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Relationship Between Urinary Angiotensinogen and Mortality in Patients with Heart Failure with Reduced Ejection Fraction

ABSTRACT

Background: Activation of the renin–angiotensin–aldosterone system has an important role in the pathophysiology of heart failure with reduced ejection fraction. While the effects of systemic renin–angiotensin–aldosterone system activation on heart failure with reduced ejection fraction are well known, the impact of the local renin–angiotensin–aldosterone system on heart failure with reduced ejection fraction is not fully understood because of limited clinical research. This study aimed to investigate the effect of urinary angiotensinogen level, an accepted indicator of local renin–angiotensin–aldosterone system activation, on all-cause mortality in patients with heart failure with reduced ejection fraction.

Methods: This retrospective, single-center study included 60 patients with baseline urinary angiotensinogen data and survival/mortality data at 4 years. Urinary angiotensinogen values were standardized to the urinary creatinine value measured from the same urine sample. The median urinary angiotensinogen/urinary creatinine value among all patients (114 μg/g) was used as a cutoff to divide the patients into 2 groups. Mortality data were obtained from the national registry systems or by telephone.

Results: Comparison of all-cause mortality in the 2 groups showed that 22 deaths (71%) occurred in the group with a urinary angiotensinogen/urinary creatinine ratio above the median and 10 deaths (35.5%) occurred in the group of patients with urinary angiotensinogen/urinary creatinine equal to or below the median value ($P = .005$).

Conclusion: Our study suggests that urinary angiotensinogen can be used as a new biomarker in the prognosis and follow-up of heart failure patients.

Keywords: Heart failure with reduced ejection fraction, local renin–angiotensin–aldosterone system, urinary angiotensinogen

ORIGINAL INVESTIGATION

INTRODUCTION

Heart failure (HF) is a clinical syndrome with cardinal symptoms of dyspnea, ankle edema, or fatigue and accompanied by signs such as elevated jugular venous pressure, rales, and peripheral edema. It occurs as a result of structural/functional impairment that causes increased intracardiac pressures and/or decreased cardiac output at rest or during exercise. Determining the underlying etiology of HF is important in terms of treatment planning. Although usually of myocardial origin, HF may also develop in association with arrhythmias, valve pathologies, and endocardial or pericardial disease.[1] While better management of cardiovascular disease in developed countries is lowering the age-adjusted incidence of HF, the overall prevalence of HF is increasing due to population aging.[2,3] Studies have shown that the prevalence of HF in adults is approximately 1%-2%.[2,4] The HF prevalence is around 1% before 55 years of age and increases to over 10% after 70 years of age.[5,6] Although many drugs have been introduced to treat HF over the years and have improved the prognosis, mortality remains high. Studies report a mortality rate of about 60% within 5 years of being diagnosed with HF.[7,8]

Typical symptoms and/or findings of HF in the presence of low ejection fraction (EF ≤40%) on echocardiography is diagnosed as HF with reduced ejection fraction (HFrEF).[1] Activation of the renin–angiotensin–aldosterone system (RAAS) is

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considered an important neurohumoral mechanism in HFrEF. Renin–angiotensin–aldosterone system blockade has been shown to reduce mortality and morbidity in patients with HFrEF.[9] In addition, independent of the systemic RAAS, activation of the local RAAS also plays a role in the pathophysiology of chronic kidney disease (CKD) and HF.[10] Systemic angiotensinogen (AGT) is synthesized by the liver and released into the systemic circulation. Angiotensinogen, which is abundant in the plasma, is converted to angiotensin (AT)-I by renin. Because of its high molecular weight, plasma AGT cannot pass through the glomerular membrane. Therefore, urinary AGT (UAGT) is synthesized by the kidneys and is considered an indicator of direct intrarenal RAAS activation.[11]

In our previous study of patients with HFrEF, we found that UAGT values were higher among patients in New York Heart Association (NYHA) functional class III-IV than those in NYHA class I-II.[11] Similarly, we determined that UAGT levels were significantly higher in patients with a history of 2 or more hospital admissions.[11] The present study aimed to investigate the effect of UAGT level on 4-year all-cause mortality in HFrEF patients whose UAGT levels were previously evaluated.

METHODS

This single-center retrospective study initially included 63 patients aged 18-89 years who were being followed up in the cardiology department for HF between May 2017 and August 2017, had EF ≤40% on transthoracic echocardiography, and had UAGT values measured during the same period. The patients' demographic characteristics (age and sex), clinical history, biochemical examination results, transthoracic echocardiography measurements, and cardiac rhythm (sinus rhythm, atrial fibrillation, and pacemaker rhythm) during the same period were recorded from the data archive system. The medicines used by the patients were determined from the national health data system. Current medications were recorded for surviving patients and last used medications were recorded for deceased patients. The study was approved by the Local Clinical Research Ethics Committee (2022/17).

