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Prevalence of elevated gamma-glutamyltransferase (GGT) and prognostic significance of GGT in chronic heart failure

Gerhard Poelzl, Christian Eberl, Helene Achrainger, Jakob Doerler, Otmar Pachinger, Matthias Frick and Hanno Ulmer

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1 **Prevalence of elevated gamma-glutamyltransferase (GGT) and prognostic significance**
2 **of GGT in chronic heart failure**

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4 **Poelzl: Gamma-glutamyltransferase in heart failure**

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6 Poelzl Gerhard, MD, Assoc. Prof., FESC, Clinical Division of Cardiology, Innsbruck Medical
7 University, Austria

8 Eberl Christian, MD, Clinical Division of Cardiology, Innsbruck Medical University, Austria

9 Achrainer Helene, Clinical Division of Cardiology, Innsbruck Medical University, Austria

10 Doerler Jakob, MD, Clinical Division of Cardiology, Innsbruck Medical University, Austria

11 Pachinger Otmar, MD, Prof., FESC, FACC, Clinical Division of Cardiology, Innsbruck
12 Medical University, Austria

13 Frick Matthias, MD, Assoc. Prof., Clinical Division of Cardiology, Innsbruck Medical
14 University, Austria

15 Ulmer Hanno, PhD, Prof., Department of Medical Statistics, Informatics and Health
16 Economics, Innsbruck Medical University, Austria

17

18 Address for correspondence:

19 Poelzl Gerhard, MD, Assoc. Prof., FESC, Clinical Division of Cardiology, Innsbruck Medical
20 University, Anichstrasse 35, 6020 Innsbruck

21 Fax: 0043 512 504 23264

22 Tel: 0043 512 504 81318

23 Gerhard.poelzl@uki.at

24

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1 **Abstract**

2 Background:

3 Serum gamma-glutamyltransferase (GGT) is associated with incident cardiovascular diseases
4 and is a potential risk factor for disease mortality. We aimed to investigate the relevance of
5 circulating GGT in chronic heart failure.

6 Methods and results:

7 From 2000 to 2007 clinical and laboratory variables of 1033 consecutive outdoor heart failure
8 patients were evaluated. Follow-up (mean 34.4 months) was available in 998 patients. The
9 endpoint was defined as death from any cause or heart transplantation. A forward stepwise
10 Cox proportional hazards regression model for sex-stratified data was used.

11 Prevalence of elevated GGT was 42.9% in men (GGT >65 U/l) and 50.2% in women (GGT
12 >38 U/L), which was higher than for sex and age-matched healthy subjects (18.6% in men,
13 19.2% in women) derived from a large historical control group. GGT was associated with
14 severity of heart failure as assessed by NYHA class, LV ejection fraction, and NT-proBNP.

15 The endpoint was recorded in 302 patients. Compared to the lowest GGT quintile, sex-
16 stratified HR for patients in the highest quintile was 2.88 (1.99 – 4.17) in the univariate model
17 and 1.87 (1.28-2.74) in the adjusted model ($p<0.001$). Corresponding five-year cumulative
18 event rates were 47% and 74%, respectively. Adjusted HR for elevated GGT was 2.9 (1.64 –
19 5.17) for patients in NYHA I/II, and 1.2 (0.75 – 2.05) for patients in NYHA III/IV,
20 respectively ($p=0.003$, for the GGT – NYHA class interaction).

21 Conclusions:

22 Prevalence of elevated GGT is high in chronic heart failure patients. GGT levels are
23 associated with disease severity. Increased GGT is an independent predictor of death or heart
24 transplantation. GGT may provide additional prognostic information, especially in patients
25 with mild heart failure.

26 Key words: gamma-glutamyltransferase, heart failure, prognosis, liver enzymes

1 Introduction

2 Chronic heart failure (CHF) is a highly prevalent syndrome throughout the industrialized
3 world and is associated with significant morbidity and mortality. In addition to traditional risk
4 factors, biomarkers reflecting neurohumoral activation, systemic inflammation, oxidative
5 stress, metabolism, and renal dysfunction as well as anaemia have been associated with
6 disease severity and disease progression¹.

7 Serum gamma-glutamyltransferase (GGT) analysis is an inexpensive and easily accessible,
8 highly sensitive laboratory test that is traditionally considered to be an index of hepatobiliary
9 dysfunction and alcohol abuse². Recent work has also indicated its possible role in the
10 pathogenesis of atherosclerosis and plaque instabilization³⁻⁶. Furthermore, epidemiologic
11 studies have established GGT in predicting the clinical evolution of cardiac and
12 cerebrovascular diseases towards life-threatening events, such as myocardial infarction,
13 stroke, and cardiac death, namely independently from the occurrence of hepatic disease,
14 alcohol consumption, and established risk factors⁷⁻¹³. GGT is also correlated with most
15 cardiovascular risk factors, including diabetes, hypertension, dyslipidemia, and the metabolic
16 syndrome¹⁴⁻¹⁶.

