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Prevalence and Prognostic Significance of Elevated γ-Glutamyltransferase in Chronic Heart Failure

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Background—Serum γ-glutamyltransferase (GGT) is associated with incident cardiovascular diseases and is a potential risk factor for disease mortality. We investigated the relevance of circulating GGT in chronic heart failure.

Methods and Results—From 2000 to 2007 clinical and laboratory variables of 1033 consecutive outdoor patients with heart failure were evaluated. Follow-up (mean, 34.4 months) was available in 998 patients. The end point was defined as death from any cause or heart transplantation. A forward stepwise Cox proportional hazards regression model for sex-stratified data was used. Prevalence of elevated GGT was 42.9% in men (GGT >65 U/L) and 50.2% in women (GGT >38 U/L), which was higher than for sex- and age-matched healthy subjects (18.6% in men, 19.2% in women) derived from a large historical control group. GGT was associated with severity of heart failure as assessed by New York Heart Association class, left-ventricular ejection fraction, and amino-terminal pro-B-type natriuretic peptide. The end point was recorded in 302 patients. Compared with the lowest GGT quintile, sex-stratified hazard ratios for patients in the highest quintile were 2.88 (1.99 to 4.17) in the univariate model and 1.87 (1.28 to 2.74) in the adjusted model ($P<0.001$). Corresponding 5-year cumulative event rates were 47% and 74%, respectively. Adjusted hazard ratios for elevated GGT was 2.9 (1.64 to 5.17) for patients in New York Heart Association I/II, and 1.2 (0.75 to 2.05) for patients in New York Heart Association III/IV, respectively ($P=0.003$, for the GGT–New York Heart Association class interaction).

Conclusions—Prevalence of elevated GGT is high in patients with chronic heart failure. The GGT levels are associated with disease severity. Increased GGT is an independent predictor of death or heart transplantation. GGT may provide additional prognostic information, especially in patients with mild heart failure. **(*Circ Heart Fail*. 2009;2:294-302.)**

Key Words: γ-glutamyltransferase ■ heart failure ■ prognosis ■ liver ■ enzymes

Chronic heart failure (CHF) is a highly prevalent syndrome throughout the industrialized world and is associated with significant morbidity and mortality. In addition to traditional risk factors, biomarkers reflecting neurohumoral activation, systemic inflammation, oxidative stress, metabolism, and renal dysfunction as well as anemia have been associated with disease severity and disease progression.[1]

Clinical Perspective on p 302

Serum γ-glutamyltransferase (GGT) analysis is an inexpensive and easily accessible, highly sensitive laboratory test that is traditionally considered to be an index of hepatobiliary dysfunction and alcohol abuse.[2] Recent work has also indicated its possible role in the pathogenesis of atherosclerosis and plaque instabilization.[3–6] Furthermore, epidemiological studies have established GGT in predicting the clinical evolution of cardiac and cerebrovascular diseases toward life-threatening events, such as myocardial infarction, stroke, and cardiac death, namely independently from the occurrence of hepatic disease, alcohol consumption, and established risk factors.[7–13] GGT is also correlated with most cardiovascular risk factors, including diabetes, hypertension, dyslipidemia, and the metabolic syndrome.[14–16]

A large epidemiological Austrian study covering 163 944 volunteers confirmed the prognostic value of serum GGT activity for fatal events from ischemic or hemorrhagic stroke and coronary heart disease. In addition, this study revealed for the first time evidence for the prognostic value of GGT with regard to fatal events caused by CHF in apparently healthy subjects.[8] Elevation of GGT levels in patients with heart failure has already been suggested by previous data.[17–19] However, the predictive significance of GGT has not yet been studied in a specific cohort of heart failure patients.

On the basis of these findings, we postulated that serum GGT activity might not only be elevated in patients with heart failure but could also be associated with the severity of heart failure and adverse prognosis. Therefore, we analyzed serum GGT activity in a large series of consecutive patients with CHF due to ischemic or nonischemic cardiomyopathy.

