

# The relationship between Gamma-Glutamyltransferase activity and atrial fibrillation in patients with reduced ejection fraction heart failure

## Azalmış ejeksiyon fraksiyonu kalp yetersizliğinde Gama-Glutamyltransferaz aktivitesi ve atriyal fibrilasyon arasındaki ilişki

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### SUMMARY

**Objective:** Clinically, gamma-glutamyltransferase (GGT) activity is generally used as a diagnostic test for liver function, biliary tract pathologies, and alcohol consumption. GGT is the enzyme that manages the extracellular catabolism of the main antioxidant glutathione, thus increasing the oxidative stress or inflammatory state. Recently studies reported that GGT is related to cardiovascular mortality and morbidity independently alcohol consumption. Elevation of GGT in heart failure (HF), atrial fibrillation (AF), coronary artery disease, myocardial infarction, and metabolic syndrome is explained with inflammation and oxidative stress. Aim of this study, we have examined the relation between GGT and AF in reduced ejection fraction heart failure (HFrEF) patients group.

**Method:** Totally one hundred and sixty-three ischemic HF patients were included in the study retrospectively. Electrocardiographically 63 patients have AF (40 male, 23 females, mean age: 73±8 years) and 100 patients have normal sinus rhythm (75 male, 25 female, mean age: 71±7 years). All patients had the echocardiographic examination, ejection fraction (EF) > 40%, severe valvular heart disease, and nonischemic HF patients were excluded.

**Results:** Presence of hypertension, age, gender, dislipidemia history, diabetes, smoking condition, fasting glucose, and cholesterol levels were compared between two groups, and there were not statistically different ( $p > 0.05$  for all). However, serum GGT activity was increased in patients group with AF compared to those without AF (35(10-121) U/L versus 27(6-113)U/L,  $p=0.01$ ). The optimal cut-off GGT activity for AF patients were >23,5 IU/l with a sensitivity of 81% and a specificity of 46% (AUC =0.660, 95% CI=0.575 - 0.744)

**Conclusions:** In this study, serum GGT activity was concluded to be increased in HFrEF patients with AF compared to without AF group. More comprehensive studies should be planned to improve the clinical use of GGT in patients with HFrEF and to investigate the relationship between GGT and AF. **Keywords:** Gamma-glutamyltransferase, atrial fibrillation, heart failure, inflammation

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## ÖZET

**Amaç:** Klinik olarak, gamma-glutamyltransferaz (GGT) aktivitesi, genellikle karaciğer fonksiyonu, safra yolu patolojileri ve alkol tüketimi için tanısasal bir test olarak kullanılır. GGT, oksidatif stres veya enflamatuvar durumlarda artan ve önemli bir antioksidan glutatyonun hücre dışı katabolizmasında görev alan bir enzimdir. Son zamanlarda yapılan çalışmalar GGT'nin alkol tüketiminden bağımsız olarak kardiyovasküler mortalite ve morbidite ile ilgili olduğunu göstermiştir. GGT'nin kalp yetersizliğinde (KY), atriyal fibrilasyonda (AF), koroner arter hastalığında, miyokard enfarktüsünde ve metabolik sendromda yükselmesi, enflamasyon ve oksidatif stres ile açıklanmaktadır. Bu çalışmanın amacı, düşük ejeksiyon fraksiyonlu kalp yetersizliği (DEFKY) hastalarında GGT ile AF arasındaki ilişkiyi araştırmaktır.

**Yöntem:** Çalışmaya retrospektif olarak toplam yüz altmış üç iskemik KY hastası dahil edildi. Elektrokardiyografik olarak 63 hastada AF (40 erkek, 23 kadın, ortalama yaş:  $73 \pm 8$  yıl) ve 100 hastada normal sinüs ritmi (75 erkek, 25 kadın, ortalama yaş:  $71 \pm 7$  yıl) vardı. Tüm hastalarda ekokardiyografik inceleme yapıldı, ejeksiyon fraksiyonu (EF) > % 40, ciddi kalp kapak hastalığı ve iskemik olmayan KY hastaları dışlandı.

