Kardiologia Polska 2014; 72, 8: 735–739; DOI: 10.5603/KP.a2014.0048 ISSN 0022–9032

ARTYKUŁ ORYGINALNY / *ORIGINAL ARTICLE*

Serum gamma-glutamyl transferase levels and in-hospital mortality in patients with acute heart failure

Murat Turfan, Abdurrahman Tasal, Ercan Erdogan, Mehmet Akıf Vatankulu, Parviz Jafarov, Osman Sonmez, Gokhan Ertas, Ahmet Bacaksız, Mehmet Ergelen, Omer Goktekın

Department of Cardiology, Bezmialem Vakif University, Turkey

Abstract

Background: Acute heart failure (AHF) is a major cause of hospitalisation, morbidity and mortality worldwide. Gamma-glutamyl transferase (GGT) is an enzyme responsible for the extracellular catabolism of antioxidant glutathione and a potential risk indicator of cardiac mortality. Limited data exists on the prognostic value of circulating levels of GGT in patients hospitalised due to AHF.

Aim: To study the association between baseline GGT activity and in-hospital mortality in AHF patients.

Methods: The study cohort consisted of 183 AHF patients with left ventricular ejection fraction (LVEF) < 50%. The primary endpoint was in-hospital mortality. Patients were divided into two groups according to in-hospital mortality. The relationship between GGT activity and in-hospital mortality was tested using logistic regression models, adjusting for clinical characteristics and echocardiographic findings.

Results: After adjustment for possible confounders, GGT level was significantly related (OR 1.056, 95% CI 1.018–1.096, p = 0.04) to in-hospital mortality

Conclusions: Elevated GGT activity is an independent predictor of short-term mortality in patients with AHF and reduced LVEF.

Key words: gamma-glutamyl transferase, in-hospital mortality, acute heart failure

Kardiol Pol 2014; 72, 8: 735–739

INTRODUCTION

Acute heart failure (AHF) is a major cause of hospitalisation, morbidity and mortality worldwide [1]. Therefore, early identification of patients with a high risk of AHF is important. Many markers are now firmly established as independent prognostic factors for AHF and are classified based on their mechanism of action: neuro-endocrine activation, systemic inflammation, oxidative stress, metabolism and renal dysfunction [2–4]. Oxidative stress occurs due to a local imbalance between antioxidant defence mechanisms and the reactive oxygen species, which is thought to be a contributor to HF [5].

Serum gamma-glutamyl transferase (GGT) is an ectoplasmic enzyme responsible for the extracellular catabolism of the antioxidant glutathione [6]. Increased activity of GGT may be linked to greater oxidative stress. Therefore, the relationship between various diseases and GGT levels has been investigated in several studies [7–11]. A large Austrian study showed for the first time the prognostic value of GGT with regard to fatal events caused by congestive heart failure (CHF) in apparently healthy subjects [12]. Other studies have examined the association between HF and elevated GGT activity [13–15]. However, limited data exists on the prognostic value of circulating levels of GGT in patients hospitalised due to AHF. The aim of the present study was to investigate this issue.

METHODS

Subjects from our centre who were hospitalised due to AHF between January 2010 and July 2013 were eligible for this analysis. The data collection included demographic and baseline clinical characteristics, past medical history, echocardio-

Address for correspondence:
Dr Murat Turfan, Department of Cardiology, Bezmialem Vakif University, Turkey, tel: +905053197199, e-mail: turphan@gmail.com
Received: 20.06.2013 **Accepted:** 30.01.2014 **Available as AoP:** 10.02.2014

graphy data and in-hospital outcomes. Included patients were required to be characterised by the following: progressive dyspnoea associated with clinical signs of pulmonary congestion that required hospitalisation and a left ventricular ejection fraction (LVEF) < 50%. Participants with known evidence of acute myocardial ischaemia, sepsis, history of cancer, alcohol intake, haematologic disease, chronic liver diseases, renal failure and other extracellular fluid-increasing diseases (e.g. hypothyroidism) were excluded. The hospital's institutional review board approved the study.

