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Distribution, Determinants, and Prognostic Value of γ-Glutamyltransferase for All-Cause Mortality in a Cohort of Construction Workers from Southern Germany[1]

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Background. **Serum γ-glutamyltransferase (GGT) is commonly measured as a marker of hepatobiliary disorders in clinical practice, but little is known about its distribution and prognostic value for all-cause mortality.**

Methods. **Distribution and determinants of serum GGT levels were assessed among 8,043 construction workers ages 25–64 who underwent occupational health examinations in six centers in Southern Germany from 1986 to 1988. Study participants were followed for all-cause mortality until 1994.**

Results. **Serum GGT levels were considerably higher in this cohort than among male employees examined in a national survey conducted during the same period. The factors most strongly related to serum GGT were self-reported alcohol consumption, body mass index, diabetes, and hypertension, but relations of GGT levels were also found with nationality, occupation, and smoking. There was a strong dose–response relation between serum GGT levels and all-cause mortality (*P* value for trend <0.001). Compared with men with GGT levels below 15 U/liter (measured at 25°C), relative risks (95% CI) were 1.46 (0.86–2.49), 1.78 (1.08–2.94), 2.09 (1.26–3.45), and 3.44 (2.20–5.38) for men with GGT levels of 15–19, 20–29, 30–49, and ⩾50 U/liter, respectively. This relation was reduced but not eliminated by control for body mass index, diabetes, hypertension, alcohol consumption, and other covariates in multivariable analysis.**

Conclusion. **Serum GGT is a strong risk indicator of all-cause mortality.**

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Key Words: **γ-glutamyltransferase; mortality; risk factors.**

INTRODUCTION

γ-Glutamyltransferase (GGT) is a sensitive indicator of hepatobiliary disorders. Elevated levels are often ascribed to excessive alcohol consumption and are commonly used as a marker for excessive alcohol consumption in clinical practice [*1,2*]. GGT elevations may also be due to other factors, however, such as hepatotoxic drugs, diabetes mellitus, obesity, congestive heart failure, and pancreatic, renal, and pulmonary disorders [*3,4*].

Several studies have assessed the population distribution of GGT levels. For example, Nilssen et al. assessed GGT levels in more than 20,000 males and females ages 20–59 in the municipality of Tromsø, Norway, in 1986–1987 [*5*]. Median serum levels (measured at 37°C) were 17 and 12 units/liter for males and females, respectively, and 5.5% of the males and 1.5% of the females had values exceeding 50 units/liter. Somewhat lower levels had been reported in an earlier population survey in Tromsø conducted in 1979–1980 [*6*]. In the baseline examination of the British Regional Heart Study, the mean (geometric) level among men ages 40–59 was 15.6 units/liter (range 3.0–524.0) [*7*].

Very few population studies have assessed the prognostic value of GGT levels for mortality [*7–9*]. In a study from Malmö, Sweden, a significant association was seen between GGT and all-cause mortality, which was mainly due to an excess of alcohol-related deaths [*8*]. In the British Regional Heart Study, GGT levels were also strongly associated with all-cause mortality, largely due to a significant increase in deaths from ischemic heart disease and noncardiovascular disease causes other than cancer, but the increased mortality was seen only in the top quintile of GGT distributions [*7*].

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Alcohol consumption is common among construction workers in many countries [*10*]. Furthermore, construction workers are exposed to a variety of potentially hepatotoxic chemicals, such as organic solvents [*11,12*]. This occupational group is therefore at increased risk of hepatobiliary disorders. In this study, we analyzed distribution and prognostic value of GGT levels for all-cause mortality in a cohort of construction workers from Southern Germany.

MATERIAL AND METHODS

Design and Study Population

A retrospective cohort study was conducted in 1992–1995 among all construction workers who had undergone routine occupational health examinations in six occupational health centers of the Workmen's Compensation Board for construction workers in Württemberg (in the South of Germany) between August 1986 and December 1988. In Germany, employees in the construction industry are periodically invited to occupational health examinations by the occupational health service of the Workmen's Compensation Board. In the period of investigation, about 78% of the invited employees in Württemberg participated in the examinations.