**Bulgular:** Hipertansiyon, yaş, cinsiyet, dislipidemi, diyabet, sigara, açlık glukozu ve kolesterol düzeyleri iki grup arasında karşılaştırıldı ve istatistiksel olarak farklı değildi (hepsi için  $p > 0.05$ ). Ancak, AF'li hasta grubunda serum GGT aktivitesi AF olmayanlara göre artmış olduğu görüldü (35 (10-121) U / L, 27 (6-113) U / L,  $p = 0.01$ ). AF hastaları için en uygun kesme GGT aktivitesi % 81 duyarlılık ve % 46 özgüllük ile  $> 23,5$  IU / l idi (AUC = 0.660, % 95 CI = 0.575 - 0.744).

**Sonuç:** Bu çalışmada serum GGT aktivitesinin, AF'li DEFKY hastalarında AF olmayan gruba kıyasla artmış olduğu sonucuna varıldı. DEFKY olan hastalarda GGT'nin klinik kullanımı ve GGT ile AF arasındaki ilişkiyi araştırmak için daha kapsamlı çalışmalar planlanmalıdır.

**Anahtar sözcükler:** Gama-glutamyltransferaz, atriyal fibrilasyon, kalp yetersizliği, inflamasyon

## INTRODUCTION

Chronic heart failure (HF) is a prevalent cause of mortality and morbidity, especially in developed countries. Neurohumoral activation, systemic inflammation, and oxidative stress are an important cornerstone of HF pathogenesis<sup>1</sup>. Atrial fibrillation (AF), the prevalence of approximately 3% in adults, is one of the most common cardiac arrhythmias, especially in HF patients, and its incidence increases with age<sup>2</sup>.

Gamma-glutamyltransferase (GGT) is normally found in the membranes of all cells except erythrocytes, in the serum and therefore in the plasma. An important antioxidant in mammals, glutathione is involved in extracellular catabolism. Serum GGT activity is elevated when inflammation and oxidative stress are elevated due to its role in antioxidative reactions. The elevation is parallel to increased of acute phase reactors. GGT activity has been associated with arterial hypertension, diabetes, metabolic syndrome, systemic inflammation, oxidative stress, embolic disease, stroke, arrhythmia, and cardiac death known as traditional cardiovascular risk factors and condition<sup>3</sup>. Serum GGT activity can be reversed with antioxidant vitamin and elevated with dietary heme iron<sup>4</sup>. Elevated GGT levels were associated with an increased risk of AF, especially in nonobese patients in a prospective large population-based study<sup>5</sup>. Increased GGT levels were associated with HF severity, and it was an independent predictor of heart transplantation and death<sup>1</sup>. Since inflammation

and oxidative stress increase in both HF and AF, it is thought that inflammation and oxidative stress can be increased and GGT will be higher in AF patients with HF.

Our study aimed to examine whether serum GGT activity is an indicator of inflammation and oxidative stress in HF patients with and without AF.

## MATERIAL AND METHODS

Patients with ischemic origin HF with EF who admitted our cardiology clinic between January 2016 and April 2018 reviewed retrospectively. A total of 163 patients with heart failure clinic defined as the New York Heart Association (NYHA) Functional Class I-IV patients with an ejection fraction (EF) of < 40% were analyzed in the study. The study was approved by the local Ethics Committee for Human Research.

Patients demographic, clinical, medical data, and laboratory test results were obtained from the hospital database based on the records. The clinical and demographic parameters of the patients were collected as follows: age, gender, hypertension, diabetes mellitus, hyperlipidemia, and smoking. The presence of hypertension was accepted as patients using antihypertensive drugs or measuring at least two measures of blood pressure 140/90 mmHg and above. Patients with diabetes mellitus, known diabetes mellitus (patients using antidiabetic drugs), patients whose blood sugar was controlled by dieting, or patients whose blood sugar was 126 mg/dl after an eight-

hour fasting. Known hypercholesterolemia, treated with antihyperlipidemic drug or fasting or nonfasting serum cholesterol concentrations higher than 200 mg/dL were defined as hypercholesterolemia.

Clinical history of coronary heart disease (CAD), pathologic Q waves on electrocardiogram, ischemia evidence in the treadmill stress test, shown segmental left ventricular dyskinesia or akinesia on echocardiogram, or luminal narrowing of any epicardial coronary arteries >50% on a coronary angiogram whom coronary angiography was performed previously was defined as coronary heart disease. Smoking is still considered to be smokers who are currently smoking or who have quit within the past year.