Patients <18 or ≥90 years of age and those with a history of end-stage CKD, active infection, chronic obstructive pulmonary disease, liver failure, and malignancy were excluded from the study. In addition, patients with a history of coronary intervention, pulmonary edema, or cardiogenic shock within 3 months before the study period were not included in the study. Three of the initial 63 patients were excluded because they could not be contacted.

HIGHLIGHTS

- There are few clinical and biochemical markers to predict prognosis in patients with heart failure with reduced ejection fraction.
- Although there is strong evidence linking activation of the plasma renin–angiotensin–aldosterone system with poor prognosis, local renin–angiotensin–aldosterone system activation has not been adequately studied.
- Urinary angiotensinogen elevation is an indicator of local renin–angiotensin–aldosterone system activation that can be used to detect patients with high mortality risk.

All patients' echocardiographic parameters had been recorded with a GE Vivid E9 echocardiography device in accordance with American Heart Association recommendations and were obtained from the data archive system.[12] Systolic and diastolic blood pressure values were noted from the patients' records. Body mass index (BMI) was calculated using the formula of weight (kg)/height (m^2) measured at the initial examination.

The results of blood and urine analyses performed between May 2017 and August 2017 were recorded from the hospital records system. Urinary AGT measurements had been performed using the sandwich enzyme-linked immunosorbent assay method (YHB20.60901646, YH Biosearch Laboratory, Shanghai, China). Urinary AGT values were standardized to the urinary creatinine (UCre) value measured from the same urine sample (UAGT/UCre). After recording the measured UAGT/UCre results, the median value was calculated. Those with UAGT/UCre values equal to or below the median value were classified as group 1, and those with UCre values above the median value were classified as group 2.

All-cause mortality among the patients in the study was evaluated by 2 cardiologists. The hospital database and the national death notification system were searched, and the date of death was recorded for nonsurvivors. Patients who did not have available data were contacted using their registered phone numbers to determine their survival status.

Statistical analyses were performed using MedCalc Statistical Software version 17.9.7® (MedCalc Software bv, Ostende, Belgium). The Kolmogorov-Smirnov test was used to determine whether continuous variables showed normal distribution. Normally distributed variables were evaluated using parametric tests. Continuous variables were expressed as mean ± SD, and categorical variables were expressed as median and range. For comparisons of 2 groups, an independent-samples *t*-test was used for normally distributed continuous variables, and Mann–Whitney *U*-test was used for nonnormally distributed continuous variables. The chi-square test was used to compare categorical variables. A Kaplan–Meier curve was used to evaluate 4-year all-cause mortality in patients with UAGT/UCre ratios above the median value and equal to or below the median value. Results were evaluated within a 95% CI and $P < .05$ was accepted as statistically significant.

RESULTS

The study included a total of 60 patients who met the inclusion criteria and whose survival/mortality status could be ascertained. The median UAGT/UCre value was 144.01 µg/g. Patient group 1 included 29 patients whose UAGT/UCre ratio was equal to or lower than 144 µg/g, and group 2 included 31 patients whose UAGT/UCre ratio was higher

than 144 µg/g. The 2 groups were similar in terms of age, sex, history, medications used, and vital signs. Analysis of biochemical parameters showed that group 2 had significantly lower hemoglobin ($P = .032$) and higher high-sensitivity C-reactive protein (Hs-CRP) ($P < .001$) and N-terminal pro-brain natriuretic peptide (NT-proBNP) ($P < .001$) levels. The baseline characteristics of both groups are shown in Table 1.

Comparison of transthoracic echocardiographic parameters revealed no significant difference in EF, posterior wall thickness, left ventricular end-diastolic, end-systolic, or left atrial diameters (Table 2).