The present study includes employees ages 25–64 and belonging to one of the following occupational groups at the time of the baseline examination: plumbers, carpenters, painters or varnishers, plasterers, bricklayers, and unskilled workers and a group of white-collar employees, consisting of office employees, engineers, and architects.

Data Collection

Baseline occupational health examinations included a physician-explored working history (including alcohol and smoking habits), a self-reported occupational and medical history, a physical exam, a lung function test, a test of visual acuity, audiometry, and a blood and serum analysis. In addition, an electrocardiogram or chest X ray was done if necessary. The exams were conducted and recorded by occupational physicians according to a standardized protocol. Serum GGT levels were measured at 25°C with Hitachi 705/717 (reference range 6–28 U/liter). Average daily amount of ethanol uptake was calculated from frequency, type of beverage, and amount of alcohol consumption, assuming that 1 liter of beer, 0.5 liter of wine, or 1 liter of cider corresponds to 50 g ethanol and that alcohol content of 1 unit of liquor (0.02 liters) is approximately 8 g ethanol. These figures reflect typical alcohol concentrations of alcoholic beverages in Southern Germany.

Active follow-up was carried out by the occupational health service between October 1992 and July 1994. Employers, employees, or their relatives (if necessary) were recontacted, in that order, to ascertain life status. Follow-up information was completed by the system of population registries in Germany for workers who could not otherwise be traced. Vital status could be ascertained for 96.4% of study participants. Completeness of follow-up was somewhat lower for foreign employees (93.6%) than for German employees (97.4%) due to migration.

Statistical Analysis

Distribution of GGT levels was analyzed by age, nationality, occupational group, self-reported alcohol consumption, smoking status, body mass index, and presence or absence of a diagnosis of diabetes, hypertension, or ischemic heart disease at the baseline examination. Alcohol consumption was categorized at cutpoints of 50 and 100 g per day among drinkers. These cutpoints correspond to 2 and 4 customary units of alcohol consumption in Southern Germany (0.5 liters of beer or 0.25 liters of wine), respectively. A minority of study participants who reported occasional alcohol consumption without further quantitative information were included in the category of men consuming 1–49 g per day. Study participants were classified as current, former, or never smokers regardless of the type of smoking (smoking of cigars and pipes was very rare in this study population).

In addition to bivariate analyses, multiple linear regression with the natural logarithm of GGT levels as the dependent variable was performed to quantify the independent effect of the aforementioned factors on GGT levels. Log transformation was performed and geometric rather than arithmetric means were calculated because of the highly skewed distribution of GGT. The age-specific (geometric) mean GGT levels among construction workers of German nationality were compared with the corresponding levels (also measured at 25°C) among male employees of German nationality in a representative national survey carried out in the Federal Republic of Germany in 1987–1988 [*13*].

All-cause mortality was assessed in relation to GGT levels in both bivariate and multivariae analyses. The following covariates were considered in multivariable analyses: age, nationality, occupation, smoking, body mass index, and presence or absence of a diagnosis of diabetes, hypertension, or ischemic heart disease at the baseline examination. Multivariable analyses were repeated with additional adjustment for self-reported alcohol consumption. The multivariable survival analyses were carried out with the proportional hazards model by Cox [*14*].

For most study variables, the proportion of missing values was very low (e.g., 0.0% for age and occupation, 0.3% for nationality, and 2.0% for serum GGT). Alcohol consumption and smoking status had been recorded less completely, however, in two of the six occupational health centers (overall completeness for these vari-

ables: 83 and 77%, respectively). Separate categories were created for individuals with unrecorded alcohol consumption or smoking status in multivariable analyses involving the respective variables.

All analyses were carried out on PC with the SAS statistical software package [*15*].