Patients with EF  $\geq$ 40% on echocardiography, non-ischemic HF, acute coronary syndrome, acute heart failure, valvular heart disease (moderate-to-severe), presence of pacemaker, hepatic or renal failure (>2-fold of normal serum alanine aminotransferase and aspartate aminotransferase levels; >1.5 mg/dL serum level of creatinine), hypothyroidism or hyperthyroidism, presence of acute or chronic infection, malignancy, connective tissue disease, stroke history, alcohol use, hematological, respiratory, immunological, inflammatory disorders were excluded from the study.

The blood samples were drawn under appropriate conditions after 8 hours of fasting. Beckman Coulter Synchron LX20 (Brea, CA, USA) autoanalyzer and its original kits were used to measure GGT activity and other biochemical tests.

The transthoracic echocardiographic evaluation was done with the Vivid seven cardiac ultrasonography system (GE Healthcare, Medical Systems) by experienced echocardiographers, with 2.5- to 5-MHz probes. The modified Simpson method was used to calculate the left ventricular ejection fraction (LVEF) and chamber sizes according to recent guidelines<sup>6</sup>.

Statistical analysis was performed using the SPSS 16.0 packet computer program (SPSS Inc. Chicago, IL, USA), and the value of P <0.05 was approved statistically significant. The Kolmogorov-Smirnov test was used to confirm the normality of the distribution of continuous variables. Continuous variables were expressed as

the mean  $\pm$  standard deviation in the presence of normal distribution and median (min-max) in the presence of skewed distribution, and categorical variables as percentages. Comparisons between groups for categorical variables, the chi-square or Fisher's exact test were used. Continuous variables were compared using the independent samples t-test for normally distributed variables and Mann-Whitney U test for skewed distributed variables. Receiver operator characteristic (ROC) curve analysis was performed to identify the optimal cut-off point of GGT (at which sensitivity and specificity would be maximum) for the prediction of AF. The area under the curve (AUC) with 95% confidence interval was estimated in the prediction of AF. The optimal cut-off value of GGT was identified as the value parallel with the highest sum of sensitivity and specificity-1.

