Clinical Chemistry 61:9
1173–1181 (2015)

γ-Glutamyl Transferase Is Associated with Mortality Outcomes Independently of Fatty Liver

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BACKGROUND: High serum enzyme activity levels of γ-glutamyl transferase (GGT) are associated with increased risk of mortality, but whether this is mediated by fatty liver, as a common cause of high GGT levels, is uncertain. Our aim was to test whether GGT levels are associated with all-cause, cancer, and cardiovascular (CVD) mortality, independently of fatty liver.

METHODS: In an occupational cohort (n = 278 419), causes of death (*International Statistical Classification of Diseases and Related Health Problems*, 10th revision) were recorded over 7 years. Liver function tests and liver fat [measured by ultrasonographic standard criteria or fatty liver index (FLI)] were assessed at baseline. We used Cox proportional hazards models to estimate adjusted hazard ratios (HRs) and 95% CIs of all-cause, cancer, and CVD mortality for GGT quartiles (with lowest GGT quartile as reference).

RESULTS: There were 136, 167, 265, and 342 deaths across increasing GGT quartiles. After adjusting for liver fat (by ultrasound diagnosis) in the fully adjusted model, all-cause and cancer mortality were increased in the highest GGT quartile [HR 1.50 (95% CI 1.15–1.96) and 1.57 (1.05–2.35), respectively]. For CVD mortality, the hazard was attenuated: HR 1.35 (95% CI 0.72–2.56). After adjusting for FLI in the fully adjusted model, HRs for all-cause, cancer, and CVD mortality were 1.46 (0.72–2.56), 2.03 (1.02–4.03), and 1.16 (0.41,3.24), respectively.

CONCLUSIONS: There were similar hazards for all-cause and cancer mortality and attenuated hazards for CVD mortality for people in the highest GGT quartile, adjusting for fatty liver assessed by either ultrasound or FLI.

γ-Glutamyl transferase (GGT)[9] serum enzyme activity is frequently measured in primary care or as part of health checkups. Modestly increased results are often reported and are of uncertain clinical relevance. In addition to an association with liver disease, it is now evident that modestly increased GGT levels may also occur with other conditions for which early diagnosis and treatment may be appropriate *(1)*.

GGT may be involved in the pathogenesis of cardiovascular disease (CVD), especially ischemic heart disease, and it has been suggested that investigation of the role of GGT in the mechanism of cardiovascular diseases will be helpful in developing preventive strategies and treatment methods *(2)*. Additionally, it has been shown that GGT levels are a strong risk indicator of occupational disability even at levels of GGT in the reference interval *(3)*.

Recent evidence and metaanalyses suggest that GGT is associated with cardiovascular mortality and all-cause mortality *(4–9)*. However, to date, no large cohort studies have evaluated associations between GGT and mortality outcomes after accounting for fatty liver.

Consequently, exploring relationships between serum enzyme activity of GGT and mortality outcomes after adjustment for fatty liver for both alcoholic liver disease and nonalcoholic fatty liver disease (NAFLD) would provide valuable insight to help inform the true nature of relationships between liver function test results and cardiovascular, cancer, and all-cause mortality.

In this study of a large (approximately 250 000) Korean occupational cohort of predominantly a single ethnicity, in which we were able to adjust for multiple potential confounders, our aim was to test whether GGT serum enzyme activity values are associated with all-cause, cancer, and CVD mortality, independently of fatty liver.

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Received February 27, 2015; accepted June 18, 2015.
Previously published online at DOI: 10.1373/clinchem.2015.240424

[9] Nonstandard abbreviations: GGT, γ-glutamyl transferase; CVD, cardiovascular disease; NAFLD, nonalcoholic fatty liver disease; ALT, alanine aminotransferase; BMI, body mass index; FLI, fatty liver index; HR, hazard ratio.

Materials and Methods

STUDY POPULATION

The study population consisted of individuals who participated in a comprehensive health screening program at Kangbuk Samsung Hospital, Seoul, Korea, from 2002 to 2009 (n = 278 419). The purpose of the screening program was to promote health through early detection of chronic diseases and their risk factors. Additionally, the Korean Industrial Safety and Health Law mandates that working individuals participate in an annual or biennial health examination. About 60% of the participants were employees of companies or local governmental organizations, and the remaining participants were spouses who registered individually for the program.

For this analysis, individuals were excluded for at least 1 of the following reasons: 1963 individuals with alanine aminotransferase (ALT) ≥120 IU/L; 80 individuals with missing data on GGT at baseline; 2627 individuals with histories of malignancy; 11 individuals with unknown vital status; 12 016 individuals with positive serologic markers for hepatitis B or C virus; and 2386 individuals with total bilirubin ≥2.34 mg/dL (40 μmol/L). As some individuals met >1 criterion for exclusion, the total number of eligible individuals for the study was 260 260.

This study was approved by the Institutional Review Board of Kangbuk Samsung Hospital. Requirement for informed consent was waived, as deidentified information was retrieved retrospectively.