An echocardiographic examination was undertaken as soon as clinical stability of the patients was achieved after admission to our intensive care unit. All patients were evaluated by two-dimensional echocardiography using the Vivid 5 system (General Electric) with a 2.5–5 MHz transducer. LVEF was measured using the biplane Simpson rule.

All venous blood samples were obtained upon patient presentation before administration of drugs. Serum GGT activity was measured using the enzymatic calorimetric test at 37°C and l-gamma-glutamyl-3-carboxy-4-nitroanilide was used as a substrate. To perform this evaluation, the Roche/Hitachi analyser (Mannheim, Germany) was used. In our laboratory, the normal reference value of GGT levels for a healthy individual was 8–49 U/L for a male, 5–36 U/L for a female.

Statistical analysis

All analyses were performed using SPSS V 15.0 for Windows (SPSS, Chicago, IL, USA). The distribution of continuous variables for normality was tested with one-sample Kolmogorov-Smirnov test and data is presented as mean ± standard deviation (SD). Categorical variables are reported as frequencies and group percentages. Independent sample t-test was used to compare groups. To find the optimal values for GGT to detect hospital mortality, the receiver operating characteristics curve was used. Backward logistic regression analyses were performed to assess independent effects. Odds ratios (OR) and corresponding 95% confidence intervals (CI) were reported for each covariate. For all tests, which were two-sided, a p value < 0.05 was considered as indicating statistically significant differences.

RESULTS

Subjects who fulfilled all the inclusion, and none of the exclusion, criteria (183 subjects) were registered for the study. Table 1 presents the baseline clinical characteristics according to in-hospital mortality. Group 1 consisted of patients who died in the hospital. Compared to the other group, Group 1 included older individuals. Atrial fibrillation was more frequently monitored at admission in Group 1, and in addition this group was characterised by higher GGT levels and lower LVEF values.

In the receiver operating characteristics curve analysis, the value for GGT levels to detect in-hospital mortality with a sensitivity of 68.8% and specificity of 62.8% was 40.5 U/L. The area under the curve was 0.712 (Fig. 1).

Table 1. Baseline characteristics of patients

	Group 1	Group 2	P
N	16	167	
Age	76 ± 8	68 ± 9	0.002
Male	43.8%	65.9%	0.07
Ischaemic heart failure	56.3%	61.1%	0.450
Hypertension	62.5%	58.1%	0.475
Diabetes mellitus	56.3%	48.5%	0.371
Hyperlipidaemia	56.3%	38.3%	0.129
History of percutaneous intervention	43.8%	97.5%	0.469
History of coronary artery bypass grafting	18.8%	16.8%	0.532
Atrial fibrillation	62.5%	31.1%	0.016
NYHA class III or IV	81.3	72.5	0.353
Presentation of pulmonary oedema	31.3	25.3	0.398
Use of beta-blocker	37.5%	41.9%	0.475
Use of ACEI	75%	63.9%	0.274
Use of spironolactone	25%	33.5%	0.274
Presence of ICD or CRT	25	22.8	0.523
Use of diuretics	43.8%	41.9%	0.544
Ejection fraction [%]	29 ± 6	33 ± 7	0.009
Haemoglobin [g/dL]	12.3 ± 1.6	12.2 ± 1.8	0.734
White blood cell count [× $10^3/\mu L$]	9.7 ± 4.1	8.2 ± 2.9	0.076
Serum Na levels [mmol/L]	132 ± 4	133 ± 5	0.200
Serum creatinine [mg/dL]	1.4 ± 0.8	1.2 ± 0.6	0.203
Serum alanine aminotransferase levels [U/L]	33 ± 13	30 ± 12	0.324
Serum aspartate aminotransferase levels [U/L]	33 ± 13	29 ± 12	0.353
International normalisation rate values	1.8 ± 0.7	1.6 ± 0.7	0.352
Serum total bilirubin [mg/dL]	0.75 ± 0.3	0.8 ± 0.2	0.405
Serum GGT levels [U/L]	46 ± 14	35 ± 16	0.008

NYHA — New York Heart Association; ACEI — angiotensin converting enzyme inhibitors; ICD — implantable cardioverter-defibrillator; CRT — cardiac resynchronisation therapy device; GGT — gamma-glutamyl transferase

The patients were also divided into two groups according to GGT levels. Group H consisted of patients with GGT levels greater than 40.5 U/L, and Group L consisted of the remaining patients. Group H was associated with a higher mortality ratio (15.3% vs. 4.6%).