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Methods

Study Population

In a retrospective analysis 1053 consecutive white patients with heart failure were recruited from the specialized heart failure clinic of a university hospital that serves as a tertiary center in western Austria. Recruitment was started in April 2000 and terminated in December 2007. Eligible patients were ≥18 years and suffered from specific heart failure symptoms. The diagnosis of CHF was based on the existence of current or previous symptoms or characteristic clinical signs and the evidence of left ventricular dysfunction obtained by echocardiography or contrast ventriculography. Patients were included irrespective of the underlying etiology of the disease. Treatment, including neurohormonal modulation and diuretics, was performed according to the prevailing CHF guidelines. Patients were followed from their initial evaluation until death or heart transplantation, which constituted the combined end point, or the time of data censoring in June 2008. Death events were taken from the Tyrolean Death Registry and from personal contacts with patients and their families. The cohort considered for the present analysis was restricted to 1033 participants with full GGT data at enrolment. For this reason 20 patients (1.9%) were excluded from this study. Follow-up information was available for 998 patients (96.6%). Thirty-five nonresident patients who were not registered in the Death Registry or could not be contacted by phone were lost to follow-up.

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

Measurements

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

Statistical Analysis

Prevalence of elevated GGT was given separately for men (>65 U/L) and women (>38 U/L) using the 95% CI based on binomial distribution. Univariate associations among GGT, patient characteristics, and disease severity were assessed by means of χ^2, ANOVA, or the Kruskal-Wallis Test, as appropriate. In addition, partial correlation coefficients adjusted for age and sex and logistic regression analysis were used to show dependencies between log GGT levels and clinical and biochemical factors.

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

Hazard ratios (HRs) and their 95% CI for sex-specific quintiles of GGT and logarithmically transformed GGT levels were determined in a sex pooled with stratification for sex Cox proportional hazards regression analysis adjusted for age, body mass index (BMI), diabetes, hypertension, ischemic etiology, New York Heart Association (NYHA) class, heart rate, serum alkaline phosphatase (SAP), uric acid glomerular filtration rate, and amino-terminal pro-B-type natriuretic peptide (NT-proBNP).

Significance testing of age and NYHA class as potential effect modifiers of the relation between GGT and the combined end point was performed by assessing the interaction terms in the multivariate model. The discriminative ability of GGT was tested with the receiver operating characteristics (ROC) analysis. C-statistics were calculated in adjusted and unadjusted models with and without inclusion of NT-proBNP.

Results

Clinical Characteristics

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

GGT Levels Are Significantly Increased in Patients With Heart Failure

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

The prevalence of elevated GGT levels in CHF was comparably high in young (<60 years) and elderly (≥60 years) patients (43.1% versus 46.1%), patients with ischemic and nonischemic cardiomyopathy (43.3% versus 45.4%), patients with and without diabetes (49.8% versus 43.5%), and patients with impaired (<35%) and preserved (≥35%) left ventricular ejection fraction (46.5% versus 41.3%). Prevalence of GGT elevation was significantly higher in patients with reported alcohol consumption (59.8% versus 42.8%; $P<0.001$), although the corresponding percentage in nonalcohol consumers with CHF was still higher than in healthy subjects. Baseline characteristics of patients with normal as compared with patients with elevated GGT levels are illustrated in Table 1.

GGT Levels Correlate With the Severity of Heart Failure

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

A significant stepwise increase in GGT levels according to decreasing categories of LVEF was seen in men but not in women ($P=0.037$ in men versus $P=0.63$ in women, $P=0.036$ in the entire cohort; Figure 1B). Moreover, GGT

