAGT/UCR). All laboratory values are those obtained at the time of admission.

Statistical analyses were performed using 64-bit Windows version of SPSS (version 22.0, SPSS, Chicago, IL, USA). Continuous variables were tested for normal distribution using the Kolmogorov-Smirnov test. Variables with normal distribution were assessed using parametric tests. Continuous variables were expressed as mean±SD for parametric variables and median and minimum–maximum values for nonparametric variables. Comparisons of parametric variables between the two groups were performed using independent samples t-test. Comparisons of nonparametric values between the two groups were performed using the Mann–Whitney U test. Categorical variables were compared using the chi-square test. Correlation analysis was performed using the Spearman's correlation method. Multiple linear regression analysis was used to study the predictive factors for prehospitalization. Analysis results were evaluated within a 95% confidence interval, and $p<0.05$ was interpreted as a statistically significant difference.

Results

Among the patients included in the study, 30 had NYHA functional classes I-II symptoms and 33 had NYHA functional classes

Table 1. Basal Characteristics of Patients according to NYHA Classification

	NYHA classes I-II (n=30)	NYHA classes III-IV (n=33)	*P*
Age (year)	63.0±12.9	66.2±10.5	0.088
Gender (F/M)	22/8	26/7	0.613[a]
Duration of HF (months)	32 (10-200)	45 (10-240)	0.615
Number of days hospitalized in the previous year	0 (0-20)	16 (3-60)	**<0.001**
Number of hospitalization in the previous year	0 (0-3)	3 (1-10)	**<0.001**
BMI (kg/m^2)	25.8±3.1	27.7±3.3	**0.022**
Heart rhythm			
Sinus rhythm	28	20	
Atrial fibrillation	0	11	
Pacemaker rhythm	2	2	
Disease history			
Diabetes mellitus	9	15	0.235[a]
Hypertension	20	18	0.321[a]
Coronary artery disease	21	23	0.971[a]
Coronary artery bypass grafting	7	14	0.122[a]
Device history			
Implantable cardioverter defibrillator	11	15	0.632[a]
Cardiac resynchronization therapy	1	3	
Drug Information			
Beta-blocker	27	31	0.661[a]
Ace-i/ARB	29	27	0.056[a]
MRA	25	29	0.722[a]
Furosemide	17	30	**0.005[a]**
Ivabradine	8	10	0.960[a]

Ace-i - angiotensin-converting enzyme; ARB - angiotensin II receptor blocker; BMI - body mass index; F/M - female/male; HF - heart failure; MRA - mineralocorticoid receptor antagonist; NYHA - New York Heart Failure Association functional classification
Normally distributed values are presented as mean±standard deviation, non-normally distributed values are presented as median (range), and categorical values are presented as number of patients.
[a]*P*=chi-square value

III-IV symptoms. When the patients were grouped as NYHA functional class I-II and III-IV, there were no differences between the groups in terms of age, gender, or duration of HF (p>0.05). Compared with the other patients, patients with NYHA functional classes III-IV had significantly greater number of hospitalizations and total length of hospital stay (p<0.001). In addition, patients with NYHA functional classes III-IV had significantly higher BMI and higher use of furosemide compared with those with better functional classes (p=0.02, p=0.005, respectively). Data for both groups regarding demographics, medications used, medical history, device therapy received, and cardiac rhythm are given in Table 1.

Comparison of laboratory values of patients with NYHA classes I-II and classes III-IV revealed that the group with poorer functional capacity (NYHA classes III-IV) had significantly higher UAGT, NT-proBNP, and high-sensitivity C-reactive protein (Hs-CRP) levels [82.4 (12.5–338.3) and 226.3 (10.7–1233), p<0.001; 523 (67–5112) and 5270 (850–19971), p<0.001; 2.6 (0.33–25) and 15.5 (0.89–82), p<0.001, respectively].