17 A large epidemiological Austrian study covering 163 944 volunteers confirmed the prognostic
18 value of serum GGT activity for fatal events from ischemic or haemorrhagic stroke, and
19 coronary heart disease. In addition, this study revealed for the first time evidence for the
20 prognostic value of GGT with regard to fatal events caused by CHF in apparently healthy
21 subjects⁸. Elevation of GGT levels in patients with heart failure has already been suggested by
22 previous data¹⁷⁻¹⁹.

23 However, the predictive significance of GGT has not yet been studied in a specific cohort of
24 heart failure patients.

25 On the basis of these findings we postulated that serum GGT activity might not only be
26 elevated in patients with heart failure but could also be associated with the severity of heart

1 failure and adverse prognosis. Therefore, we analyzed serum GGT activity in a large series of
2 consecutive patients with CHF due to ischemic or non-ischemic cardiomyopathy.



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1 **Methods**

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3 **Study Population**

4 In a retrospective analysis 1053 consecutive Caucasian heart failure patients were recruited
5 from the specialized heart failure clinic of a university hospital that serves as a tertiary centre
6 in western Austria. Recruitment was started in April 2000 and terminated in December 2007.
7 Eligible patients were ≥ 18 years of age and suffered from specific heart failure symptoms.
8 The diagnosis of CHF was based on the existence of current or previous symptoms or
9 characteristic clinical signs, and evidence of left ventricular dysfunction obtained by
10 echocardiography or contrast ventriculography. Patients were included irrespective of the
11 underlying aetiology of the disease. Treatment including neurohormonal modulation and
12 diuretics was performed according to prevailing CHF guidelines. Patients were followed from
13 their initial evaluation until death or heart transplantation, which constituted the combined
14 endpoint, or the time of data censoring in June 2008. Death events were taken from the
15 Tyrolean Death Registry and from personal contacts with patients and their families.

16 The cohort considered for the present analysis was restricted to 1033 participants with full
17 GGT data at enrolment. For this reason 20 patients (1.9%) were excluded from the present
18 study. Follow-up information was available in 998 patients (96.6%). Thirty-five non-resident
19 patients, who were not registered in the Death Registry or could not be contacted by phone
20 were lost to follow-up.

21 The study conformed to the principles outlined in the Declaration of Helsinki and was
22 approved by the local ethics committee of the Medical University of Innsbruck. The authors
23 had full access to the data and take responsibility for its integrity. All authors have read and
24 agree to the manuscript as written.

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1 **Measurements**

2 All laboratory variables were measured by a central laboratory that undergoes regular internal
3 and external quality controls. Serum GGT levels were measured at 37°C in fasting blood
4 samples on day of blood collection and are given as units per liter. Measurements were
5 performed with a Roche/Hitachi analyzer until 2003 and with a Modular P800 analyzer
6 thereafter using reagents from Roche Diagnostics. The lower limit of detection was 3 U/L;
7 inter-assay and intra-assay coefficients of variation were 1.3% and 1.5%, respectively. The
8 upper laboratory reference limit differs significantly by sex and was set at 38 U/L for women
9 and 65 U/L for men **according to the test kit specification.**



11 **Statistical analysis**

12 Prevalence of elevated GGT was given separately for men (>65 U/L) and women (>38 U/L)
13 using the 95% confidence intervals based on binomial distribution.

14 Univariate associations between GGT, patient characteristics and disease severity were
15 assessed by means of Chi-square, ANOVA or the Kruskal-Wallis Test, as appropriate.

16 Additionally, partial correlation coefficients adjusted for age and sex and **logistic regression**
17 **analysis** were used to show dependencies between log GGT levels and clinical and
18 biochemical factors.

19 Selection of variables for the univariate Cox proportional hazards regression analysis was
20 based on clinical relevance and data from the existing literature. Only variables that proved to
21 be significant in the univariate analysis were candidates for the final multivariate model that
22 was finally determined in a forward stepwise variable selection procedure. For inclusion and
23 exclusion the significance criteria were set at 0.05 and 0.1, respectively. Additional multiple
24 sensitivity analyses with important confounders such as alcohol consumption were performed
25 to verify stability of the final multivariate model.

1 Hazard ratios (HR) and their 95% confidence intervals for sex-specific quintiles of GGT and
2 logarithmically transformed GGT levels were determined in a **sex-pooled with stratification**
3 **for sex** Cox proportional hazards regression analysis adjusted for age, BMI, diabetes,
4 hypertension, ischemic aetiology, NYHA class, heart rate, SAP, uric acid GFR, and NT-
5 proBNP.

6 Significance testing of age and NYHA class as potential effect modifiers of the relation
7 between GGT and the combined endpoint was performed by assessing interaction terms in the
8 multivariate model. The discriminative ability of GGT was tested with the Receiver Operating
9 Characteristics (ROC) analysis. C statistics were calculated in adjusted and unadjusted
10 models with and without inclusion of NT-proBNP.