MEASUREMENTS

As part of the health screening program, individuals completed questionnaires related to their medical and social history and medication use. Individuals were asked about duration of education (years), frequency of exercise [none, less than once a week, at least once a week, or ≥3 times per week (regular exercise)], smoking history (never, former, or current), and alcohol consumption (g/week).

Trained staff also collected anthropometric measurements and vital statistics. Body weight was measured in light clothing with no shoes to the nearest 0.1 kg with a digital scale. Height was measured to the nearest 0.1 cm. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared. Blood pressure was measured with standard mercury sphygmomanometers.

Blood samples were collected into serum-separating tubes after ≥10 h of fasting and analyzed in the same core clinical laboratory. The core clinical laboratory has been accredited and participates annually in inspections and surveys by the Korean Association of Quality Assurance for Clinical Laboratories. Reference intervals were 10–90 IU/L for GGT and 10–40 IU/L for ALT. Serum glucose was measured by the hexokinase method, and lipid concentrations were measured by an enzymatic colorimetric assay with Bayer Reagent Packs. Measurements including GGT and ALT were undertaken on an automated chemistry analyzer (Advia 1650™ Autoanalyzer, Bayer Diagnostics). The CVs for quality control samples of low and high concentrations, respectively, were 0.8%–1.9% and 0.6%–1.6% for total cholesterol, 1.2%–2.7% and 0.9%–3.1% for HDL cholesterol, 0.9%–1.8% and 0.2%–1.1% for triglycerides, and 0.9%–2.4% and 0.8–2.2% for LDL cholesterol. Serum GGT levels were measured with the same reagent on the same autoanalyzer between 2002 and 2009, and the CVs for QC samples of low and high levels were 1.3%∼3.1% and 0.7%∼1.7% during the period for samples within the reference interval (10–90 IU/L).

Abdominal ultrasonography (Logic Q700 MR, GE) with a 3.5-MHz probe was performed in all participants by experienced clinical radiologists, and fatty liver was diagnosed or excluded on the basis of standard criteria, including hepatorenal echo contrast, liver brightness, and vascular blurring. Fatty infiltration was classified as an increase in echogenicity of the liver compared with that of the renal cortex where the diaphragm and intrahepatic vessels appeared healthy *(10)*. Metabolic syndrome was defined according to the international harmonized classification *(11)*. To identify people with fatty liver due to probable NAFLD, we diagnosed NAFLD by the presence of fatty liver in people who consume no alcohol or modest amounts of alcohol [daily intake <20 g (2.5 U) in women and <30 g (3.75 U) in men]. We also assessed fatty liver by estimation of the fatty liver index (FLI), which is calculated with an algorithm on the basis of BMI, waist circumference, triglycerides, and GGT and has an accuracy of 0.84 (95% CI 0.81–0.87) for detecting fatty liver *(12)*.

ASCERTAINMENT OF MORTALITY

With identification numbers assigned to individuals at birth, we identified deaths among participants by matching the information to death records from the National Statistical Office. Causes of death were coded centrally by trained coders by use of the *International Statistical Classification of Diseases and Related Health Problems*, 10th revision.

STATISTICAL ANALYSES

We performed statistical analysis with STATA version 11.2 (StataCorp LP). Reported *P* values were 2-tailed, and those <0.05 were considered statistically significant. The distribution of continuous variables was evaluated, and transformations were conducted for non–normally distributed variables.

We used Cox proportional hazards models to estimate hazard ratios (HRs) and 95% CIs for mortality in each quartile, compared with the lowest quartile as reference for GGT. For testing linear risk trends, we used the quartile rank as a continuous variable in the regression models. We checked the proportional hazards assumption by examining graphs of estimated log (–log) survival. The models were initially adjusted for baseline age and sex, smoking status, alcohol intake, regular exercise, BMI, LDL cholesterol, HDL cholesterol, and triglyceride concentrations (model 1). In model 2, the models were further adjusted for hypertension, diabetes, history of heart disease, and history of stroke. In model 3, the models were further adjusted for fatty liver (NAFLD or AFLD). Associations between GGT quartiles and all-cause, cancer, and CVD mortality were examined in clinically relevant subgroups. In an alternative analysis, model 3 was adjusted for fatty liver index, rather than ultrasound-detected fatty liver. *P* values are presented for the significance of the trend in HRs across GGT quartiles. $P < 0.05$ was considered significant.

Results

Table 1 shows the baseline characteristics of all individuals who were alive at the beginning of the study period, compared with the baseline characteristics of those who died during the follow-up period. During the follow-up period, 910 people died; of those, 178 died from CVD and 390 from cancer. At baseline, measured GGT enzyme activities were markedly higher in the group who died during follow-up compared with survivors. The proportion of individuals consuming >20 g/day of alcohol at baseline was higher in those who died during the follow-up period. Additionally, the proportion of individuals who reported not consuming alcohol (0 g/day) at baseline was slightly higher in the group who died during the follow-up period. Table 2 shows the GGT enzyme activity levels in different categories of individuals at baseline. GGT levels were found to be higher in people who smoked, consumed alcohol, had metabolic syndrome, had hypertension, had NAFLD, and had AFLD compared with individuals without each of these risk factors.