Table 2 shows a comparison of the patients based on re-hospitalizations. In terms of demographics, patients who were hospitalized more than two times in the previous year had higher NYHA functional classes (p<0.001), and these patients were mostly males (p=0.008). These patients also had significantly lower systolic blood pressures (p=0.007). Biochemical analyses showed that patients who were re-hospitalized had significantly lower serum potassium, total cholesterol, and triglyceride levels (p=0.005, p=0.03, p=0.01, respectively). Compared with patients with fewer hospitalizations, patients who were hospitalized more than two times in the previous year had significantly higher NT-proBNP, UAGT, and Hs-CRP levels [709 (67–19971) and 4254 (81–14598), p<0.001; 99 (13.3–1233) and 193.2 (10.7–804), p=0.007;

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Table 2. Basal characteristic and biochemical variables according to re-hospitalization

	Hospitalized <2 times (n=27)	Hospitalized ≥2 times (n=36)	*P*
Age (year)	66.4±13.1	63.4±10.5	0.313
Gender (F/M)	11/16	4/32	**0.008**[a]
Duration of HF (months)	40 (10-200)	33 (10-240)	0.873
NYHA classes III-IV (%)	5 (15.2%)	28 (84.8%)	**<0.001**[a]
Hemoglobin (g/L)	13.3±1.6	12.4±2	0.066
Platelet count (×1000/mm^3)	223±84	229±75	0.771
White blood cell count (10^3/μL)	8.6±2.4	8.7±2.8	0.865
BMI (kg/m^2)	26.2±2.9	27.2±3.6	0.253
Systolic blood pressure (mm Hg)	129.2±21.6	114.1±21	**0.007**
Diastolic blood pressure (mm Hg)	75.5±12.4	70.6±14.3	0.161
Heart rate (beat/min)	74.7±12.9	82±15.6	0.051
Biochemical parameters			
Creatinine (mg/dL)	1.0±0.27	1.0±0.34	0.573
Serum sodium (mEq/L)	139.7±3.6	137.7±4.6	0.088
Serum potassium (mEq/L)	4.8±0.5	4.4±0.6	**0.005**
eGFR (mL/min per 1.73 m^2)[§]	68.6 (35-115)	75.4 (30.6-133.9)	0.560
Fasting total cholesterol (mg/dL)	181.8±51	152.7±51.4	**0.030**
Fasting LDL cholesterol (mg/dL)	100.1±39.3	91.6±41.5	0.421
Fasting triglyceride (mg/dL)	201.8±149.5	125.9±58	**0.012**
NT-proBNP (pg/mL)	709 (67-19971)	4254 (81-14598)	**<0.001**
UAGT/UCre (μg/g)	99 (13.3-1233)	193.2 (10.7-804)	**0.007**
Hs-CRP (mg/dL)	3.2 (0.33-70)	14 (1.32-82)	**<0.001**
Heart rhythm			
Sinus rhythm	24	24	
Atrial fibrillation	1	10	
Pacemaker rhythm	2	2	
Disease history			
Diabetes mellitus	8	16	0.344[a]
Hypertension	21	17	**0.028**[a]
Coronary artery disease	21	23	0.971[a]
Coronary artery bypass grafting	7	14	0.138[a]
Device history			
Implantable cardioverter defibrillator	13	13	0.117[a]
Cardiac resynchronization therapy	0	4	
Drug information			
Beta-blocker	24	34	0.645[a]
Ace-i/ARB	26	29	0.121[a]
MRA	24	30	0.729[a]
Furosemide	17	30	0.338[a]
Ivabradine	8	10	0.903[a]
Echocardiographic parameters			

Table 2. Cont.