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1 Results

2 **Clinical characteristics**

3 Characteristics of study patients are shown in Table 1. Of 1033 patients, 396 (38.2%) had
4 heart failure of ischemic and 637 (61.8%) of non-ischemic origin. Patients had a median age
5 of 61 years (18 - 93) and included 778 men (75.3%) and 255 women (24.7%).

7 **GGT levels are significantly increased in patients with heart failure**

8 Prevalence of elevated GGT was higher in women at 50.2% (95%CI 43.9 - 56.5%) than in
9 men at 42.9% (39.4 - 46.5%). In a historical control group **from 1985 – 2001** including 38
10 885 age-matched healthy subjects from the Vorarlberg Health Monitoring and Promotion
11 Program (VHM&PP) corresponding percentages were 18.6% (18.0 – 19.1%) in men and
12 19.2% (18.7 – 19.7) in women, namely significantly different ($p < 0.001$)⁸. Median GGT **in**
13 **our study cohort** was 54 U/L (10 - 1740) in men and 39 U/L (6 - 690) in women.

14 The prevalence of elevated GGT levels in CHF was **comparably high** in young (< 60 years
15 of age) and elderly (≥ 60 years of age) patients (43.1% vs. 46.1%), patients with ischemic and
16 non-ischemic cardiomyopathy (43.3% vs. 45.4%), patients with and without diabetes (49.8%
17 vs. 43.5%), and in patients with impaired ($< 35\%$) and preserved ($\geq 35\%$) left-ventricular
18 ejection fraction (LV-EF) (46.5% vs. 41.3%). Prevalence of GGT elevation was significantly
19 higher in patients with reported alcohol consumption (59.8% vs. 42.8%; $p < 0.001$), although
20 the corresponding percentage in non-alcohol consumers with CHF was still higher than in
21 healthy subjects.

22 Baseline characteristics of patients with normal as compared to patients with elevated GGT
23 levels are illustrated in Table 1.

24

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1 **GGT levels correlate with the severity of heart failure**

2 Because data were obtained from patients in an outpatient clinic, the vast majority of the
3 examinees had symptoms that placed them in NYHA functional class I (n=229; 24.8%), II
4 (n=416; 45.2%), or III (n=262; 28.5%). Only a minority of the patients included were
5 classified NYHA class IV (n=13; 1.4%). Therefore, patients in NYHA classes III and IV were
6 pooled for further analysis. Median GGT levels for patients in NYHA class I were 36 U/L (6 -
7 880), in NYHA class II 49 U/L (8 - 1740), and in NYHA classes III/IV 69 U/L (11 - 940)
8 (Figure 1a). The difference between groups was significant for both men and women
9 (p<0.001).



10 A significant stepwise increase in GGT levels according to decreasing categories of LV-EF
11 was seen in men but not in women (p=0.037 in men versus p=0.63 in women, **p=0.036 in the**
12 **entire cohort**) (Figure 1b).

13 Moreover, GGT levels were closely related to NT-proBNP in a subgroup of patients
14 (p<0.001) (Figure 1c).

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16 **Association between GGT and clinical and biochemical factors**

17 Age- and sex-adjusted associations between GGT levels and clinical and biochemical markers
18 are given in Table 2. Patients with elevated levels of GGT more often had a history of alcohol
19 consumption than did patients with normal GGT levels. Increased levels of GGT were also
20 associated with higher levels of NT-proBNP, uric acid and CRP. Of note, there was a close
21 correlation between GGT and elevated levels of hepatobiliary dysfunction variables, such as
22 serum alkaline phosphatase (SAP), aspartate aminotransferase (AST), and alanine
23 aminotransferase (ALT). SAP was also associated with NYHA functional class (p<0.001),
24 whereas AST and ALT did not differ across NYHA classes (p=0.127 and p=0.50,
25 respectively). **In a multivariate logistic regression model alcohol consumption, LV-EF**
26 **and liver enzymes remained significant predictors of elevated GGT.**

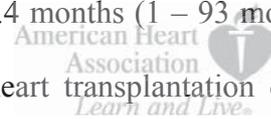
1 **GGT predicts death or heart transplantation in patients with heart failure**

2 Given that GGT levels were significantly elevated in patients with heart failure and also
3 correlated with functional status, we sought to evaluate whether GGT could also provide
4 prognostic information in the present study cohort.

5 For this reason, GGT levels were categorized in quintiles for men (1st ≤28, n=168; 2nd 28.1-
6 43, n=145; 3rd 43.1-72, n=158; 4th 72.1-133, n=152; 5th ≥133.1, n=155) and women (1st ≤19,
7 n=52; 2nd 19.1-30; n=53, 3rd 30.1-46, n=49; 4th 46.1-84.5, n=50; 5th ≥84.51, n=51).