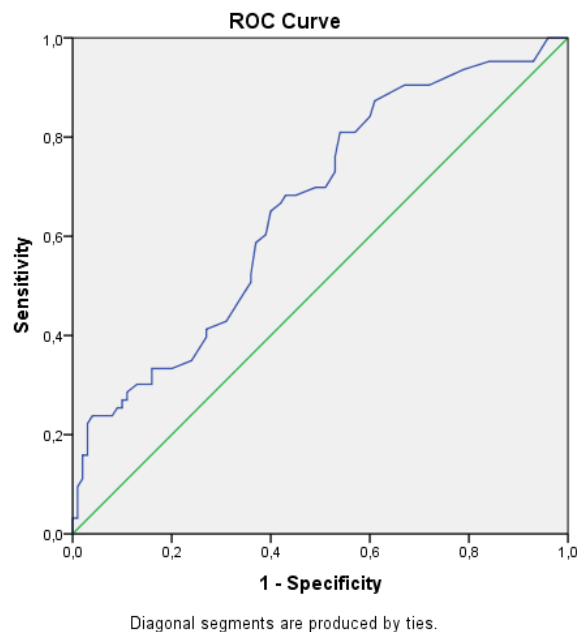
## RESULTS

A total of 163 HF patients were included in the study and compared, 63 patients were AF (23 women, 40 men, mean age 73  $\pm$  eight years) and 100 patients (25 women, 75 men, mean age 71  $\pm$  seven years) (p=0.36) were normal sinus rhythm. The demographic characteristics, biochemical, and echocardiographic values of the patients are shown in Table 1. There was no statistically significant difference between the two groups in terms of age, gender, hypertension, the presence of diabetes mellitus, and smoking status (p> 0.05). There was no statistically significant difference between groups in terms of biochemical tests, including glucose, total cholesterol, triglyceride, HDL-cholesterol, LDL-cholesterol, aspartate aminotransferase, and alanine aminotransferase (p> 0.05). In the AF group, the elevation of serum GGT values was statistically significant (35(10-121)U/L vs. 27(6-113) U/L, p = 0.01). There was no statistically significant difference between groups in terms of ejection fractions (p=0.16) but left atrial diameter (LA) (43 $\pm$ 6 vs. 38 $\pm$ 5, p <0.001) and left ventricular end-diastolic diameter (LVEDD) (56 $\pm$ 7 vs. 52 $\pm$ 6, p=0.001) were significantly higher in the AF group. In the Receiver operating characteristic analysis, the optimal cut-off GGT activity in patients with AF was >23.5 IU/l with a sensitivity of 81% and a specificity of 46% (AUC =0.660, 95% CI=0.575 - 0.744, p=0.001)(Figure 1.).

**Table1:** Baseline characteristics of the patients.

Variables	Patients With Normal Sinus Rhythm (n:100)	Patients With Atrial Fibrillation (n:63)	P Values
Mean age (years)	71±7	73 ±8	0.36
Gender, male, n (%)	75(%75)	40(%64)	0.12
Hypertension, n (%)	81(%81)	53(%84)	0.60
Diabetes mellitus, n (%)	20(%20)	20(%31)	0.15
Hyperlipidemia, n (%)	63(%63)	46(%73)	0.18
Current smoking, n (%)	52(%52)	33(%53)	0.80
White blood cell, (x 10 <sup>3</sup> /μL)	7.4±1.9	7.7±1.8	0.34
Hemoglobin (g/dl)	14±1.8	13±1.3	0.17
Platelet ( 10 <sup>3</sup> /mL)	219(129-391)	225(108-388)	0.69
Glucose, (mg/dL)	101(68-208)	105(71-274)	0.19
Blood urea nitrogen (mg/dL)	17(7-40)	19(6-47)	0.64
Creatinine (mg/dl)	1.01±0.1	1.01±0.2	0.84
Total cholesterol (mg/dL)	158(84-307)	161(86-279)	0.59
Triglyceride (mg/dL)	98(40-248)	84(15-350)	0.44
HDL-cholesterol (mg/dL)	34(13-62)	33(15-69)	0.12
LDL-cholesterol (mg/dL)	105(36-215)	107(35-185)	0.79
AST (IU/L)	21(12-160)	24(13-173)	0.22
ALT (IU/l)	17(7-71)	19(5-155)	0.30
GGT (IU/l)	27(6-113)	35(10-121)	0.01
Left ventricle ejection fraction (%)	35±5.9	33±6.4	0.16
Left atrial diameter, mm	3.8±0.5	4.3±0.6	<0.001
LVEDD, mm	5.2±0.6	5.6±0.7	0.001

AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; GGT: Gamma-glutamyl transferase; HDL: High-density lipoprotein; LDL: Low-density lipoprotein; LVEDD: Left ventricular end diastolic diameter



**Figure 1:** Receiver operating characteristic (ROC) curve for gamma-glutamyl transferase (GGT) activity in patients with AF.

## DISCUSSION

GGT is an essential enzyme that plays an important role in the metabolism of glutathione, the most important antioxidant produced in humans cell. Serum GGT activity is known to be a marker of oxidative stress<sup>3</sup>. These study findings revealed that GGT was related to AF in HF<sub>rEF</sub> patients. Previous studies showed that GGT levels were associated with both HF<sup>1</sup> and AF<sup>7,8</sup> separately. However, serum GGT activity is not well analyzed in AF patients with HF<sub>rEF</sub>.

In a routine health screening, GGT is a biochemical parameter that is easily accessible, inexpensive, highly sensitive, and clinically diagnostic for hepatic, biliary diseases, and alcohol consumption. Serum GGT activity has also been associated with diet. Dietary components containing plant foods and fruits were negatively associated with serum GGT activity, but meat consumption was positively associated<sup>9</sup>. Aside this classical well knew, the importance of GGT in anti-inflammatory and antioxidant reactions were determined in many studies such as hypertension, diabetes, metabolic syndrome, HF, AF, arrhythmias, stroke, CHD and mortality<sup>1,7,10-14</sup>.