RESULTS

Study Population

Overall, 8,043 men met the inclusion criteria for this analysis (see Table 1). Among these were 850 plumbers (10.6%), 959 carpenters (11.9%), 1,087 painters (13.5%), 880 plasterers (10.9%), 2,703 bricklayers (33.6%), 1,221 unskilled workers (15.2%), and 343 white-collar employees (4.3%). The mean age was 42.8 years. The majority of study participants were of German nationality (74.3%), and 9.4, 8.4, 5.9, and 2.0% of study participants were of Yugoslavian, Italian, Turkish, or other nationality, respectively.

Distribution and Determinants of GGT

Serum GGT levels were significantly associated with all of the covariates considered in this analysis except for a diagnosis of ischemic heart disease (see Table 1). With regard to age, lowest levels were observed among 25- to 34-year-old employees and highest levels were observed among 45- to 54-year-old employees. GGT levels were considerably lower among Turkish employees than among employees of all other nationalities and among white-collar employees than among all blue-collar occupational groups included in this study. As expected, GGT levels were strongly associated and showed a clear dose–response relation with alcohol consumption. Although GGT levels were highest among former smokers, differences between never, former, and current smokers were of limited magnitude. There was a strong positive association between body mass index and serum GGT levels. Men with a diagnosis of diabetes or hypertension had considerably higher levels of GGT than men without such diagnoses.

The association of GGT levels with self-reported alcohol consumption is illustrated in more detail in Table 2. Overall, abstainers were a small minority in this cohort (n = 481), while a considerable proportion of men reported drinking 50–99 (n = 1,734) and ⩾100 g (n = 852) of alcohol per day. While only a minority of 4.2% of abstainers had serum GGT levels ⩾50 U/liter, this applied to more than one-third of men who consumed ⩾100 g of alcohol per day. Conversely, the majority of abstainers (54.9%) but only 12.2% of the heaviest drinkers had serum GGT levels below 15 U/liter.

The strong association of self-reported alcohol consumption, body mass index, diabetes, and hypertension with GGT levels was confirmed in the multiple regression analysis, with the natural logarithm of GGT levels as the dependent variable and age, nationality, occupation, alcohol consumption, body mass index, and a diagnosis of diabetes, hypertension, or ischemic heart disease as independent variables (see Table 3). Additional analyses did not reveal relevant interactions between alcohol consumption and the other covariates, and therefore no interaction terms were included in the final model. Our analysis also confirmed minor though statistically significant associations of GGT levels with age, occupation, and smoking. All of the adjusted regression coefficients for the blue-collar occupational

TABLE 1

Levels of GGT by Sociodemographic Variables, Occupation, Alcohol Consumption, Smoking, Body Mass Index, and Preexisting Diseases