8 Corresponding quintiles for both genders were pooled for further analysis.

9 Minimum follow-up was one month, and mean follow-up was 34.4 months (1 – 93 months).



10 Of 998 patients, 222 (21.5%) died and 80 (7.7%) underwent heart transplantation during
11 follow-up. In the overall patient cohort, the 12-, 24-, 36-, 48-, and 60-month event-free rates
12 were 87%, 78%, 70%, 67%, and 62%, respectively.

13 Non-survivors and heart transplant recipients had higher GGT values at study entry than did
14 survivors or non-transplant recipients with median levels of 72 (11 to 712) U/L versus 43 (6
15 to 1740) U/L.

16 There was a graded relationship between the level of GGT at study entry and the risk of death
17 and heart transplantation during follow-up. Although outcome did not differ significantly
18 between GGT levels in the 1st to 3rd quintiles, GGT levels in the 4th and 5th quintiles were
19 associated with significantly higher event rates (Fig. 2). **Hazard ratios for the 2nd, 3rd, 4th,
20 and 5th quintile were 1.39 (0.91-2.11), 1.47 (0.98-2.21), 1.74 (1.17-2.59), and 2.88 (1.99-
21 4.17), respectively.**

22 Event-free survival rates at 60 months were 74% in the 1st GGT quintile, 66% in the 2nd, 65%
23 in the 3rd, 60% in the 4th, and 47% in the 5th quintile (p<0.001).

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1 **GGT in the context of other markers of increased mortality**

2 Univariate sex-stratified Cox regression analysis showed age, lower BMI, diabetes, SAP, uric
3 acid, GFR, ischemic aetiology, higher NYHA functional class, heart rate and increased levels
4 of GGT and NT-proBNP to be associated with an increased risk of death or heart
5 transplantation during follow-up (Table 3). Reported alcohol consumption and reduced LV-
6 EF were not related to outcome.

7 Age, BMI, diabetes, ischemic aetiology, NYHA functional class, uric acid, GFR, SAP, and
8 GGT were included in the final model. Multiple sex-stratified stepwise Cox regression
9 analysis showed age per one-year increment, NYHA class II vs. I, NYHA class III/IV vs. I,
10 lower BMI per kg/m², ischemic aetiology and GGT per log unit to still be independent
11 predictors of outcome. As compared to the lowest GGT quintile, sex-stratified adjusted HR
12 for patients in the highest quintile was 1.87 (1.28-2.74); per log unit of GGT the adjusted HR
13 was 1.72 (1.28-2.30).

14 When NT-proBNP was included in the final model in a sub-cohort of 461 patients (**event rate**
15 **18.6 %, NYHA class III/IV 21.9%, and GGT 42 (6-1740)U/L as compared to 40.6%,**
16 **35.2%, and 56 (8-940)U/L, respectively, in 537 patients with no NT-proBNP available**),
17 NT-proBNP proved to be a significant predictor of outcome, HR 1.56 (1.0 – 2.46; p=0.05),
18 whereas GGT was only of borderline significance, HR 1.76 (0.971 – 3.193; p=0.06).
19 However, given the higher HR for GGT it **is conceivable** that the lacking significance for
20 GGT is due to a type 2 statistical error.

21 With regard to hepatobiliary variables a significant correlation was seen between elevated
22 levels of SAP, but not of ALT or AST, and the combined endpoint in the univariate analysis.
23 SAP was, however, no longer significant in the final multivariate model.

24 Severity of heart failure as assessed by NYHA class proved to be a significant effect modifier
25 for the relation between GGT and total event rate. HR in the multivariate Cox model for the
26 5th quintile of GGT for prediction of total mortality or heart transplantation was 2.9 (1.64 –

1 5.17) for patients in NYHA classes I and II versus 1.2 (0.75 – 2.05) for patients in NYHA
2 classes III and IV.

3 Interaction between age and GGT was only of borderline significance, HR 0.98 (0.96 – 1.001;
4 $p=0.064$). However, HR for GGT to predict outcome tended to be higher in patients younger
5 than the median (<60 yrs), HR 1.82 (1.16 – 2.86), as compared to patients >60 yrs, HR 1.67
6 (1.12 – 2.47). Interaction between age and GGT became even more obvious when in patients
7 >70 yrs ($n=216$) GGT was no longer significant, HR 1.05 (0.57 – 1.93; $p=0.88$).

8
9 Unadjusted ROC curve analysis further illustrated that GGT is a strong predictor of
10 unfavourable outcome, with a C statistic of 0.65. The best GGT level for outcome prediction
11 was 67 U/L in men (sensitivity 56.5%, specificity 64.8%), and 54.5 U/L in women (sensitivity
12 50.8%, specificity 73.5%). In a subgroup of patients C statistic for NT-proBNP was 0.70. The
13 best NT-proBNP level for predicting outcome was 1710 ng/L (sensitivity 68%, specificity
14 64%). When ROC curve analysis was applied to the overall cohort including all covariates the
15 C statistic was 0.76, which was slightly improved to 0.78 by adding GGT to the model.