Table 1. 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*
Clinical characteristics				
Age, y	59.7 (13.1)	59.2±14.2	60.3±11.6	<0.001
Male gender, n (%)	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, n (%)	207 (20)	104 (18.3)	103 (22.3)	0.62
Hypertension, n (%)	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, n (%)	141 (14.6)	57 (10.8)	84 (19.2)	<0.001
Ischemic etiology	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
LVEF, n (%)	28 (8 to 72)	28 (13 to 58)	29 (12 to 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 to 42014)	1159 (72 to 8695)	2110 (17 to 16713)	<0.001
AST, U/L	27.5 (10 to 230)	24 (16 to 56)	34 (20 to 120)	<0.001
ALT, U/L	24 (2 to 362)	20 (11 to 52)	37 (11 to 291)	<0.001
SAP, U/L†	72 (7 to 425)	60 (35 to 151)	83 (8 to 153)	<0.001
CRP, mg/dL‡	0.67 (0.07 to 4.0)	0.59 (0.1 to 2.6)	0.77 (0.1 to 4.0)	<0.001
Uric acid, mg/dL§	6.8 (1.5 to 18.3)	6.7 (2.4 to 16.3)	7.6 (2.6 to 13.7)	<0.001
Sodium, mg/dL	139.6±5.9	140.1±3.2	139.0±8	0.006
GFR, mL min^{-1} 1.73^{-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
β-Blocker	627 (60.9)	342 (60.1)	285 (61.8)	0.58
Spironolactone	285 (27.7)	123 (21.6)	162 (35.1)	<0.001
Diuretic	739 (71.7)	357 (62.7)	382 (82.9)	<0.001

Data from 1033 patients are reported as n (%), median (interquartile range), or mean±SD. Data available from *485, †669, ‡512, and §587 patients. Missing data amounted to <5% for diabetes, hypertension, cholesterol, reported alcohol consumption, etiology, LVEF, heart rate, AST, ALT, sodium, and GFR. The relationships between GGT and gender, etiology, diabetes, hypertension, reported alcohol consumption, NYHA functional class, and baseline medication were assessed with the χ^2 test. The relationships between GGT and age, BMI, cholesterol, sodium, and GFR were assessed with the unpaired *t* test. All other relationships were tested with the Mann–Whitney *U* test. ACE indicates angiotensin-converting enzyme; ARB, angiotensin receptor blocker; CRP, C-reactive protein; GFR, glomerular filtration rate.

levels were closely related to NT-proBNP in a subgroup of patients ($P<0.001$; Figure 1C).

Association Between GGT and Clinical and Biochemical Factors

Age- and sex-adjusted associations between GGT levels and clinical and biochemical markers are given in Table 2. Patients with elevated levels of GGT more often had a history of alcohol consumption than did patients with normal GGT levels. Increased levels of GGT were also associated with higher levels of NT-proBNP, uric acid and C-reactive protein. Of note, there was a close correlation between GGT and elevated levels of hepatobiliary dysfunction variables, such as SAP, aspartate aminotransferase (AST), and alanine aminotransferase (ALT). SAP was also associated with NYHA functional class ($P<0.001$), whereas AST and ALT did not differ across NYHA classes ($P=0.127$ and $P=0.50$, respectively). In a multivariate logistic regression model alcohol consumption, left ventricular ejection fraction, and liver enzymes remained significant predictors of elevated GGT.

GGT Predicts Death or Heart Transplantation in Patients With Heart Failure

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

For this reason, GGT levels were categorized in quintiles for men (first: ≤28, n=168; second: 28.1 to 43, n=145; third: 43.1 to 72, n=158; fourth: 72.1 to 133, n=152; and fifth:

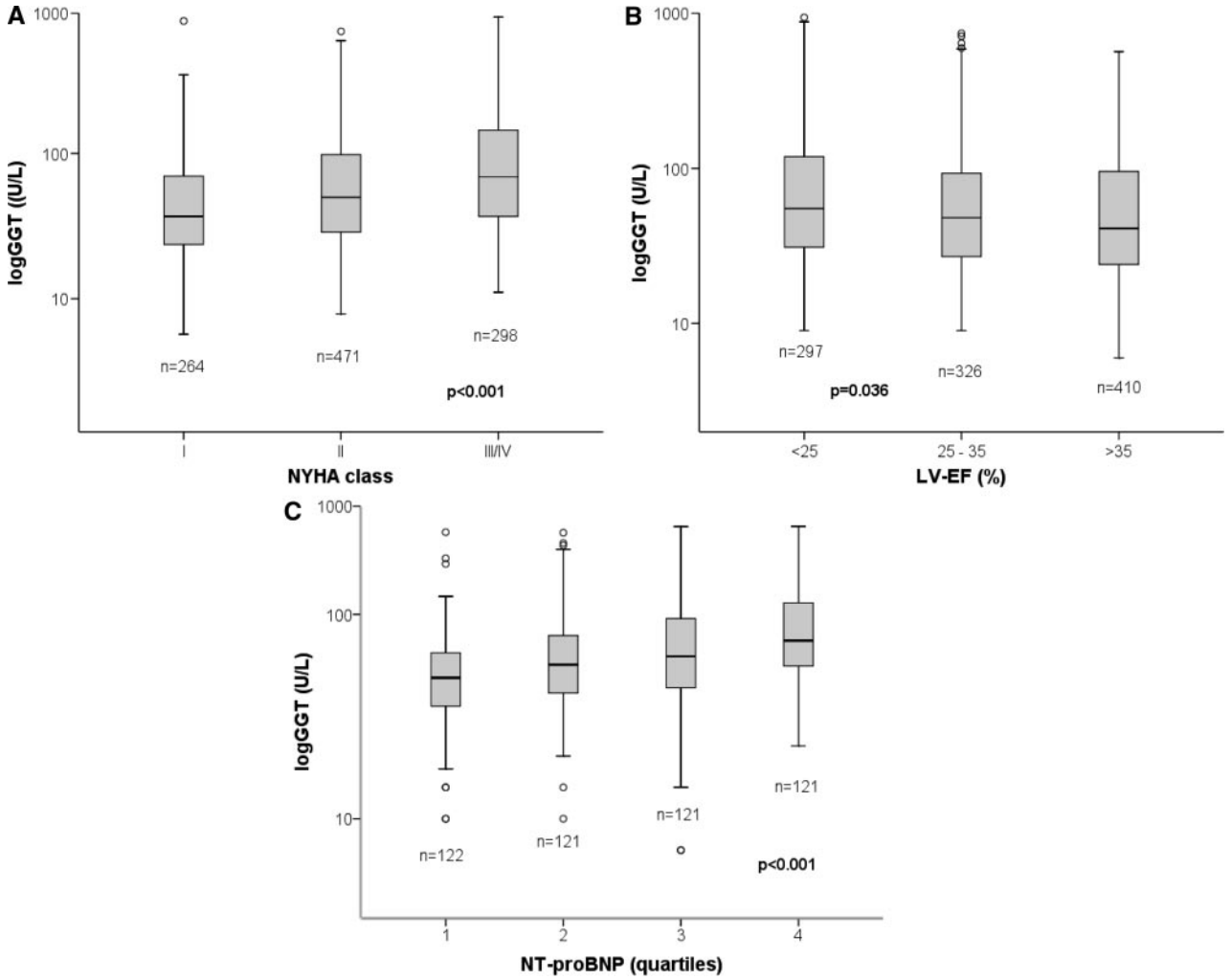

Figure 1. GGT levels in patients with CHF stratified according to NYHA functional class, LVEF or NT-proBNP levels at study entry. Patients were stratified according to NYHA functional class (A), 3 categories of LVEF (B), or NT-proBNP quartiles (C). Logarithmically scaled GGT levels are presented as box (25th percentile, median, 75th percentile) and whisker (19th and 90th percentiles) plots. Patient numbers are indicated. The NT-pro BNP levels in the first quartile ranged from10 to 450 ng/L, in the second quartile from 461 to 1254 ng/L, in the third quartile from 1266 to 2911 ng/L, and in the fourth quartile from 2955 to 42014 ng/L. LVEF indicates left ventricular ejection fraction.

≥133.1, n=155) and women (first: ≤19, n=52; second: 19.1 to 30; n=53, third: 30.1 to 46, n=49; fourth: 46.1 to 84.5, n=50; and fifth: ≥84.51, n=51). Corresponding quintiles for both genders were pooled for further analysis.

Minimum follow-up was 1 month, and mean follow-up was 34.4 months (1 to 93 months). Of 998 patients, 222 (21.5%) died and 80 (7.7%) underwent heart transplantation during the follow-up. In the overall patient cohort, the 12-, 24-, 36-, 48-, and 60-month event-free rates were 87%, 78%, 70%, 67%, and 62%, respectively. Nonsurvivors and heart transplant recipients had higher GGT values at study entry than did survivors or nontransplant recipients with median levels of 72 U/L (11 to 712 U/L) versus 43 U/L (6 to 1740 U/L).