	Hospitalized <2 times (n=27)	Hospitalized ≥2 times (n=36)	*P*
Left ventricle end-diastolic diameter (mm)	57.2±7.4	61.5±8.6	**0.041**
Left ventricle end-systolic diameter (mm)	46.2±6.9	5.0±8.4	0.074
Left ventricular ejection fraction (%)	30.8±5.4	26.9±7.5	**0.026**
Systolic pulmonary artery pressure (mm Hg)	46±19.3	54.1±14.6	0.176
Left atrium diameter (mm)	41±7.4	49±8.4	**<0.001**

Ace-i - angiotensin-converting enzyme; ARB - angiotensin II receptor blocker; BMI - body mass index; eGFR - estimated glomerular filtration rate; F/M - female/male; HF - heart failure; Hs-CRP - high-sensitivity C-reactive protein; MRA - mineralocorticoid receptor antagonist; NYHA - New York Heart Failure Association functional classification; NT-proBNP - N-terminal fragment of B-type natriuretic peptide; LDL - low-density lipoprotein; UAGT - urinary angiotensinogen; UCre - urine creatinine
[§]Calculated formula by the Modification of Diet in Renal Disease
Normally distributed values are presented as mean±standard deviation, non-normally distributed values are presented as median (range), and categorical values are presented as number of patients.
[a]*P*=chi-square value

Table 3. Correlation matrices of UAGT/UCre and number of hospitalizations with other variables

	UAGT/UCre		Number of hospitalization in the previous year		Number of days hospitalized in the previous year		NT-proBNP		Hs-CRP		eGFR sodium		Serum blood pressure		Systolic		Hemoglobin	
	r	*P*	r	*P*	r	*P*	r	*P*	r	*P*	r	*P*	r	*P*	r	*P*	r	*P*
UAGT/UCre	-	-	0.432	**<0.001**	0.464	**<0.001**	0.514	**<0.001**	0.437	**<0.001**	-0.046	0.71	-0.242	0.056	-0.239	0.06	-0.283	**0.023**
Number of hospitalizations in the previous year	0.432	**<0.001**	-	-	-	-	0.507	**<0.001**	0.511	**<0.001**	0.019	0.88	-0.26	**0.041**	-0.283	**0.021**	-0.419	**0.001**

eGFR - estimated glomerular filtration rate; Hs-CRP - high-sensitivity C-reactive protein; NT-proBNP - N-terminal fragment of B-type natriuretic peptide; UAGT - urinary angiotensinogen; UCre - urine creatinine

Table 4. Multiple linear regression analysis of the predictive factors for re-hospitalization (r^2=0.308)

Variables	Beta	*P*
UAGT/UCre (µg/g)	-0.19	0.24
NT-proBNP (pg/mL)	-0.37	**0.042**
Hs-CRP (mg/dL)	0.39	**0.032**
Hemoglobin (g/L)	-0.38	**0.028**
Serum sodium (mEq/L)	-0.08	0.6
Systolic blood pressure (mm Hg)	0.08	0.58

Hs-CRP - high-sensitivity C-reactive protein; NT-proBNP - N-terminal fragment of B-type natriuretic peptide; UAGT - urinary angiotensinogen; UCre - urine creatinine

3.2 (0.33–70) and 14 (1.32–82), p<0.001, respectively]. Similarly, patients who were re-hospitalized had significantly greater left ventricular diastolic diameters and left atrial diameters and significantly lower EF compared with the other group (p=0.04, p<0.001, p=0.02, respectively).

Univariate correlations of selected markers for all 63 patients are given in Table 3 and Figure 1. Within the entire study group, UAGT was significantly correlated with NT-proBNP (r=0.514, p<0.001), Hs-CRP (r=0.437, p<0.001), hemoglobin (r=–0.283, p=0.02), number of hospitalizations in the previous year (r=0.432,