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16 To evaluate a potential additive effect of GGT on the prognostic value of NT-proBNP, 461
17 patients were stratified according to the cut-off levels for both markers as defined by ROC
18 analysis. 5-year event rates were significantly higher in patients in whom both GGT and NT-
19 proBNP levels were elevated as compared to patients with one or both markers below the cut-
20 off levels (Fig. 3). Sex-stratified and age-adjusted HR for the purpose of predicting outcome
21 increased from 2.40 (1.34 – 4.31) in the group of NT-proBNP+/GGT- patients to 4.14 (2.32 –
22 7.34) in NT-proBNP+ / GGT+ patients. When ROC curve analysis including all covariates
23 was applied to the sub-cohort with NT-proBNP data available, the addition of GGT did not
24 improve the C statistic (0.793 vs. 0.795, respectively).

25

26

1 Discussion

2 The present study demonstrates that **the prevalence of elevated** GGT serum levels **is high** in
3 patients with CHF. Moreover, in these patients GGT plasma levels are significantly associated
4 with disease severity and also provide prognostic information independently of established
5 clinical and biochemical markers including age, BMI, ischemic aetiology, NYHA stage, and
6 NT-proBNP.

7

8 **Role of GGT in heart failure**

9 Several population-based studies have consistently shown that serum GGT levels, mostly
10 within normal ranges, were strongly associated with most cardiovascular risk factors and
11 predicted the development of heart disease, hypertension, stroke and type 2 diabetes^{7, 9, 11, 14}.

12 In this sample of patients with stable heart failure symptoms, serum GGT concentrations were
13 elevated in and strongly and positively associated with severity of the syndrome. This positive
14 association was consistently demonstrated in all subgroups examined in this study. Of note,
15 this association was also given in non-alcohol consumers, although prevalence of elevated
16 GGT levels and absolute GGT levels was clearly higher in patients with reported alcohol
17 consumption.

18

19 Although the mechanism underlying this association remains largely unknown, several
20 explanations for this phenomenon can be considered:

21 Hepatic congestion is an obvious mechanistic explanation for the elevation of GGT in heart
22 failure. We and others have previously reported that severe heart failure is associated with a
23 cholestatic liver enzyme profile with elevated plasma levels of GGT, serum alkaline
24 phosphatase (SAP), and bilirubin¹⁷⁻¹⁹. Local damage to the bile canaliculi caused by increased
25 pressure within the hepatic sinusoid or ischemia as well as proinflammatory cytokine release
26 may be involved in this process²⁰. However, sparsely available literature does not provide

1 conclusive evidence for a definite or exclusive correlation between GGT and right atrial and
2 pulmonary artery pressures as well as severity of reduced cardiac output^{17-19, 21}.

3 Hence, besides hepatic congestion a/o ischemia, other causative factors for GGT elevation in
4 heart failure also have to be considered.

5 A potential involvement of GGT in the pathogenesis of heart failure is conceivable. For
6 instance, GGT has been repeatedly associated with atherogenesis^{3, 4, 22}. Membrane-bound
7 GGT catalyses the initial step in the extracellular degradation of antioxidant glutathione
8 (GSH), which ultimately results in the amino acids cysteine and glycine². The reactive thiol of
9 cysteinyl-glycine can generate superoxide anion radicals and hydrogen peroxide through its
10 interaction with free iron⁶. These GGT-mediated reactions have been shown to catalyze the
11 oxidation of LDL lipoproteins, which may contribute to oxidative events influencing plaque
12 evolution and rupture⁵. Elevation of GGT levels has also been postulated as a marker for
13 evolution of the metabolic syndrome^{14, 23, 24}. Coronary artery disease and myocardial
14 infarction are generally regarded as the number one causes of CHF and metabolic syndrome is
15 an established risk factor for CHF^{25, 26, 27}.

16 Cysteine and glycine constitute the precursors of intracellular GSH. Hence, GGT also
17 provides a supply for uptake and reutilization in intracellular GSH synthesis. In this way,
18 GGT serves as a rescue enzyme for cellular GSH synthesis and thus plays an important role in
19 antioxidant defence systems^{28, 29}. Accordingly, it has been suggested that an increase in serum
20 GGT activity could be used as a marker for increased oxidative stress in humans^{15, 30}. GGT is
21 also strongly related to systemic inflammation, as suggested by Lee et al.³¹. Oxidative stress
22 and systemic inflammation are involved in ventricular remodelling and endothelial
23 dysfunction, both of which contribute to progression of the heart failure syndrome^{1, 32, 33}. In
24 fact, a relationship between GGT and arterial stiffness as a potential marker of endothelial
25 dysfunction was recently suggested³⁴. Moreover, C-reactive protein and uric acid, which are
26 considered indicators of inflammation and oxidative stress, respectively, have been associated

1 with the development and progression of heart failure^{35, 36}. The fact that in our cohort of
2 patients GGT levels were associated with both C-reactive protein and uric acid may support
3 the potential association between GGT and inflammation and oxidative stress in heart failure
4 patients.

