

Serum Uric Acid Levels among Patients who Died in Recent Year due to Heart Failure with Reduced Ejection Fraction

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ABSTRACT

Objective: To examine the relationship of uric acid levels in the last one year with exitus due to heart failure (HF) with clinical and demographic data of patients.

Study Design: Cross-sectional, descriptive study.

Place and Duration of Study: Bilecik State Hospital, Bilecik, Turkey, from January 2019 to January 2020.

Methodology: The files of 90 people who had exitus due to HF were scanned retrospectively. Demographic data and echocardiography results were recorded. Serum uric acid levels were noted in the 2nd month, 6th month, and 12th month by taking the baseline in the last year before exitus. Mean repeated measurements of uric acid levels that changed over time in patients were compared with ANOVA variance analysis. $P < 0.05$ were accepted as statistically significant.

Results: The mean of the left ventricular ejection fraction (LVEF) of the patients was $35.6 \pm 6.6\%$. Mean serum uric acid levels of the patients for one year before exitus were 5.6 ± 2.2 mg/dL (baseline), 6.1 ± 2.3 mg/dL (2th month), 7.1 ± 2.6 mg/dL (6th month), 8.5 ± 3.0 mg/dL (12th month) respectively. There was a statistically significant difference between the basal uric acid mean with the 6th and 12th month uric acid levels both $p < 0.001$. Age and LVEF were not significantly associated with the uric acid increase over time ($p = 0.250$ and $p = 0.327$, respectively) but were statistically different according to gender ($p = 0.036$).

Conclusion: In heart failure with reduced ejection fraction (HFrEF), the uric acid level increases progressively towards the last periods before exitus. This increase is more pronounced in men.

Key Words: Heart failure, Serum uric acid levels, Prognosis, Gender.

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INTRODUCTION

Heart failure (HF) is a preventable clinical syndrome with cardiac structural or functional disorders.¹ HF is classified into 3 groups according to pump dysfunction. It is classified as HF with reduced ejection fraction (HFrEF) (EF $< 40\%$), HF with mid-range ejection fraction (HFmEF, EF 40% to 49%), and HF preserved ejection fraction (HFpEF, EF $> 50\%$).¹ To estimate the prognosis of HF, it can be obtained from easily available data such as age, etiology, New York Heart Society (NYHA) symptom classification, left ventricular ejection fraction (LVEF), concomitant diseases (kidney dysfunction, diabetes, anemia, thyroid dysfunctions, hyperuricemia) and plasma natriuretic peptide concentrations.

However, many variables can provide information about the prognosis of the diseases.²⁻⁴ Uric acid is the end product that occurs as a result of purine metabolism in humans, and high uric acid levels in coronary artery disease and many cardiovascular diseases have been reported to be associated with poor results.^{5,6} Hyperuricemia may occur or worsen as a result of diuretic therapy in HF. This effect is more pronounced in patients with systolic dysfunction or reduced LVEF.

In recent years, although many studies have argued that increased serum uric acid levels are associated with the risk of cardiovascular disease, this is still controversial, since it has not been fully clarified whether the height of uric acid causes cardiovascular diseases or increases as a result of the disease.⁷

The aim of this study was to examine the relationship of uric acid levels in the last one year with exitus due to heart failure with clinical and demographic data in patients.

METHODOLOGY

The study was conducted by scanning archives from January 2019 to January 2020 in Bilecik State Hospital.

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Table I: Evaluation of serum uric acid levels by repeated variance analysis over time.

Uric acid levels		Mean difference (I-J)	Std. error	p-value	95% Confidence interval for difference
Second month	Baseline	0.505	.188	0.052	-0.002 -1.012
Sixth month	Baseline	1.468*	.248	<0.001	0.800 -2.136
	2 nd month	0.963*	.264	0.003	0.250 -1.677
Twelfth month	Baseline	2.875*	.320	<0.001	2.013 - 3.738
	2 nd month	2.370*	.321	<0.001	1.503 - 3.237
	6 th month	1.407*	.231	<0.001	0.785 - 2.029

* $p < 0.05$ **Table II: The relationship of serum uric acid levels over time with clinical and demographic data.**