We also performed univariate logistic regression including serum GGT levels, serum creatinine, LVEF, age and other

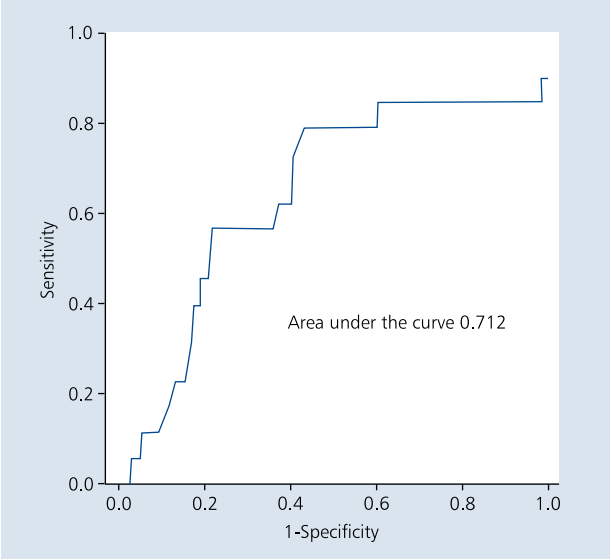

Figure 1. Receiver operating characteristics curve for gamma--glutamyl transferase levels

Table 2. Univariate analysis for risk factors

	Odds ratio	95% CI	P
Age	1.103	1.034–1.176	0.003
Male	2.481	0.879–7.007	0.086
Hypertension	1.203	0.418–3.464	0.732
Diabetes mellitus	1.365	0.486–3.836	0.555
Hyperlipidaemia	2.069	0.734–5.830	0.169
Ischaemic heart failure	0.819	0.291–2.308	0.706
Atrial fibrillation	3.585	1.238–10.381	0.019
NYHA class III or IV	1.598	0.435–5.871	0.480
Pulmonary oedema	1.342	0.441–4.086	0.635
Serum Na levels	0.927	0.825–1.042	0.203
Serum creatinine	1.643	0.758–3.563	0.208
Gamma-glutamyl transferase	1.043	1.009–1.078	0.012
Haemoglobin	1.053	0.786–1.414	0.732
White blood cell count	1.140	0.984–1.321	0.081
Ejection fraction	0.902	0.832–0.977	0.012

CI — confidence interval; NYHA — New York Heart Association

Table 3. Results of stepwise logistic regression analysis with in-hospital mortality as dependent variable

Variables	Odds ratio	P	95% CI
Step 1			
Ejection fraction	0.870	0.008	0.785–0.964
Age	1.087	0.017	1.015–1.064
GGT	1.057	0.017	1.015–1.164
Atrial fibrillation	2.600	0.119	0.785–8.663
Step 2			
Ejection fraction	0.876	0.01	0.793–0.969
Age	1.099	0.05	1.029–1.173
GGT	1.056	0.04	1.018–1.096

CI — confidence interval; GGT — gamma-glutamyl transferase

risk factors for mortality (Table 2). In multivariate analyses for in-hospital mortality, GGT activity, LVEF value, atrial fibrillation at admission and age were analysed with the multivariate logistic regression model. High GGT levels (OR 1.056, 95% CI 1.018–1.096, p = 0.04) were independent predictors of in-hospital mortality (Table 3).

DISCUSSION

This study demonstrates that high GGT activity predicts in-hospital mortality in patients hospitalised due to AHF, independently of established risk factors. To the best of our knowledge, this is the first study to examine this relationship.