5
6 Taken together, current data do not provide conclusive evidence for the cause and effect
7 relationship between elevated GGT levels and heart failure. It is well possible that GGT
8 elevation reflects the magnitude of overall disease burden including all the possible
9 mechanisms given above and provides integrated information on oxidative stress and
10 inflammation as part of heart failure syndrome.



11
12 There is an obvious difference between GGT, ALT and AST in heart failure. In an early study
13 by Kubo et al. patients with the most severe heart failure, as evidenced by the lowest cardiac
14 index and the highest filling pressures, demonstrated significantly higher levels of ALT, AST,
15 lactate dehydrogenase, and bilirubin, but not of GGT and SAP²¹. In our current study, GGT
16 was strongly correlated with SAP, and modestly associated with ALT and AST. In addition,
17 SAP but not ALT or AST, was related to CHF severity. This is well in line with data from
18 Vasconcelos et al. showing in a small sample of 50 patients that CHF is characterized by a
19 progressive cholestatic profile of laboratory elevations, while transaminase values are
20 elevated only in advanced heart failure¹⁹.

21
22 **GGT as a potential novel biomarker in heart failure**

23 Risk stratification is of critical importance in heart failure patients. Biomarkers, especially
24 brain natriuretic peptide (BNP), have been shown to add useful information to clinical
25 variables in the management of heart failure. However, it is unlikely that a single marker will
26 provide all the information needed for clinical decision making, and an integrated “multi-

1 marker strategy” may be preferable³⁷. In this study, GGT was an independent predictor of
2 death or heart transplantation in stable heart failure patients. Moreover, it appears that GGT
3 levels above the cut-off may provide additional prognostic information in patients with
4 elevated levels of NT-proBNP.

5 Of note, we provide evidence that the prognostic value of GGT is of particular interest in
6 patients with mild heart failure symptoms, who, in general, are most difficult to risk-stratify
7 and to advise. The predictive value of elevated GGT levels was clearly greater in mildly
8 symptomatic patients than in severely symptomatic patients. **Conceivably, GGT reflects**
9 **different aspects of disease severity than does clinical judgement per se. This finding,**
10 **though, remains to be validated in other cohorts.** Also, the predictive value of serum GGT
11 proved significant in those aged less than 70 years, but appears to be of restricted validity in
12 older patients. This finding is well in line with recent data published by Lee DH, et al.
13 suggesting that serum GGT within its normal range may be of limited usefulness in predicting
14 cardiovascular disease mortality in patients older than 70 years³⁸.

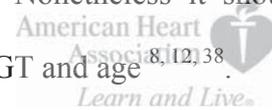
15 In light of the demonstrated findings it can be speculated that GGT may be useful for risk
16 stratification in CHF. Thus, GGT may emerge not only as a risk marker for cardiovascular
17 disease and metabolic syndrome in apparently healthy subjects, but also as a new biomarker
18 in stable CHF. However, it needs to be emphasized that GGT is not cardiac-specific.
19 Accordingly, GGT cannot be used to diagnose heart failure.

20

21 **Study limitations and future directions**

22 This study is limited by its observational nature. Although the study works with longitudinal
23 data from an unselected cohort, its observational character does not permit conclusions on
24 causal relationships. Even though medication was generally similar at study entry, patients
25 were not monitored for changes in medication during follow-up. Also, we did not account for
26 the effects of devices such as implanted defibrillators and biventricular pacemakers. Hence,

1 differences in medication and/or implanted devices may constitute potential confounders of
2 the study results. Furthermore, although most of the documented risk factors for fatal events
3 were included in the analysis, the possibility of residual confounding by factors that were not
4 accounted for can not be entirely excluded. Data on NT-proBNP was available only in a
5 subgroup of patients, since this marker was not established at our institution before 2004.
6 Thus, statements on the relationship between GGT and NT-proBNP must be interpreted with
7 caution. A point of concern relates to the interactions between GGT and NYHA class and age
8 that were not pre-specified hypotheses. However, the very low p for the interaction between
9 GGT and NYHA class suggests it is unlikely due to chance. Nonetheless it should be
10 confirmed elsewhere as it already exists for interaction between GGT and age.
11 Finally, a further limitation arises from the fact that data derive from a single centre study.
12 Results, therefore, need to be confirmed elsewhere.



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Summary

16 In conclusion, the prevalence of GGT is high in patients with CHF. Furthermore, GGT is
17 positively associated with CHF severity and with long-term outcome in both men and women.
18 GGT elevation appears to be largely a reflection of overall disease burden. Although the
19 clinical relevance of these findings remains to be determined, GGT as a supplement to
20 established biomarkers in CHF may be of particular interest in patients younger than 70 years
21 with mild to modest symptoms. Future studies are needed to clarify the exact role of GGT in
22 CHF.

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1 Acknowledgments

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3 contribution to data acquisition.