When 4-year all-cause mortality was examined, there were significantly more nonsurvivors in group 2 (n = 22, 71%) than in group 1 (n = 10. 35.5%) (Table 3). The 4-year survival analysis

Table 1. Baseline Characteristics of the Patient Groups Based on UAGT/UCre Ratio

	Group 1 (UAGT/UCre ≤ 144.01 µg/g) (n = 29)	Group 2 (UAGT/UCre > 144.01 µg/g) (n = 31)	*P*
Age (years)	61.20 ± 11.95	67.93 ± 11.22	.052
Gender (female/male)	6/23	9/22	.324
Risk factors and blood pressures			
Coronary artery disease (n, %)	21, 72.4%	20, 65.5%	.352
DM (n, %)	9, 31.0%	15, 48.4%	.136
HT (n, %)	20, 69.0%	17, 54.8%	.194
BMI (kg/m^2)	26.64 ± 3.56	27 ± 3.31	.785
SBP (mm Hg)	123 ± 23	118 ± 21	.463
DBP (mm Hg)	74 ± 12	71 ± 15	.484
Heart rhythm			
Sinus rhythm (n, %)	25, 86.2	20, 64.5	
Atrial fibrillation (n, %)	2, 6.9	9, 29.0	
Pacemaker rhythm (n, %)	2, 6.9	2, 6.5	
History of device			
ICD (n, %)	12, 41.3	14, 45.1	.803
CRT (n, %)	2, 6.9	2, 6.5	1.000
Medication			
ACE-i/ARB (n, %)	27, 93.1	29, 93.5	1.000
Beta-blocker (n, %)	28, 96.5	30, 96.7	1.000
MRA (n, %)	27, 93.1	27, 87.0	.672
SGLT-2 inhibitors (n, %)	9, 31.0	15, 48.4	.194
Ivabradine (n, %)	9, 31.0	9, 29.0	1.000
Biochemical and hematological parameters			
Fasting blood glucose (mg/dL)	134.68 ± 64.34	134.38 ± 51.82	.783
Creatinine (mg/dL), median (range)	1.00 (0.60-1.80)	0.98 (0.55-2.1)	.962
Serum sodium (mEq/L)	139.68 ± 4.37	137.93 ± 3.78	.144
Serum potassium (mEq/L)	4.67 ± 0.52	4.55 ± 0.63	.435
AST (U/L)	24.20 ± 10.08	26.92 ± 21.94	.591
ALT (U/L)	22.40 ± 15.96	15.98 ± 9.41	.090
WBC (10^3/µL)	8.88 ± 2.13	8.08 ± 3.10	.133
Hg (g/L)	13.18 ± 2.10	12.4 ± 1.71	**.032**
hs-CRP (mg/dL)	5.66 ± 5.64	20.21 ± 21.38	**<.001**
NT-proBNP (pg/mL), median (range)	568.5 (67-7071)	4147 (518-19971)	**<.001**
Fasting total cholesterol (mg/dL)	173.31 ± 58.80	161.17 ± 47.78	.524
Fasting LDL cholesterol (mg/dL)	100.44 ± 46.95	92.42 ± 34.43	.726
Fasting triglycerides (mg/dL)	166.72 ± 128.69	159.71 ± 105.16	.475

P-value of less than .05 was statistically significant. ACE-I, angiotensin-converting enzyme inhibitor; ALT, alanin aminotransferase; ARB, angiotensin-II receptor blocker; AST, aspartate aminotransferase; BMI, body mass index; CRT, cardiac resynchronization therapy; DBP, diastolic blood pressure; DM, diabetes mellitus; Hg, hemoglobin; hs-CRP, high-sensitivity C-reactive protein; HT, hypertension; ICD, implantable cardioverter defibrillator; LDL, low-density lipoprotein; MRA, mineralocorticoid receptor antagonist; SBP, systolic blood pressure; SGLT-2, sodium glucose cotransporter-2; UAGT, urinary AGT; UCre, urinary creatinine; WBC, white blood cell count.

Table 2. Echocardiographic Parameters in the Groups

	Group 1 (UAGT/UCre ≤ 144.01 µg/g) (n = 29)	Group 2 (UAGT/UCre > 144.01 µg/g) (n = 31)	*P*
Ejection fraction (%)	28.75 ± 5.45	29.38 ± 7.81	.625
LVEDd (cm)	5.9 ± 0.66	6.01 ± 0.97	.843
LVESd (cm)	4.73 ± 0.68	4.92 ± 0.9	.561
PWd (cm)	1.05 ± 0.17	0.97 ± 0.17	.172
LAd (cm)	4.51 ± 0.76	4.62 ± 1.01	.774

LAd, left atrial diameter; LVEDd, left ventricular end-diastolic diameter; LVESd, left ventricular end-systolic diameter; PWd, posterior wall thickness; UAGT, urinary AGT; UCre, urinary creatinine.

Table 3. Differences in All-Cause Mortality Between the Patient Groups

	Group 1 (UAGT/UCre ≤ 144.01 µg/g) (n = 29)	Group 2 (UAGT/UCre > 144.01 µg/g) (n = 31)	*P*
Survived (%)	19, 65.5	9, 29	**.005**
Mortality (%)	10, 35.5	22, 71	

P-value of less than .05 was statistically significant. UAGT, urinary AGT; UCre, urinary creatinine.