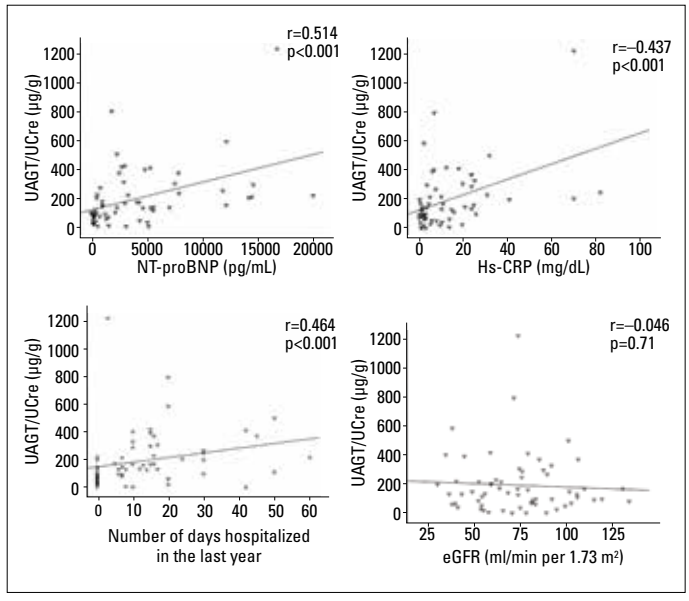

Figure 1. Univariate correlates of selected markers in all 63 study participants

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p<0.001), and hospitalization time (r=0.464, p<0.001). There were also significant correlations between the number of hospitalizations within the previous year and NT-proBNP (r=0.507, p<0.001), Hs-CRP (r=0.511, p<0.001), hemoglobin (r=–0.419, p=0.001), serum sodium (r=–0.26, p=0.04), and systolic blood pressure (r=–0.283, p=0.02).

The independence of multiple correlations was assessed using multiple linear regression analysis (Table 4). In the model, UAGT, NT-proBNP, Hs-CRP, hemoglobin, and serum sodium levels and systolic blood pressure were used as independent variables and ≥2 hospitalizations was used as the dependent variable. According to this analysis, NT-proBNP, Hs-CRP, and hemoglobin levels are independent predictors of re-hospitalization, whereas UAGT, serum sodium, and systolic blood pressure are not.

Discussion

This study was conducted to investigate the potential role of UAGT, an important indicator of intrarenal RAS activity, in patients with HFrEF. Our results showed that NT-proBNP, Hs-CRP, and UAGT levels were significantly higher in patients with a history of re-hospitalizations within the previous year. In addition, patients with higher NYHA functional classes were found to have high UAGT levels. The number of hospitalizations within the previous year was also significantly positively correlated with UAGT, NT-proBNP, and Hs-CRP levels and significantly negatively correlated with hemoglobin and serum sodium levels and systolic blood pressure. Regression analysis revealed that UAGT is not an independent predictor for re-hospitalizations.

HF is a common syndrome worldwide and is the leading cause of hospitalizations in the adult population. Although the overall prevalence is estimated to be 2%, it exponentially increases with age and affects more than 10% of people aged >65 years (2). With poor survival rates and 10-year mortality rates of approximately 100% in the follow-up of patients with newly diagnosed HF, it has been emphasized that this disease is even deadlier than cancer (13). Previous studies have shown that re-hospitalization because of pre-existing HF is a predictor of mortality (6, 14, 15). This has led scientists to look for new markers for predicting hospitalizations and mortality because of HF (7).

RAS plays a key role in the pathogenesis of HF (8, 9, 16). This compensatory system activated in chronic HF has been shown to be associated with cardiac remodeling and poor prognosis (17). Clinical trials have shown that ACE-i, ARB, and MRA, which block RAS, effectively improve the prognosis of HF. As a result, these drugs are recommended in contemporary guidelines for HF management (8). The increase in renin, a rate-limiting enzyme, in the formation of angiotensin I from systemic AGT leads to RAS activation. In contrast, AGT is abundant in the plasma and is not a rate-limiting molecule for RAS activity. However, it has been reported that AGT, which is 103–104 times locally scarcer in the kidney than in the plasma, may activate RAS (10). Systemic AGT is produced by the liver but cannot pass through the glomerular basement membrane because of its high molecular weight. Therefore, UAGT is considered to reflect locally produced AGT released from proximal tubular cells. Kobori et al. (18) showed that UAGT was a specific marker of intrarenal RAS status in hypertensive rats, independent of plasma AGT. In addition, elevated UAGT levels have been demonstrated to be an indicator of intrarenal RAS status in various patient populations such as those with HT, CKD, DM, and amyloidosis (19-22). Schunkert et al. (23) found that renal AGT, renin, and angiotensin II levels were high in rats with HF. However, there are no studies in the literature on intrarenal RAS activity status in humans with HF.