HF and AF comorbidity are common, and one can be the cause or result of the other. The presence of one can trigger the other, and coexistence worsens the prognosis. In both conditions, age, hypertension, valvular disease, myocardial infarction, and genetic causes are common risk factors<sup>15</sup>.

AF is one of the most common cardiac arrhythmias with increasing prevalence with age and rising to 10% by the age of 80 years<sup>16</sup>. The inflammatory process plays an important role in the pathogenesis of AF<sup>16,17</sup>. GGT is known as a marker of oxidative stress, which plays an important role in the defense system<sup>15</sup>. Large, prospective, community-based cohort The Atherosclerosis Risk in Communities (ARIC) study showed that elevated GGT levels associated with AF incidence even at in the normal range during mean follow-up 12 years<sup>7</sup>. A Korean nationwide population-based study included 266550 patients during a median 8-year follow-up period and reported that 5034 patients (1.9%) had new AF patients. The elevation of GGT levels was associated with AF, especially in the non-obese population. Furthermore, the intensity elevation of GGT levels was related to the occurrence of AF. However, there was no relationship in the obese population<sup>5</sup>.

GGT levels were found high and associated with disease severity in patients with both ischemic and non-ischemic chronic heart failure. Poelzl et al. followed up 1053 consecutive white patients for mean 34.4 months and evaluated for death from any cause or heart transplantation. The GGT levels were found an independent predictor of death or heart transplantation. Also, high GGT levels were positively associated with increased levels of NT-proBNP, uric acid, and C-reactive protein<sup>1</sup>.

GGT activity was evaluated by the British Regional Heart Study in 7613, middle-aged British men. The patients followed 11.5 years, and serum GGT activity was declared that was associated with cardiovascular risk factors and all-cause mortality even within the normal limit (GGT >24 U/L)<sup>18</sup>. In the Framingham Heart Study, 3451 patients were followed up for 19 years, and the highest quartile of GGT was detected in 67% of the increased incidence of CVD. Serum GGT also predicted the onset of metabolic syndrome and death<sup>19</sup>. GGT activity was associated with CV risk factors and increased CV mortality in prospectively designed Austrian and Finnish study<sup>20,21</sup>.

Elevation of GGT was associated with the development of hypertension, both diabetic and non-diabetic patients. GGT elevation was significant for systolic blood pressure, but there was no significance for diastolic blood pressure in diabetic patients<sup>11</sup>. Serum GGT activity has been associated with microalbuminuria in diabetic or hypertensive patients, and an effective mechanism is thought to be oxidative mechanisms<sup>10</sup>. Serum GGT activity associated with vascular events and stroke<sup>12-14</sup>. The relationship between GGT activity and risk factors that increase cardiovascular events can be explained by oxidative stress and inflammation<sup>4</sup>.

Increased of GGT was associated with both ischemic and hemorrhagic stroke in the age and sex-adjusted population. The association didn't attenuate even if the adjustment of confounding variables such as drug use, history of myocardial infarction, total cholesterol, and diabetes mellitus<sup>13</sup>. Serum GGT concentration was associated with intracerebral hemorrhage in men, the risk of subarachnoid hemorrhage in women, and increased risk of ischemic stroke in both genders<sup>14</sup>.

**Study Limitations:** There were some limitations to our study. The study design was retrospective, the number of patients was relatively small, and all of the patients were the single center. That's

why the results cannot be generalized of all HF patients. Furthermore, since our study is not prospective, it is not clear whether the increase in GGT levels is the cause or result of AF development.

GGT activity and its relation on AF in HFrEF patients should be assessed with prospectively designed and long-term follow-up study in the bigger number of participants. In prospective studies, natriuretic peptides, inflammatory markers such as cytokines and interleukins, as well as GGT activity, should be included in the study. Confirmation of AF relationship with GGT activity and its relationship with mortality may provide a significant contribution to the prognosis and survival of HFrEF patients. GGT was found to be elevated in AF patients with ischemic HFrEF, but further extensive studies are needed to use as routine examinations.

## CONCLUSION

Patients with AF had higher serum GGT activity in patients with HFrEF. But this study does not provide information that elevated GGT levels are cause or outcome of AF.

### Declaration of Conflicting Interests

The authors declared no potential conflicts of interest concerning the research, authorship, and publication of this article.

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