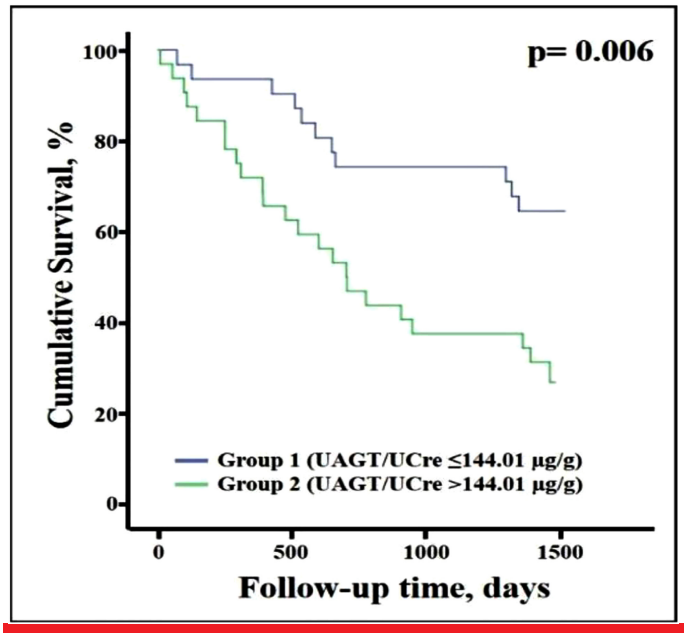

Figure 1. Kaplan–Meier curves of patient groups for all-cause mortality.

of the study groups also demonstrated higher all-cause mortality in group 2 (log-rank *P* = .006) (Figure 1).

DISCUSSION

The prevalence of HF is increasing with population aging, and it remains an important cause of mortality despite therapeutic advances. Therefore, quantitative parameters are needed to predict clinical prognosis and mortality in these patients. This study investigated the effect of intrarenal RAAS activity on mortality in HFrEF patients and showed that all-cause mortality at 4-year follow-up was higher in the group with a UAGT/UCre ratio above the median value.

The RAAS plays an important role in regulating the functions of various organs, especially the heart and kidney, through its active end product, AT-II (Figure 2). Components of the RAAS have been identified in various tissues, including the heart, blood vessels, and kidneys. Renin–angiotensin–aldosterone system overactivity in the heart and kidneys plays a role in the pathogenesis of cardiovascular and kidney diseases. Reduced renal perfusion in HF results in increased RAAS activity.[10] Both in the circulation and tissues, AGT is cleaved by renin to form AT-I. This is then converted to AT-II by angiotensin-converting enzyme (ACE) found in the plasma and pulmonary vessels. Angiotensin-II formed in both the circulation and tissues regulates the function of the brain, heart, lungs, kidneys, adrenal gland, and blood vessels. Angiotensin-II stimulates aldosterone synthesis in the adrenal glands. The main role of AT-II in healthy individuals is to regulate arterial blood pressure, renal hemodynamics, and fluid-electrolyte homeostasis.[13,14]

Renin–angiotensin–aldosterone system plays a key role in the pathogenesis of HF.[15-17] This compensatory system is activated in chronic HF and was shown to be associated with cardiac remodeling and poor prognosis.[18] The systemic RAAS, sympathetic nervous system, and neurohumoral factors, as well as the intrarenal RAAS, are reported to play a role in the pathophysiology of HF.[19-21] Renin–angiotensin–aldosterone system blockade is also known to reduce mortality in patients with HF. However, the effects of RAAS activity on the heart at the tissue level have not been fully determined.

Studies have indicated that UAGT, which cannot be evaluated through plasma renin activity or plasma AT-II, is a reliable marker for intrarenal RAAS activity.[22,23] Systemic AGT is produced by the liver but is too large to pass through the glomerular basement membrane. Therefore, UAGT is regarded as a marker of locally produced AGT released from the proximal tubular cells. Kobori et al[24] showed that UAGT was a

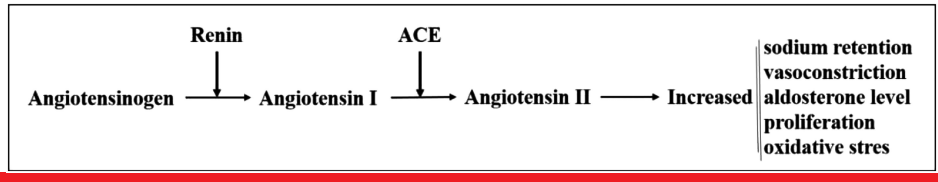

Figure 2. The renin–angiotensin–aldosterone system. ACE, angiotensin-converting enzyme.

specific marker of intrarenal RAAS activity in hypertensive rats, independent of plasma AGT.