4 Disclosures

5 None

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1 **Table and Figure Legends**

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3 Table 1

4 Data from 1033 patients are reported as number (percentage), median (interquartile range), or
5 mean \pm SD. Data available from * 485, † 669, ‡ 512, and § 587 patients. Missing data
6 amounted to less than 5% for diabetes, hypertension, cholesterol, reported alcohol
7 consumption, aetiology, LV-EF, heart rate, AST, ALT, sodium, and GFR.

8

9 The relationships between GGT and gender, aetiology, diabetes, hypertension, reported
10 alcohol consumption, NYHA functional class, and baseline medication were assessed with the
11 chi-square test. The relationships between GGT and age, BMI, cholesterol, sodium and GFR
12 were assessed with the unpaired T Test. All other relationships were tested with the Mann-
13 Whitney U Test.

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15 ACE = angiotensin-converting enzyme; ALT = alanine aminotransferase; ARB = angiotensin
16 receptor blocker; AST = aspartate aminotransferase; BMI = body mass index; CRP = C-
17 reactive protein; GFR = glomerular filtration rate; GGT = serum gamma-glutamyltransferase;
18 LV-EF = left ventricular ejection fraction; NT-proBNP = amino-terminal pro-B-type
19 natriuretic peptide; NYHA = New York Heart Association; SAP = serum alkaline
20 phosphatase.

21

22 Table 3

23 Sex-stratified Cox proportional hazards regression analysis for the combined endpoint in
24 relation to biochemical, demographic, and clinical factors.

25 * Hazard ratio for GGT per log unit to predict death was 1.73 (1.2 – 2.4; $p=0.002$), and to
26 predict heart transplantation was 1.87 (1.07 – 3.28; $p=0.029$), respectively.

1 ALT = alanine aminotransferase; AST = aspartate aminotransferase; BMI = body mass index;
2 GFR = glomerular filtration rate; GGT = serum gamma-glutamyltransferase; LV-EF = left
3 ventricular ejection fraction; NT-proBNP = amino-terminal pro-B-type natriuretic peptide;
4 NYHA = New York Heart Association; SAP = serum alkaline phosphatase

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7 Figure 1 GGT levels in patients with chronic heart failure stratified according to NYHA
8 functional class, LV-EF or NT-proBNP levels at study entry

9



10 Patients were stratified according to NYHA functional class (A), three categories of LV-EF
11 (B), or NT-proBNP quartiles (C). Logarithmically scaled GGT levels are presented as box
12 (25th percentile, median, 75th percentile) and whisker (19th and 90th percentiles) plots. Patient
13 numbers are indicated. The NT-pro BNP levels in the first quartile ranged from 10 to 450 ng/l,
14 in the second quartile from 461 to 1254 ng/l, in the third quartile from 1266 to 2911 ng/l, and
15 in the fourth quartile from 2955 to 42014 ng/l.

16 GGT = serum gamma-glutamyltransferase; LV-EF = left ventricular ejection fraction; NT-
17 proBNP = amino-terminal pro-B-type natriuretic peptide; NYHA = New York Heart
18 Association.

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20 Figure 2 Correlation between GGT in quintiles and combined endpoint

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22 Cumulative five-year event rates estimated by univariate sex-stratified Cox proportional
23 hazard regression analysis in 998 patients with CHF according to quintiles of GGT levels at
24 study entry. Numbers of patients at risk and event rates are shown below the graphs.

25 GGT = serum gamma-glutamyltransferase

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1 Figure 3 Additive value of GGT to NT-proBNP in predicting the combined endpoint

2

3 Additive value of GGT in predicting three-year event rate in 461 patients. Patients were
4 stratified for GGT and NT-proBNP levels according to the cut-off defined by ROC analysis.

5 Cut-off level for GGT = 67 U/L in men and 54.5 U/L in women; cut-off level for NT-proBNP
6 = 1710 ng/L. The non-significant HR in the small group of GGT+NTproBNP patients is
7 **probably** due to a type 2 statistical error.