There was a graded relationship between the level of GGT at study entry and the risk of death and heart transplantation during the follow-up. Although outcome did not differ significantly between GGT levels in the first to third quintiles, GGT levels in the fourth and fifth quintiles were associated with significantly higher event rates (Figure 2). HRs for the second, third, fourth, and fifth quintile were 1.39 (0.91 to 2.11), 1.47 (0.98 to 2.21), 1.74 (1.17 to 2.59), and 2.88 (1.99 to 4.17), respectively. Event-free survival rates at 60 months were 74% in the first GGT quintile, 66% in the second, 65% in the third, 60% in the fourth, and 47% in the fifth quintile ($P<0.001$).

GGT in the Context of Other Markers of Increased Mortality

Univariate sex-stratified Cox regression analysis showed age, lower BMI, diabetes, SAP, uric acid, glomerular filtration rate, ischemic etiology, higher NYHA functional class, heart rate, and increased levels of GGT and NT-proBNP to be associated with an increased risk of death or heart transplantation during the follow-up (Table 3). Reported alcohol consumption and reduced left ventricular ejection fraction were not related to outcome.

Age, BMI, diabetes, ischemic etiology, NYHA functional class, uric acid, glomerular filtration rate, SAP, and GGT

Table 2. Cross-Sectional Correlations Between GGT and Clinical and Biochemical Factors

	Correlation Coefficient*	*P*
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
C-reactive protein	0.202	<0.001
Uric acid	0.244	<0.001
Cholesterol	−0.004	0.901

*Pearson's partial correlation coefficients, age- and sex-adjusted. GGT, NT-proBNP, ALT, AST, SAP, and CRP were logarithmically transformed.

were included in the final model. Multiple sex-stratified stepwise Cox regression analysis showed age per 1-year increment, NYHA Class II versus I, NYHA Class III/IV versus I, lower BMI per kilogram per square meter, ischemic etiology and GGT per log unit to still be independent predictors of outcome. As compared with the lowest GGT quintile, sex-stratified–adjusted HR for patients in the highest quintile was 1.87 (1.28 to 2.74); per log unit of GGT the adjusted HR was 1.72 (1.28 to 2.30).

When NT-proBNP was included in the final model in a subcohort of 461 patients (event rate, 18.6%; NYHA Class III/IV, 21.9%; and GGT, 42 U/L [6 to 1740 U/L] as compared with 40.6%, 35.2%, and 56 U/L [8 to 940 U/L], respectively, in 537 patients with no NT-proBNP available), it proved to be a significant predictor of outcome (HR, 1.56 [1.0 to 2.46; $P=0.05$]) whereas GGT was only of borderline significance (HR, 1.76 [0.971 to 3.193; $P=0.06$]). However, given the higher HR for GGT it is conceivable that the lacking significance for GGT is due to a Type 2 statistical error.

With regard to hepatobiliary variables, a significant correlation was seen between elevated levels of SAP, but not of ALT or AST, and the combined end point in the univariate analysis. SAP was, however, no longer significant in the final multivariate model. Severity of heart failure as assessed by NYHA class proved to be a significant effect modifier for the relation between GGT and total event rate. HR in the multivariate Cox model for the fifth quintile of GGT for prediction of total mortality or heart transplantation was 2.9 (1.64 to 5.17) for patients in NYHA Classes I and II versus 1.2 (0.75 to 2.05) for patients in NYHA Classes III and IV.