Characteristic	Distribution (n = 8,043)	GGT		P value[a]
		Geometric mean	Proportion >50 U/L	
Age				
25–34	27.2%	18.5 U/L	11.1%	
35–44	22.7%	23.6 U/L	15.7%	
45–54	36.1%	24.8 U/L	18.7%	
55–64	14.0%	23.1 U/L	13.6%	<0.001
Nationality				
German	74.3%	23.6 U/L	16.9%	
Italian	8.4%	21.3 U/L	10.8%	
Yugoslavian	9.5%	20.7 U/L	13.4%	
Turkish	5.9%	13.6 U/L	2.4%	
Other	1.9%	24.0 U/L	16.8%	<0.001
Occupational group				
White collar	4.3%	17.8 U/L	5.8%	
Plumbers	10.6%	21.3 U/L	13.3%	
Carpenters	11.9%	21.1 U/L	14.8%	
Painters	13.5%	23.6 U/L	17.8%	
Plasterers	10.9%	23.1 U/L	15.3%	
Bricklayers	33.6%	23.6 U/L	16.4%	
Unskilled workers	15.2%	21.3 U/L	14.5%	<0.001
Alcohol consumption				
None	7.4%	14.4 U/L	4.2%	
1–49 g/day	53.3%	18.9 U/L	8.9%	
50–99 g/day	26.4%	28.8 U/L	22.5%	
⩾100 g/day	12.9%	39.6 U/L	36.5%	<0.001
Smoking status				
Never	18.0%	20.7 U/L	12.8%	
Former	20.2%	24.8 U/L	16.6%	
Current	61.7%	23.1 U/L	17.0%	0.003
Body mass index				
<25.0 kg/m^2	35.9%	18.2 U/L	10.9%	
25.0–29.9 kg/m^2	48.8%	23.6 U/L	16.0%	
⩾30.0 kg/m^2	15.3%	30.6 U/L	23.1%	<0.001
Diabetes				
No	95.1%	22.0 U/L	14.6%	
Yes	4.9%	32.7 U/L	27.6%	<0.001
Hypertension				
No	77.8%	20.2 U/L	11.9%	
Yes	22.2%	32.3 U/L	26.7%	<0.001
Ischemic heart disease				
No	94.7%	22.3 U/L	15.2%	
Yes	5.3%	24.2 U/L	15.4%	0.924

[a] For χ^2 test of independence of proportion >50 U/L from group.

TABLE 2

Distribution of Serum GGT by Self-Reported Alcohol Consumption

GGT	Self-reported alcohol consumption			
	None	1–49 g/day	50–99 g/day	⩾100 g/day
	(n = 481)	(n = 3,490)	(n = 1,734)	(n = 852)
<15 U/L	54.9%	39.3%	21.3%	12.2%
15–19 U/L	23.9%	19.0%	15.8%	11.9%
20–29 U/L	11.0%	18.7%	19.3%	18.1%
30–49 U/L	6.0%	13.8%	20.6%	20.7%
⩾50 U/L	4.2%	9.3%	23.0%	37.2%

TABLE 3

Results of Multiple Linear Regression with the Natural Logarithm of GGT Levels as the Dependent Variable

Predictor variable	b (SE)	t
Age		
25–34	0[a]	
35–44	0.159 (0.025)	6.41
45–54	0.120 (0.023)	5.25
55–64	0.017 (0.029)	0.57
Nationality		
German	0[a]	
Italian	−0.117 (0.032)	−3.70
Yugoslavian	−0.194 (0.030)	−6.42
Turkish	−0.368 (0.040)	−9.31
Other	0.077 (0.060)	1.29
Occupational group		
White collar	0[a]	
Plumbers	0.099 (0.048)	2.05
Carpenters	0.065 (0.048)	1.36
Painters	0.165 (0.047)	3.52
Plasterers	0.100 (0.049)	2.05
Bricklayers	0.104 (0.044)	2.35
Unskilled workers	0.095 (0.048)	1.98
Alcohol consumption		
None	0[a]	
1–49 g/day	0.148 (0.039)	3.81
50–99 g/day	0.509 (0.041)	12.39
⩾100 g/day	0.808 (0.045)	17.93
Smoking		
Never	0[a]	
Former	0.083 (0.031)	2.66
Current	0.121 (0.026)	4.60
Body mass index		
<25.0 kg/m^2	0[a]	
25.0–29.9 kg/m^2	0.219 (0.019)	11.58
⩾30.0 kg/m^2	0.384 (0.027)	14.29
Diabetes		
No	0[a]	
Yes	0.231 (0.039)	5.99
Hypertension		
No	0[a]	
Yes	0.284 (0.021)	13.36
Ischemic heart disease		
No	0[a]	
Yes	0.013 (0.037)	0.35

Note. b, regression coefficients; SE, standard error; t, t values.
[a] Reference group.

groups were positive, which indicates that the higher GGT levels among these groups than among white-collar employees are not fully explained by self-reported alcohol consumption and the other covariates. Strong differences in GGT levels by nationality with lower levels among employees of Italian, Yugoslavian, and Turkish nationality than among German employees persisted after control for alcohol consumption and the other covariates.