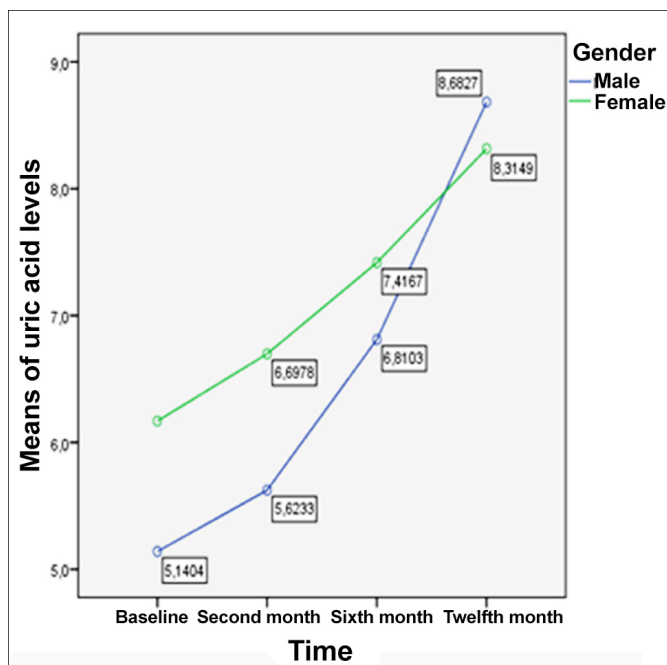
Source	Type III sum of squares	Mean square	F	P	Partial Eta squared
Time	53.314	24.074	5.771	0.003	0.063
Time *Age	12.873	5.813	1.393	0.250	0.016
Time *LVEF%	10.488	4.736	1.135	0.327	0.013
Time *Gender	30.167	13.621	3.265	0.036	0.037

*Greenhouse-Geisser, Time-change in uric acid levels over time (Baseline, second month, sixth month, twelfth month).

Table III: Serum uric acid levels over time by gender.

	Male (n:47)	Female (n:43)	p-value
Uric Acid 1 st month (mean)	5.143 ± 1.70	6.166 ± 2.63	0.034*
Uric Acid 2 nd month (mean)	5.617 ± 1.65	6.705 ± 2.72	
Uric Acid 6 th month (mean)	6.813 ± 2.15	7.414 ± 3.01	
Uric Acid 12 th month (mean)	8.688 ± 2.78	8.309 ± 3.15	

*Greenhouse-Geisser, Time*Gender-Change in uric acid levels over time by gender.

**Figure 1: The graph of the change of serum uric acid levels in one year without exitus.**

Records of 90 subjects, who had exitus due to heart failure with reduced ejection fraction (HFrEF), were evaluated retrospectively. Demographic data (age, gender) and echocardiographic evaluation results of the patients were recorded. Serum uric acid levels were retrospectively screened for the second month, sixth month, and twelfth month based on the

initial baseline of the last year. Hyperuricemia was defined as uric acid levels of >6 mg / dL in women and >7 mg / dL in men. The values measured by the modified Simpson method were used for the LVEF measurement. Patients with LVEF ≤40% were included in the study (LVEF remained stable in the past one year according to NYHA. Patients with malignancy, those treated for gout, patients with uncontrolled diabetes mellitus, pregnant women, patients with hemolytic anemia, hemodialysis treatment, those who had a heart transplant and history of moderate or severe valvular heart disease were excluded from the study.

Statistical package for the social sciences (SPSS) (Version 22.0. Armonk, NY, IBM Corp., USA) programme was used for statistical analysis. The characteristics of patients were evaluated with descriptive analysis. The mean of uric acid levels varying over time in patients were repeated with variance analysis ANOVA. The globality conjecture was evaluated by the Mauchly test in SPSS. Since the p value was <0.05 in Mauchly's test, the Greenhouse and Geisser correction was preferred for the F value. The Bonferroni method was used to examine the relationship between variables; and to investigate the relationship between uric acid levels measured at different times in this study. P values below 0.05 were accepted as statistically significant.

RESULTS

The average age of the patients included in the study was 76.6 ± 8 years. Forty-three (47.8%) of the patients were

females and 47 (52.2%) were males. The mean LVEF in the study group was $35.6 \pm 6.6\%$. The mean 1-year serum uric acid levels before the exitus were basal = 5.6 ± 2.2 mg/dL, second month = 6.1 ± 2.3 mg/dL, sixth month = 7.1 ± 2.6 mg/dL, twelfth month = 8.5 ± 3.0 mg/dL.

As a result of repeated measurement variance analysis, considering the change of uric acid over time, there was no statistical difference between basal uric acid levels and the second-month uric acid levels ($p = 0.052$). However, there was a statistically significant difference between the basal uric acid levels and the 6th and 12th month uric acid levels ($p < 0.001$, $p < 0.001$, respectively). Uric acid levels were observed to increase over time and the highest mean was found to be in the 12th month (Table I).

By One-Way variance analysis, the relationship between age, gender, and LVEF were evaluated with the change of uric acid levels over time. While the increase in uric acid overtime was not statistically correlated with age and LVEF ($p = 0.250$, and $p = 0.327$, respectively). There were statistically differences according to gender ($p = 0.036$, Table II).

It was observed that while the level of uric acid was higher in women at the beginning, the level of uric acid was higher in men before exitus than in women (Figure 1).

When the change of uric acid over time was evaluated by gender, it was observed that there was more increase in uric acid level in men than in women ($p = 0.034$, Table III).