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

Unadjusted ROC curve analysis further illustrated that GGT is a strong predictor of unfavorable outcome, with a

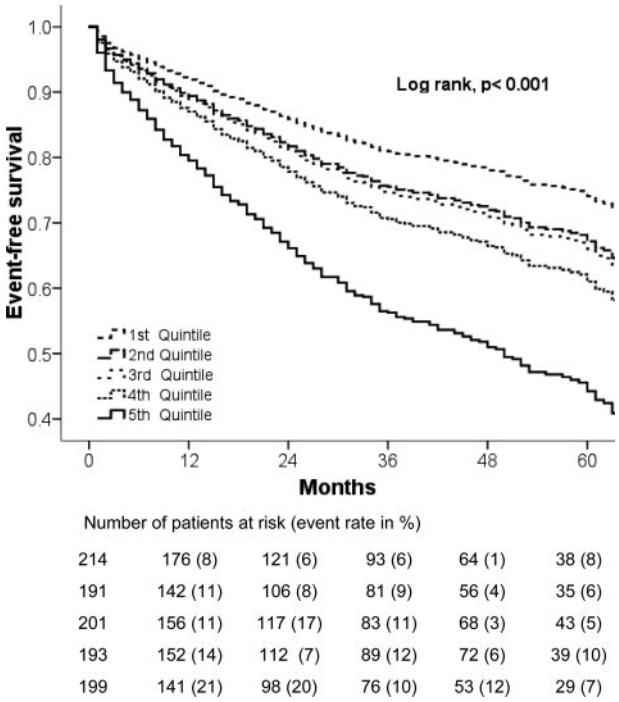

Figure 2. Correlation between GGT in quintiles and combined end point. Cumulative 5-year event rates were estimated by univariate sex-stratified Cox proportional hazard regression analysis in 998 patients with CHF according to quintiles of GGT levels at the study entry. Numbers of patients at risk and event rates are shown below the graphs.

C-statistic of 0.65. The best GGT level for outcome prediction was 67 U/L in men (sensitivity 56.5%, specificity 64.8%), and 54.5 U/L in women (sensitivity 50.8%, specificity 73.5%). In a subgroup of patients C-statistic for NT-proBNP was 0.70. The best NT-proBNP level for predicting outcome was 1710 ng/L (sensitivity 68%, specificity 64%). When ROC curve analysis was applied to the overall cohort, including all covariates, the C-statistic was 0.76, which was slightly improved to 0.78 by adding GGT to the model.

To evaluate a potential additive effect of GGT on the prognostic value of NT-proBNP, 461 patients were stratified according to the cutoff levels for both markers as defined by ROC analysis. Five-year event rates were significantly higher in patients in whom both GGT and NT-proBNP levels were elevated as compared with patients with 1 or both markers below the cutoff levels (Figure 3). Sex-stratified and age-adjusted HR for the purpose of predicting outcome increased from 2.40 (1.34 to 4.31) in the group of NT-proBNP+/GGT− patients to 4.14 (2.32 to 7.34) in NT-proBNP+/GGT+ patients. When ROC curve analysis, including all covariates, was applied to the subcohort with NT-proBNP data available, the addition of GGT did not improve the C-statistic (0.793 versus 0.795, respectively).

Discussion

This study demonstrates that the prevalence of elevated GGT serum levels is high in patients with CHF. Moreover, in these patients, GGT plasma levels are significantly associated with disease severity and also provide prognostic information independently of established clinical and biochemical mark-

Table 3. Univariate and Multivariate Sex-Stratified Cox Regression Analysis for Death and Heart Transplantation

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

Sex-stratified Cox proportional hazards regression analysis for the combined point in relation to biochemical, demographic, and clinical factors. GFR indicates glomerular filtration rate.

*HR for GGT per log unit to predict death was 1.73 (1.2 to 2.4; *P*=0.002) and to predict heart transplantation was 1.87 (1.07 to 3.28; *P*=0.029), respectively.

ers, including age, BMI, ischemic etiology, NYHA stage, and NT-proBNP.

Role of GGT in Heart Failure

Several population-based studies have consistently shown that serum GGT levels, mostly within normal ranges, were strongly associated with most cardiovascular risk factors and predicted the development of heart disease, hypertension, stroke, and Type 2 diabetes.[7,9,11,14] In this sample of patients with stable heart failure symptoms, serum GGT concentrations were elevated in and strongly and positively associated with severity of the syndrome. This positive association was consistently demonstrated in all subgroups examined in this study. Of note, this association was also given in nonalcohol consumers, although prevalence of elevated GGT levels and absolute GGT levels was clearly higher in patients with reported alcohol consumption.