Reactive oxygen species production leads to a decrease of glutathione, stimulates the expression of GGT, and subsequently elevates serum GGT levels [6]. Increased GGT activity may take place in the antioxidant defence mechanisms. A Korean study found that the elevation of serum GGT is correlated with serum C-reactive protein and white blood count [16]. In addition, GGT activity may contribute to the development of atherosclerosis catalysing the oxidation of low-density lipoprotein [17]. Stojakovic et al. [18] found that serum GGT activity was positively associated with male gender and markers of metabolic syndrome. Clinical and prognostic impact of GGT activity has been shown in patients with diabetes mellitus and hypertension [8, 19, 20]. As a result, GGT activity has an important role in the pathogenesis of cardiovascular diseases and may be used as a marker of risk of cardiovascular events [21].

Several studies have investigated the relation of GGT activity and mortality in cardiovascular diseases. Wannamethee et al. [22] showed that GGT levels were strongly associated with all-cause mortality, due to a significant increase in deaths from ischaemic heart disease. Emdin et al. [9] found a significant positive association between serum GGT activity and the incidence of cardiac death and infarction in ischaemic patients with angiographically documented atherosclerotic coronary artery disease. A subgroup analysis of the Framingham Heart Study found that higher GGT activity predicted cardiovascular disease and mortality [23]. Similar results were observed in a meta-analysis study [24].

Increased GGT levels observed in HF can be explained by the relationship between oxidative stress, inflammation and GGT as previously mentioned. In addition, the liver damage caused by congestion may increase the levels of GGT. However, in a study comparing the levels of GGT before and after heart transplantation, this phenomenon was not con-

firmed [25]. Moreover, GGT activity is a weaker predictor of liver damage than alanine aminotransferase [26].

Ruttmann et al. [12] found that GGT activity was strongly and independently associated with cardiovascular mortality. This study showed for the first time that high GGT activity increased mortality in HF. Ess et al. [13] found that GGT activity was predictive of death and heart transplantation in stable HF. A subgroup analysis of the EVEREST study found that baseline and in-hospital changes in albumin and total bilirubin provide additional prognostic value. However, this relationship was not shown for GGT activity [27]. Another prospective study found that higher serum GGT levels in the normal range were connected with an increased risk of developing HF [14]. Similarly in our study, high GGT levels in the normal range were associated with mortality. In addition, aspartate aminotransferase and alanine aminotransferase levels were not different in groups with high and low levels of GGT. This difference in the levels of GGT activity may indicate oxidative stress, but not hepatic congestion. In contrast to previous studies, our study was only conducted on AHF patients and alcohol consumption was an exclusion criterion.

Limitation of the study

This study is limited by its observational nature and retrospective character. The second limitation of our study was the lack of other markers of oxidative stress such as malondialdehyde, and superoxide dismutase. In addition, we did not measure markers of neurohormonal activation and systemic inflammation. Finally, we have not analysed the pharmacotherapy.

CONCLUSIONS

As a result of our study, we found that high GGT levels predict mortality in AHF patients. Therefore, adverse effects of oxidative stress have an influence on prognosis. In addition, early identification of high-risk patients and treatment options which are more advanced and intense is vital. Moreover, the effects of oxidative stress may be neutralised by pharmacological methods. Further research in this field is needed.