DISCUSSION

Heart failure (HF) is defined as a structural or functional disorder that causes the heart to fail to supply enough oxygen to meet the metabolic needs of the tissues.¹ In developed countries, it is found in approximately 1-2% of the society with HF and its prevalence increases with aging.⁸ Information about the prognosis of HF can be obtained from easily available data such as etiology, age, NYHA class, LVEF, important concomitant diseases (such as kidney dysfunction, diabetes, hyperuricemia, anemia) and plasma natriuretic peptide concentrations. However, apart from these, it can provide prognostic information in many variables. It is clear that these variables, and of course the prognosis, have changed over time. Prognosis assessment is particularly important when advising patients about left ventricular-assist devices and surgical treatment (transplantation) and when planning end-of-life care with patients' families and caregivers. Many biochemical parameters are used in the diagnosis of the disease, in the evaluation and follow-up of the response to treatment, and these may be of prognostic importance. Uric acid is the end-product that occurs as a result of purine metabolism in humans and its relationship with cardiovascular diseases has been studied in many studies.^{9,10} Uric acid has been shown to cause vascular inflammation and endothelial dysfunction by causing

increased reactive oxygen radicals, the vascular smooth proliferation of muscle cells, and decreased production of nitric oxide.¹¹ In human and animal experiments, reactive oxygen radicals caused by increased uric acid levels have been shown to impair myocardial function.¹²⁻¹⁴ Studies have suggested that there is a relationship between reduced ejection fraction and increased uric acid levels.¹⁵ Some authors argue that the increase in serum uric acid levels usually accompanies chronic heart failure and that there is a nearby relationship between the degree of heart failure and serum uric acid levels. They also stated that this relationship is independent of diuretic use and glomerular filtration rate.^{10,11} Piepoli *et al.* have demonstrated that serum uric acid levels are associated with increased mortality in patients with congestive heart failure.¹⁶ However, it is not yet clear whether uric acid is involved in the pathophysiology of heart failure or if its level increases secondary to heart failure.

This study showed that although the patients had an LVEF average below 40% in the last year before exitus, there was no progressive decrease in systolic function. At the same time, when patients in the same stage according to the NYHA stage were included, an increase in uric acid was observed over time, but LVEF was not an effective factor in this change ($p = 0.327$). The reason for this situation may be that uric acid increased in chronic heart failure causes endothelial dysfunction by causing oxidative stress in the endothelium. Moreover, the vasodilator response to exercise is significantly impaired and a vicious cycle of uric acid rises with increasing hypoxia at the tissue level with increased oxidative stress.¹⁷ Therefore, although the ejection fraction remains stable in patients with heart failure, an increase in uric acid can be expected over time. This study also showed that although LVEF was stable, there was an increase in uric acid levels in patients over time. There are differences in the effect of gender on left ventricular ejection fraction and prognosis in heart failure patients.¹⁸ The effect of serum uric acid levels on cardiovascular outcomes is more pronounced in the female gender,¹⁹ but the role of gender on survival has not yet been clearly determined. In the study conducted by Viera Stubnov *et al.*, serum uric acid levels were reported to be an independent factor in all-cause death in women (HR 1.65, 95% CI 1.24-2.20, $p < 0.001$), while there was no such risk factor in men (HR 1.06, 95% CI 0.89-1.25, $p = 0.527$).²⁰ Adenosine, locally synthesised in vascular smooth muscle in the heart, is rapidly converted into uric acid by the endothelium and released into the vascular lumen in the case of low intracellular pH and negative membrane potential.²¹ Especially in the 12th month, it is evident that the reason for the appearance of uric acid elevation is prominent tissue ischemia in pre-death terminal period.

However, the low number of female gender in this study was the limitation of the study. In this study, exitus in the last one year and the level of uric acid looked at during this period is significantly higher in women. However, the

increase in uric acid in recent periods was more pronounced in men and was higher in men from the twelfth month.

CONCLUSION

The uric acid increase is an independent factor for mortality in patients with heart failure. Gender was evaluated as one of the factors affecting uric acid increase. Although high uric acid in women is evident in the initial period, the level of uric acid in men was found to be higher in the recent period. Further and more extensive studies are needed to evaluate this effect of gender.

ETHICAL APPROVAL:

This study was conducted in compliance with the ethical principles according to the Declaration of Helsinki, and it was approved by the local Institutional Review Board (Number: 2020/16).

PATIENTS' CONSENT:

Since it was designed as a retrospective study, the data were collected from the hospital archive after approval of the Ethics Committee.

CONFLICT OF INTEREST:

The authors declared no conflict of interest.

AUTHORS' CONTRIBUTION:

IA, MC: Conceived the study design, involved in data collection, performed the statistical analysis, interpreted data and prepared the manuscript draft.

All the authors critically reviewed the final version of the manuscript and approved the final version.

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