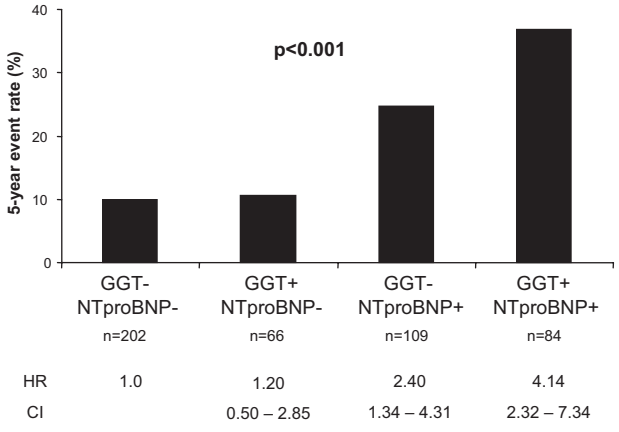

Figure 3. Additive value of GGT to NT-proBNP in predicting the combined end point. Additive value of GGT in predicting 3-year event rate in 461 patients. Patients were stratified for GGT and NT-proBNP levels according to the cutoff defined by ROC analysis. Cutoff level for GGT=67 U/L in men and 54.5 U/L in women; cutoff level for NT-proBNP=1710 ng/L. The nonsignificant HR in the small group of GGT+/NTproBNP− patients is probably due to a Type II statistical error.

Although the mechanism underlying this association remains largely unknown, several explanations for this phenomenon can be considered. Hepatic congestion is an obvious mechanistic explanation for the elevation of GGT in heart failure. We and others have previously reported that severe heart failure is associated with a cholestatic liver enzyme profile with elevated plasma levels of GGT, SAP, and bilirubin.[17–19] Local damage to the bile canaliculi caused by increased pressure within the hepatic sinusoid or ischemia as well as proinflammatory cytokine release may be involved in this process.[20] However, sparsely available literature does not provide conclusive evidence for a definite or exclusive correlation between GGT and right atrial and pulmonary artery pressures as well as severity of reduced cardiac output.[17–19,21] Hence, besides hepatic congestion and/or ischemia, other causative factors for GGT elevation in heart failure also have to be considered.

A potential involvement of GGT in the pathogenesis of heart failure is conceivable. For instance, GGT has been

repeatedly associated with atherogenesis.[3,4,22] Membrane-bound GGT catalyzes the initial step in the extracellular degradation of antioxidant glutathione, which ultimately results in the amino acids, cysteine and glycine.[2] The reactive thiol of cysteinyl-glycine can generate superoxide anion radicals and hydrogen peroxide through its interaction with free iron.[6] These GGT-mediated reactions have been shown to catalyze the oxidation of low-density lipoproteins, which may contribute to oxidative events influencing plaque evolution and rupture.[5] Elevation of GGT levels has also been postulated as a marker for evolution of the metabolic syndrome.[14,23,24] Coronary artery disease and myocardial infarction are generally regarded as the Number 1 causes of CHF, and metabolic syndrome is an established risk factor for CHF.[25–27]

Cysteine and glycine constitute the precursors of intracellular glutathione. Hence, GGT also provides a supply for uptake and reutilization in intracellular glutathione synthesis. In this way, GGT serves as a rescue enzyme for cellular glutathione synthesis and thus plays an important role in antioxidant defense systems.[28,29] Accordingly, it has been suggested that an increase in serum GGT activity could be used as a marker for increased oxidative stress in humans.[15,30] GGT is also strongly related to systemic inflammation, as suggested by Lee et al.[31] Oxidative stress and systemic inflammation are involved in ventricular remodelling and endothelial dysfunction, both of which contribute to progression of the heart failure syndrome.[1,32,33] In fact, a relationship between GGT and arterial stiffness as a potential marker of endothelial dysfunction was recently suggested.[34] Moreover, C-reactive protein and uric acid, which are considered indicators of inflammation and oxidative stress, respectively, have been associated with the development and progression of heart failure.[35,36] The fact that in our cohort of patients GGT levels were associated with both C-reactive protein and uric acid may support the potential association between GGT and inflammation and oxidative stress in patients with heart failure.