Conflict of interest: *none declared*

References

1. Cleland JG, Swedberg K, Follath F et al. The EuroHeart Failure survey programme: a survey on the quality of care among patients with heart failure in Europe. Part 1: patient characteristics and diagnosis. Eur Heart J, 2003; 24: 442–463.
2. Zairis MN, Patsourakos NG, Tsiaousis GZ et al. Plasma asymmetric dimethylarginine and mortality in patients with acute decompensation of chronic heart failure. Heart, 2012; 98: 860–864.
3. Gheorghiade M, Pang PS. Acute heart failure syndromes. J Am Coll Cardiol, 2009; 53: 557–573.
4. Avellino A, Collins SP, Fermann GJ. Risk stratification and short-term prognosis in acute heart failure syndromes: a review of novel biomarkers. Biomarkers, 2011; 16: 379–392.
5. Tsutsui H, Kinugawa S, Matsushima S. Oxidative stress and heart failure. Am J Physiol Heart Circ Physiol, 2011; 301: H2181–H2190.
6. Whitfield JB. Gamma-glutamyl transferase. Crit Rev Clin Lab Sci, 2001; 38: 263–355.
7. Acikgoz N, Ermis N, Yagmur J et al. Elevated oxidative stress markers and its relationship with endothelial dysfunction in Behcet disease. Angiology, 2011; 62: 296–300.
8. Kengne AP, Czernichow S, Stamatakis E et al. Gamma-glutamyltransferase and risk of cardiovascular disease mortality in people with and without diabetes: pooling of three British Health Surveys. J Hepatol, 2012; 10.1016/j.jhep.2012.06.034.
9. Emdin M, Passino C, Michelassi C et al. Prognostic value of serum gamma-glutamyl transferase activity after myocardial infarction. Eur Heart J, 2001; 22: 1802–1807.
10. Abdul-Rasheed OF, Al-Shamma GA, Zillo BH. Serum gamma-glutamyltransferase as oxidative stress marker in pre-and postmenopausal Iraqi women. Oman Med J, 2010; 25: 286–288.
11. Ulus T, Yildirir A, Sade LE et al. [Serum gamma-glutamyltransferase activity: a new marker for coronary artery bypass graft disease]. Turk Kardiyol Dern Ars, 2011; 39: 205–213.
12. Ruttmann E, Brant LJ, Concin H et al. Gamma-glutamyltransferase as a risk factor for cardiovascular disease mortality: an epidemiological investigation in a cohort of 163,944 Austrian adults. Circulation, 2005; 112: 2130–2137.
13. Ess M, Mussner-Seeber C, Mariacher S et al. gamma-glutamyltransferase rather than total bilirubin predicts outcome in chronic heart failure. J Card Fail, 2011; 17: 577–584.
14. Dhingra R, Gona P, Wang TJ et al. Serum gamma-glutamyl transferase and risk of heart failure in the community. Arterioscler Thromb Vasc Biol, 2010; 30: 1855–1860.
15. Poelzl G, Eberl C, Achrainer H et al. Prevalence and prognostic significance of elevated gamma-glutamyltransferase in chronic heart failure. Circ Heart Fail, 2009; 2: 294–302.
16. Lee YJ, Kim JK, Lee JH et al. Association of serum gamma-glutamyltransferase with C-reactive protein levels and white blood cell count in Korean adults. Clin Chem Lab Med, 2008; 46: 1410–1415.
17. Paolicchi A, Minotti G, Tonarelli P et al. Gamma-glutamyl transpeptidase-dependent iron reduction and LDL oxidation: a potential mechanism in atherosclerosis. J Investig Med, 1999; 47: 151–160.
18. Stojakovic T, Scharnagl H, Trauner M et al. Serum gamma-glutamyl transferase and mortality in persons undergoing coronary angiography: the Ludwigshafen Risk and Cardiovascular Health Study. Atherosclerosis, 2010; 208: 564–571.
19. Henningsen NC, Janzon L, Trell E. Influence of carboxyhemoglobin, gamma-glutamyl-transferase, body weight, and heart rate on blood pressure in middle-aged men. Hypertension, 1983; 5: 560–563.
20. Kim NH, Huh JK, Kim BJ et al. Serum gamma-glutamyl transferase level is an independent predictor of incident hypertension in Korean adults. Clin Exp Hypertens, 2012; 10.3109/10641963.2012.665539.
21. Turgut O, Yilmaz MB, Yalta K et al. Gamma-glutamyltransferase as a useful predictor for cardiovascular risk: clinical and epidemiological perspectives. Atherosclerosis, 2009; 202: 348–349.
22. Wannamethee G, Ebrahim S, Shaper AG. Gamma-glutamyltransferase: determinants and association with mortality from ischemic heart disease and all causes. Am J Epidemiol, 1995; 142: 699–708.
23. Lee DS, Evans JC, Robins SJ et al. Gamma-glutamyl transferase and metabolic syndrome, cardiovascular disease, and mortality risk: the Framingham Heart Study. Arterioscler Thromb Vasc Biol, 2007; 27: 127–133.
24. Fraser A, Harris R, Sattar N et al. Gamma-glutamyltransferase is associated with incident vascular events independently of alcohol intake: analysis of the British Women's Heart and Health Study and Meta-Analysis. Arterioscler Thromb Vasc Biol, 2007; 27: 2729–2735.
25. Dichtl W, Vogel W, Dunst KM et al. Cardiac hepatopathy before and after heart transplantation. Transpl Int, 2005; 18: 697–702.
26. Kotronen A, Yki-Jarvinen H. Fatty liver: a novel component of the metabolic syndrome. Arterioscler Thromb Vasc Biol, 2008; 28: 27–38.
27. Ambrosy AP, Vaduganathan M, Huffman MD et al. Clinical course and predictive value of liver function tests in patients hospitalized for worsening heart failure with reduced ejection fraction: an analysis of the EVEREST trial. Eur J Heart Fail, 2012; 14: 302–311.