In the present study, we found that among patients receiving optimal HF therapy to the extent that they could tolerate, those with a high NYHA class and a history of repeated hospitalization had higher UAGT levels. In their review, Kobori et al. (18) reported that renal RAS activation increased following HF induction in rats. They noted that as a result of this, water/salt retention and peripheral vascular resistance increased, subsequently initiating a vicious cycle that impaired cardiac performance and led to cardiac remodeling (18). This may explain our finding that high UAGT level (i.e., marker of intrarenal RAS activation) was associated with worse NYHA class and higher frequency of re-hospitalization.

Studies have shown that the use of ACE-i/ARB suppresses both plasma and intrarenal RAS activation (24, 25). However, approximately 5%–20% of patients treated with ACE inhibitors cannot tolerate these drugs because of dry cough, angioedema, hypotension, hyperkalemia, or renal dysfunction. Similarly, some patients have to discontinue their treatment because of the side effects of ARBs such as hypotension, hyperkalemia, renal dysfunction, and angioedema (26). In addition, as the tolerance limits for both drugs are exceeded, the dose may have to be reduced or the desired target dose may not be achieved during follow-up. In our study, drug use rates were generally high, most likely because patients with stage 4-5 CKD were excluded from the study. The frequent hospitalizations of some patients despite high rates of drug use may be because of the fact that the target doses could not be reached or that the target dose required for achieving both systemic and intrarenal RAS inhibition varied for each patient. This may explain the high UAGT ratios in patients with high NYHA class symptoms or a history of repeated hospitalizations.

Consistent with our results, previous studies have shown that serum sodium, Hs-CRP, NT-proBNP, hemoglobin, and blood pressure are important prognostic factors in patients with HF. Amin et al. (7) reported that 30-day HF readmission and mortality due to all causes were higher among patients with low serum sodium levels, and that this parameter was a predictor independent of other factors.

Although BNP value at the time of admission in previous studies was found to be correlated with mortality and prolonged hospitalization time, it could not be correlated with the number of hospitalizations (7, 27, 28). In contrast to those findings, we

observed in the present study that high NT-proBNP level at the time of admission was an independent risk factor for re-hospitalization.

There are contradictory results in the literature concerning hemoglobin and CRP levels in patients with HF. While Jug et al. (29) claimed that CRP is not an independent determinant of mortality and re-hospitalization because of HF, Lourenço et al. (30) have shown that elevated CRP level increases the risk of death due to HF or the number of re-hospitalizations independently of other prognostic predictors, consistent with our results. Anemia is a common comorbidity in patients with chronic HF, and its prevalence is 10%–50%. A study by O'Meara et al. (31) showed that anemia increases the risk of mortality and hospitalization in patients with HF, whereas another report asserted that anemia only increases mortality and has no effect on repeated hospitalizations (32). In the present study, hemoglobin level was found to be an independent risk factor for re-hospitalization.

Study limitations

The main limitations of our study were the limited number of patients. Second limitation is the lack of a healthy control group. Another limitation is that the doses of the ACE-i/ARBs used by the patients were not standardized.

Conclusion

Although UAGT levels are high in patients with poor NYHA functional class and re-hospitalizations, this marker is not valuable for predicting re-hospitalization in patients with HFrEF.

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