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

There is an obvious difference among GGT, ALT, and AST in heart failure. In an early study by Kubo et al,[21] patients with the most severe heart failure, as evidenced by the lowest cardiac index and the highest filling pressures, demonstrated significantly higher levels of ALT, AST, lactate dehydrogenase, and bilirubin, but not of GGT and SAP. In our current study, GGT was strongly correlated with SAP and modestly associated with ALT and AST. In addition, SAP, but not ALT or AST, was related to CHF severity. This is well in line with data from Vasconcelos et al[19] showing in a small sample of 50 patients that CHF is characterized by a progressive cholestatic profile of laboratory elevations, whereas transaminase values are elevated only in advanced heart failure.

GGT as a Potential Novel Biomarker in Heart Failure

Risk stratification is of critical importance in patients with heart failure. Biomarkers, especially BNP, have been shown to add useful information to clinical variables in the management of heart failure. However, it is unlikely that a single marker will provide all the information needed for clinical decision making, and an integrated "multimarker strategy" may be preferable.[37] In this study, GGT was an independent predictor of death or heart transplantation in stable patients with heart failure. Moreover, it seems that GGT levels above the cutoff may provide additional prognostic information in patients with elevated levels of NT-proBNP.

Of note, we provide evidence that the prognostic value of GGT is of particular interest in patients with mild heart failure symptoms, who, in general, are most difficult to risk stratify and to advise. The predictive value of elevated GGT levels was clearly greater in mildly symptomatic patients than in severely symptomatic patients. Conceivably, GGT reflects different aspects of disease severity than does clinical judgment per se. This finding, though, remains to be validated in other cohorts. Also, the predictive value of serum GGT proved significant in those aged <70 years, but seems to be of restricted validity in older patients. This finding is well in line with recent data published by Lee et al[38] suggesting that serum GGT within its normal range may be of limited usefulness in predicting cardiovascular disease mortality in patients older than 70 years.

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

Study Limitations and Future Directions

This study is limited by its observational nature. Although the study works with longitudinal data from an unselected cohort, its observational character does not permit conclusions on causal relationships. Even though medication was generally similar at study entry, patients were not monitored for changes in medication during the follow-up. Also, we did not account for the effects of devices, such as implanted defibrillators and biventricular pacemakers. Hence, differences in medication and/or implanted devices may constitute potential confounders of the study results. Furthermore, although most of the documented risk factors for fatal events were included in the analysis, the possibility of residual confounding by factors that were not accounted for cannot be entirely excluded. Data on NT-proBNP were available only in a subgroup of patients, because this marker was not established at our institution before 2004. Thus, statements on the relationship between GGT and NT-proBNP must be interpreted with caution. A point of concern relates to the interactions between GGT and NYHA class and age that were not prespecified hypotheses. However, the very low P for the interaction between GGT and NYHA class suggests it is unlikely due to chance. Nonetheless it should be confirmed elsewhere as it

already exists for interaction between GGT and age.[8,12,38] Finally, a further limitation arises from the fact that data derive from a single-center study. Therefore, results need to be confirmed elsewhere.

Summary

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

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Disclosures

None.

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CLINICAL PERSPECTIVE

Serum γ-glutamyltransferase (GGT) analysis is traditionally considered to be an index of hepatobiliary dysfunction and alcohol abuse. Recently, large epidemiological studies have revealed an association between GGT and incident cardiovascular diseases and its potential to predict disease mortality. In addition, elevation of GGT levels in patients with heart failure was suggested in previous studies. Therefore, we tested the hypothesis that GGT levels are associated with severity of heart failure and adverse prognosis in 1033 consecutive patients with chronic heart failure. We show that prevalence of elevated GGT levels is high in chronic heart failure. Furthermore, GGT reliably predicted disease severity and 5-year event rates in both men and women irrespective of established demographic, clinical, or biochemical risk factors, such as amino-terminal pro-B-type natriuretic peptide. The predictive value of elevated GGT levels was clearly greater in patients with mild to modest symptoms and in patients younger than 70 years. Although these findings remain to be validated in future studies, we strongly believe this inexpensive and easily accessible biomarker will be useful as a supplementary biomarker in chronic heart failure.