Overall, serum GGT levels were considerably higher among the blue-collar construction workers of German nationality included in this study than among the external comparison group of male employees of German nationality who participated in a representative national survey in 1987–1988 (see Table 4). Differences were large and statistically significant ($P < 0.001$ in t tests for differences between means) for all 5-year age groups up to age 60, and they were most prominent between ages 30 and 59.

Prognostic Value of GGT

The survival experience of the cohort is shown in Table 5. A total number of 172 deaths were recorded during the follow-up period. All-cause mortality showed a strong positive association with serum GGT levels in bivariate analyses (P value for linear trend <0.001). Compared with men with GGT levels below 15 U/liter, relative risk was 1.46 (95% CI 0.86–2.49), 1.78 (95% CI 1.08–2.94), 2.09 (1.26–3.45), and 3.44 (2.20–5.38) for men with GGT levels of 15–19, 20–29, 30–49, and ⩾50 U/liter, respectively. Relative risks were reduced to some extent by adjustment for age, nationality, occupation, smoking, body mass index, and a diagnosis of diabetes, hypertension, and ischemic heart disease in multivariable analysis. Relative risks were further reduced by additional adjustment for alcohol consumption, but there still remained a clear dose–response relation between serum GGT levels and all-cause mortality (P value for linear trend = 0.01).

TABLE 4

Age-Specific (Geometric) Mean GGT Levels among Male Construction Workers of German Nationality in the Cohort and among Male Employees of German Nationality in a National Sample

Age (years)	Construction workers	National sample
25–29	17.6 U/L	14.0 U/L
30–34	22.4 U/L	14.2 U/L
35–39	26.0 U/L	18.4 U/L
40–44	26.8 U/L	17.1 U/L
45–49	27.9 U/L	20.1 U/L
50–54	27.1 U/L	17.5 U/L
55–59	25.0 U/L	17.8 U/L
60–64	22.6 U/L	16.4 U/L

TABLE 5

Numbers of Deaths, Person-Years of Observation, Crude Death Rate, and Relative Risk of Death by Serum GGT

GGT	Deaths	Person-years	Death rate[a]	Relative risk (95% confidence interval)		
				Crude	Adjusted[b]	Adjusted[c]
<15 U/L	31	11,904	26.0	1.00[d]	1.00[d]	1.00[d]
15–19 U/L	24	6,296	38.1	1.46 (0.86–2.49)	1.31 (0.76–2.23)	1.26 (0.74–2.16)
20–29 U/L	30	6,473	46.3	1.78 (1.08–2.94)	1.54 (0.92–2.56)	1.52 (0.90–2.56)
30–49 U/L	30	5,516	54.4	2.09 (1.26–3.45)	1.61 (0.95–2.73)	1.49 (0.87–2.57)
⩾50 U/L	50	5,585	89.5	3.44 (2.20–5.38)	2.66 (1.65–4.29)	2.24 (1.35–3.72)
				$P < 0.001$[e]	$P < 0.001$[e]	$P = 0.01$[e]

[a] Deaths per 10,000 person-years.
[b] Adjusted for age, nationality (categories: German, other), occupational group (categories: white collar, blue collar), smoking (categories: never, former, current, unknown), body mass index (categories: <25.0, 25.0–29.9, and ⩾30.0 kg/m^2), diabetes, hypertension, and ischemic heart disease.
[c] Additionally adjusted for alcohol consumption (categories: none, 1–49 g/day, 50–99 g/day, ⩾100 g/day, unknown).
[d] Reference group.
[e] P value for test on linear trend.