In the Olmsted County cohort study conducted between 2000 and 2010, 1- and 5-year mortality rates for all HF patients after diagnosis were 20% and 53%, respectively.[7] A study combining the Framingham Heart Study and Cardiovascular Health Study cohorts reported a mortality rate of 67% within 5 years of diagnosis.[8] In addition to high mortality and morbidity, HF imposes a substantial economic burden. Urbich et al[25] conducted a systematic review of HF-related medical costs in the United States in 2014-2020 and determined that the total annual median medical cost for HF care was $24 383 per patient and that HF increased hospitalization costs. Determining new prognostic factors in HF is important in terms of reducing morbidity, mortality, and costs. The main factors determining the prognosis in HF are low EF, the presence of arrhythmia, low systolic blood pressure, low functional capacity, neurohormonal imbalance, and kidney failure.

Various biomarkers have been used to determine HF prognosis in recent studies. The most important and commonly used of these biomarkers is NT-proBNP. One study showed that NT-proBNP level was a strong predictor in determining HF prognosis as well as in diagnosis.[26] Other than NT-proBNP, various biomarkers are being evaluated as prognostic predictors in HF.

Yokoyama et al[27] showed in their study that changes in UAGT/UCre were correlated with change in NT-proBNP level in HF patients. Seethalakshmi et al[28] compared the UAGT levels of healthy subjects with no history of HF or hypertension and patients hospitalized for acute decompensated HF and found that UAGT levels were approximately 10 times higher in patients with acute decompensated HF compared to healthy subjects ($P < .05$). In another study, UAGT/UCre and NT-proBNP values were measured at hospital admission and discharge in patients hospitalized for HF and the authors reported a significant decrease in UAGT/UCre and NT-proBNP values at discharge in parallel with clinical improvement ($P < .01$).[29]

Like NT-proBNP, Hs-CRP is also an important biomarker in predicting the prognosis of HF patients. Lourenço et al[30] demonstrated that high CRP values at discharge were associated with a 2-fold increase in the risk of death and rehospitalization in noninfected patients with acute HF, independent of other well-established predictors of prognosis. Similarly, a relationship between high CRP and poor prognosis has also been demonstrated in chronic HF.[31,32] However, CRP is not specific to HF and may be elevated in many conditions, from infections to severe atherosclerosis. Anemia is a common comorbidity in patients with HF.[33] It has been shown that the presence of anemia in HF is associated with more severe disease, readmission for HF, and lower survival.[1] Unfortunately, high NT-proBNP and Hs-CRP levels and the presence of anemia are not sufficient biomarkers to predict the prognosis of HF patients. In our previous study, we found that NT-proBNP, Hs-CRP, and UAGT levels were independently and significantly higher in patients with a history of recurrent hospitalization for HF within the last year.[11] In the present study, we determined that HFrEF patients with a UAGT/UCre ratio higher than the median value had significantly higher Hs-CRP ($P < .001$) and NT-proBNP ($P < .001$) levels, consistent with our previous study. Similarly, we demonstrated that patients with a UAGT/UCre ratio higher than the median value had significantly lower hemoglobin levels. These results suggest that UAGT/UCre ratio may be as valuable as other important parameters in predicting the prognosis of patients with HFrEF.

Study Limitations

The most important limitation of our study is that it was conducted retrospectively, and as a result we were not able to determine the causes of death in more detail. While some of the patients continued to be followed in our institution, a substantial number were lost to follow-up. For this reason, we could only collect information about survival/mortality status and date of death. Another limitation is that renin activity, which has been emphasized in other studies, was not measured. The small number of patients included in the study is also an important limitation. In addition, as stated in the methodology, information about medications used by the patients was obtained from the national health data system. Therefore, we could not ascertain whether the patients used their cardiac drugs regularly or evaluate the effect of the drugs on the difference in mortality between the groups.

CONCLUSION

We determined that all-cause mortality was higher in HFrEF patients whose UAGT/UCre ratio was above the median value of 144 µg/g. Comprehensive randomized clinical studies are needed to further evaluate the use of UAGT to predict the prognosis of patients with HF.

Ethics Committee Approval: Ethical committee approval was received from the Ethics Committee of Mersin University (20.01.2022, Approval No: 2022/17).

Informed Consent: Written informed consent was obtained from all participants who participated in this study.

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