Aktywność gamma-glutamylotransferazy w surowicy a śmiertelność wewnątrzszpitalna u chorych z ostrą niewydolnością serca

Murat Turfan, Abdurrahman Tasal, Ercan Erdogan, Mehmet Akıf Vatankulu, Parviz Jafarov, Osman Sonmez, Gokhan Ertas, Ahmet Bacaksız, Mehmet Ergelen, Omer Goktekın

Department of Cardiology, Bezmialem Vakif University, Turcja

Streszczenie

Wstęp: Ostra niewydolność serca (AHF) jest główną przyczyną hospitalizacji, chorobowości i zgonów na świecie. Gamma-glutamylotransferaza (GGT) to enzym odpowiedzialny za pozakomórkowy katabolizm przeciwutleniacza — glutationu — i potencjalny wskaźnik ryzyka zgonu sercowego. Dane dotyczące wartości prognostycznej aktywności krążącej GGT u chorych hospitalizowanych z powodu AHF są ograniczone.

Cel: Autorzy analizowali związek między wyjściową aktywnością GGT a śmiertelnością wewnątrzszpitalną wśród pacjentów z AHF.

Metody: Badana grupa obejmowała 183 chorych na AHF z frakcją wyrzutową lewej komory (LVEF) wynoszącą < 50%. Głównym punktem końcowym badania był zgon wewnątrzszpitalny. Chorych podzielono na dwie grupy w zależności od śmiertelności wewnątrzszpitalnej. Korelacje między aktywnością GGT a śmiertelnością wewnątrzszpitalną analizowano, używając modeli regresji logistycznej skorygowanych względem parametrów demograficznych i wyników badania echokardiograficznego.

Wyniki: Po skorygowaniu względem możliwych czynników zakłócających stężenie GGT wiązało się w sposób statystycznie istotny (OR 1,056; 95% CI 1,018–1,096; p = 0,04) ze śmiertelnością wewnątrzszpitalną.

Wnioski: Zwiększona aktywność GGT jest niezależnym czynnikiem predykcyjnym śmiertelności w krótkoterminowej obserwacji u chorych z AHF i ze zmniejszoną LVEF.

Słowa kluczowe: gamma-glutamylotransferaza, śmiertelność wewnątrzszpitalna, ostra niewydolność serca

Kardiol Pol 2014; 72, 8: 735–739

Adres do korespondencji:
Dr Murat Turfan, Department of Cardiology, Bezmialem Vakif University, Turkey, tel: +905053197199, e-mail: turphan@gmail.com
Praca wpłynęła: 20.06.2013 r. **Zaakceptowana do druku:** 30.01.2014 r. **Data publikacji AoP:** 10.02.2014 r.