DISCUSSION

This study demonstrated a strong positive dose–response relationship of serum GGT levels with all-cause mortality. This association was partly explained by the impact of prognostic factors associated with GGT elevations, such as diabetes, hypertension, and alcohol consumption. Nevertheless, accounting for these factors, GGT levels were shown to have additional prognostic value. In particular, the monotonic increase of all-cause mortality with GGT levels is unlikely to simply reflect the effects of alcohol consumption, since the relation between alcohol consumption and all-cause mortality was found to be U-shaped in this cohort [*16*] like in most other pertinent studies [*17,18*].

Few other prospective population studies have examined the relation between serum GGT levels and all-cause mortality [*7–9*]. These studies also showed a positive association between GGT and all-cause mortality, which was restricted, though, to the upper end of GGT distributions. Our study differs from previous studies in that it included much higher proportions of individuals with elevated GGT levels, which allowed us to assess dose–response relations with all-cause mortality over a broad range of relevant GGT elevations. Furthermore, unlike the two other large cohort studies that addressed the prognostic value of GGT, this study was not confined to middle-aged men. While we had no information on the cause of death of individuals, the previous studies have suggested that elevated GGT levels mainly lead to an excess of deaths from ischemic heart disease and noncardiovascular disease other than cancer [*7,8*]. Excess risks for mortality from these diseases might therefore be even higher than the large excess risks observed for all-cause mortality in our cohort.

Our analyses suggest that part of the association between GGT and all-cause mortality is due to diabetes and hypertension, since control for these factors reduced this relation to some extent. Other chronic diseases, such as pulmonal disorders, congestive heart failure, and pancreatic renal and pulmonary disorders, which have been found to be related to GGT elevations in other studies [*3,4*], may account for some of the prognostic value of GGT levels that persisted after multivariable adjustment in our study.

Our results are consistent with previous studies that showed a strong association of serum GGT levels with alcohol consumption. The high level of alcohol consumption among construction workers probably also partly explains the large differences in GGT levels between the participants of this study and a sample of male employees from a national survey conducted during the same period. Similarly, alcohol consumption also explains some of the differences in GGT levels between the predominantly muslim Turkish employees and other employees and between blue-collar construction workers and white-collar employees. Nevertheless, part of these differences persisted even after control for alcohol consumption. Although this may reflect residual confounding to some extent (due to the use of broad categories or imperfect reporting of alcohol consumption, to be discussed further below), other factors, such as dietary habits or occupational exposures, may also be relevant and may be worth further study.

Despite the important role of alcohol consumption in GGT elevations, the specificity of GGT as a marker of excessive alcohol consumption is limited. Other reasons for elevated GGT levels, such as those identified in this paper (body weight, diabetes, hypertension), and other potential reasons, such as hepatotoxic drugs, congestive heart failure, or pancreatic, renal, or pulmonary disorders, also require careful consideration. While the higher levels of GGT among painters than among other occupational groups found in our study point to the potential role of hepatotoxic chemicals, our

study had insufficient power to address this question in more detail. Newer, more specific markers, such as carbohydrate-deficient transferrin, may be useful to distinguish GGT elevations due to excessive alcohol consumption from GGT elevations due to other reasons [*19*].

Like in most other pertinent epidemiologic studies, alcohol consumption is likely to be unprecisely reported with a tendency toward underreporting by part of the study participants in our investigation [*20*]. Misclassification of alcohol consumption would most likely have led to underestimation of the dose–response relation between this variable and serum GGT levels [*21*] and to imperfect control for potential confounding by alcohol consumption of the relation between other covariates and GGT levels [*22*] and of the relation between GGT levels and all-cause mortality.

In contrast to alcohol consumption, serum GGT, the variable of primary interest in this study, is not affected by reporting problems and could be almost completely ascertained in the entire cohort by a simple laboratory test. The results of our study suggest that screening for elevated serum GGT levels could be a powerful tool to identify individuals at increased risk of mortality for whom prevention and treatment of eventual underlying diseases, limitation of alcohol consumption [*23*], or protection from other relevant exposures could be most beneficial. Preferably, however, pertinent measures should be taken prior to the development of GGT elevations.

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