8 GGT = serum gamma-glutamyltransferase; NT-proBNP = amino-terminal pro-B-type
9 natriuretic peptide.



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1 Table 1

2 Patient characteristics

	All patients (n = 1033)	GGT normal m (< 65 U/L) w (< 38 U/L) (n = 571)	GGT elevated m (> 65 U/L) w (> 38 U/L) (n = 462)	p Value
Clinical characteristics				
Age	59.7 (13.1)	59.2 ± 14.2	60.3 ± 11.6	<0.001
Male gender (%)	778 (75.3)	444 (77.8)	334 (72.3)	0.026
BMI	26 ± 4.2	26.0 ± 4.1	26 ± 4.2	0.51
Diabetes (%)	207 (20)	104 (18.3)	103 (22.3)	0.62
Hypertension (%)	459 (44.9)	250 (43.9)	209 (46.1)	0.26
Cholesterol (mg/dl)	190 ± 48.4	189.9 ± 46.8	190.3 ± 50.5	0.063
Reported alcohol consumption (%)	141 (14.6)	57 (10.8)	84 (19.2)	<0.001
Ischemic aetiology	390 (38.2)	209 (36.9)	181 (39.9)	0.18
Heart failure severity and biomarkers				
NYHA functional class	2,04 ± 0.76	1.89 ± 0.75	2.24 ± 0.75	
I	264 (25.5)	186 (32.6)	78 (16.9)	
II	471 (45.7)	265 (46.6)	206 (44.6)	
III/IV	298 (28.9)	120 (21.0)	178 (38.5)	<0.001
LV-EF (%)	28 (8 – 72)	28 (13 – 58)	29 (12 – 64)	0.15
Heart rate (bpm)	76.3 ± 16.7	73.7 ± 15.6	79.5 ± 17.5	<0.001
NT-proBNP (pg/ml) *	1254 (10 – 42014)	1159 (72 – 8695)	2110 (17 – 16713)	<0.001
AST (GOT) (U/L)	27.5 (10 – 230)	24 (16 – 56)	34 (20 – 120)	<0.001
ALT (GPT) (U/L)	24 (2 – 362)	20 (11 – 52)	37 (11 – 291)	<0.001
SAP (U/L) †	72 (7 – 425)	60 (35 – 151)	83 (8 – 153)	<0.001
CRP (mg/dl) ‡	0.67 (0.07 – 4.0)	0.59 (0.1 – 2.6)	0.77 (0.1 – 4.0)	<0.001

Uric acid (mg/dl) §	6.8 (1.5 – 18.3)	6.7 (2.4 – 16.3)	7.6 (2.6 – 13.7)	<0.001
Sodium (mg/dl)	139.6 ± 5.9	140.1 ± 3.2	139.0 ± 8	0.006
GFR (ml/min/1.73 m ²)	77.9 ± 39.6	78.6 ± 32.4	77.0 ± 47.1	0.5

Medication at study entry

ACE inhibitor/ARB	860 (83.3)	462 (81)	398 (86.1)	0.32
Beta-blocker	627 (60.9)	342 (60.1)	285 (61.8)	0.58
Spirolactone	285 (27.7)	123 (21.6)	162 (35.1)	<0.001
Diuretic	739 (71.7)	357 (62.7)	382 (82.9)	<0.001

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1 Table 2

2 Cross-sectional correlations between GGT and clinical and biochemical factors

	Correlation coefficient*	p Value
Reported alcohol consumption	0.168	<0.001
Diabetes	- 0.076	0.015
Hypertension	0.003	0.921
LV-EF	- 0.100	0.002
NT-proBNP	0.304	<0.001
ALT	0.377	<0.001
AST	0.410	<0.001
SAP	0.498	<0.001
CRP	0.202	<0.001
Uric acid	0.244	<0.001
Cholesterol	- 0.004	0.901



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4 * Pearson's partial correlation coefficients, age- and sex-adjusted. GGT, NT-proBNP,

5 ALT, AST, SAP, and CRP were logarithmically transformed.

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1 Table 3

2 Univariate and multivariate sex-stratified Cox regression analysis for death and heart

3 transplantation

	Univariate analysis		Multivariate analysis	
	HR (95% CI)	p Value	HR (95% CI)	p Value
Age (per years)	1.025 (1.015 – 1.035)	<0.001	1.01 (1.001 – 1.021)	0.036
BMI (per kg/m ²)	0.95 (0.92 – 0.98)	0.001	0.95 (0.92 – 0.98)	0.02
Diabetes	1.35 (1.04 – 1.75)	0.026		0.36
Hypertension	1.07 (0.85 – 1.35)	0.57		
Alcohol consumption	0.97 (0.97 – 1.38)	0.85		
Ischemic etiology	2.14 (1.70 – 2.69)	<0.001	1.53 (1.21 – 1.94)	<0.001
LV-EF (per %)	0.99 (0.98 – 1.00)	0.56		
NYHA class (II vs I)	2.9 (1.9 – 4.5)	<0.001	2.49 (1.61 – 3.86)	<0.001
NYHA class (III/IV vs I)	8.40 (5.52 – 12.83)	<0.001	6.06 (3.92 – 9.38)	<0.001
Heart rate	1.006 (1.0 – 1.01)	0.05		0.78
GGT (per log unit)	2.43 (1.83 – 3.22)	<0.001	1.72 (1.28 – 2.30) *	<0.001
NT-proBNP (per log unit)	2.39 (1.54 – 3.70)	<0.001	1.56 (1.0 – 2.46)	0.05
SAP (>100 U/L)	4.26 (2.07 – 8.77)	<0.001		0.76
ALT (per log unit)	0.97 (0.61 – 1.55)	0.897		
AST (per log unit)	1.778 (0.97 – 3.27)	0.063		
Sodium (per log unit)	0.99 (0.98 – 0.99)	0.29		
Uric acid (per log unit)	1.12 (1.06 – 1.18)	<0.001		0.88
GFR (per log unit)	0.98 (0.98 – 0.99)	<0.001		0.08

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