The cutpoints for GGT quartiles and the relationships with all-cause mortality are described in Table 3. With increasing GGT enzyme activity level quartiles, the number of deaths was 136, 167, 265, and 342. There was an increased risk of death in people in the highest compared with the lowest quartile, with the number of deaths increasing across quartiles for a fully adjusted HR of 1.50 (95% CI 1.15–1.96) and a significant trend in increase in HR with increasing levels of GGT quartiles ($P < 0.001$). Importantly, this association was not attenuated after adjustment for fatty liver or alcohol intake.

Table 4 provides information about the association between GGT quartiles and death from cancer. With increasing GGT, the number of deaths with increasing quartiles was 64, 78, 117, and 131. There was a significantly increased risk of cancer among people in the highest quartile of GGT [HR 1.57 (95% CI 1.05–2.35)], and importantly, the *P* value for the trend across increasing quartiles was significant ($P = 0.013$).

For CVD mortality (Table 5), the number of deaths was 22, 31, 55, and 70 with increasing GGT quartiles. The effect size for the highest compared with the lowest GGT quartile was similar to that observed for all-cause and cancer mortality, but this was not statistically significant [HR 1.35 (95% CI 0.72–2.56), $P = 0.19$].

Although the associations shown in Tables 3–5 were adjusted for all measured potential confounders, we also undertook sensitivity analyses by repeating the analyses after exclusion of certain subgroups. Associations between GGT serum enzyme activities with risk of all-cause mortality are shown in Table 6; with risk of cancer mortality in Supplementary Table 1, which accompanies the online version of this article at http://www.clinchem.org/content/vol61/issue9; and with risk of CVD mortality in online Supplementary Table 2. There was a strong association between GGT and cancer mortality in nonsmokers, and there was a significant interaction between smoking status and GGT enzyme activities in the association between GGT and cancer mortality (see online Supplementary Table 1). There was an interaction between GGT and BMI in the association between GGT and all-cause mortality (Table 6) and cancer mortality (see online Supplementary Table 1). Exclusion of fatty liver or diabetes did not materially affect the results, whereas exclusion of patients with CVD did result in a weaker association between GGT and all-cause mortality in people without CVD (Table 6). Nevertheless, the association between increasing GGT and all-cause mortality remained significant in people without CVD.

Because the sensitivity of ultrasound is poor for detection of low amounts of liver fat (<30%), we also adjusted the regression models for FLI, rather than ultrasound. Waist circumference was available at baseline in only 58% of the cohort, and therefore FLI was calculated only in this group of individuals (n = 152 092). These data showing the HRs for GGT quartiles and all-cause, cancer, and CVD mortality are shown in online Supplementary Tables 3–5. After adjusting for FLI in the fully adjusted model, HRs for all-cause, cancer, and CVD mortality were 1.46 (95% CI 0.72–2.56), 2.03 (1.02–4.03), and 1.16 (0.41–3.24), respectively. The associations of serum GGT levels with all-cause, cancer, and CVD mortality were similar across subgroups of study participants, with no interactions by age group, sex, obesity, metabolic syndrome, smoking, drinking, regular ex-

Table 1. Baseline characteristics of patients according to vital status after 7 years of follow-up.[a]

Characteristics	Alive	Dead	*P*
n	259 350	910	
Age, years	40.2 (9.97)	53.4 (13.4)	<0.001
Male sex	55.9	72.9	<0.001
BMI, kg/m^2	23.5 (3.1)	23.8 (3.2)	0.0050
Systolic blood pressure, mmHg	114.8 (14.6)	124.6 (19.2)	<0.001
Diastolic blood pressure, mmHg	74.3 (10.1)	78.9 (11.8)	<0.001
Glucose, mg/dL	95.0 (16.9)	106.7 (38.2)	<0.001
Total cholesterol, mg/dL	195.4 (35.3)	203.7 (41.8)	<0.001
LDL cholesterol, mg/dL	113.0 (29.8)	116.5 (34.2)	0.0004
HDL cholesterol, mg/dL	55.4 (12.4)	54.2 (13.4)	0.0055
Triglycerides, mg/dL	106 (74–156)	128 (90–186)	<0.001
ALT, IU/L	25.4 (15.6)	26.9 (15.8)	<0.001
AST, IU/L	24.1 (8.8)	28.2 (16.4)	<0.001
GGT, IU/L	19 (12–34)	26 (16–46)	<0.001
Total bilirubin, mg/dL	0.9 (0.3)	0.9 (0.4)	0.6057
Conjugated bilirubin, mg/dL	0.3 (0.1)	0.3 (0.1)	0.065
Smoking status			<0.001
Never smoker	54.9	37.8	
Former smoker	16.8	25.2	
Current smoker	28.4	37.0	
Alcohol use, g/day			<0.001
0	40.1	40.8	
<20	46.1	36.6	
≥20	13.8	22.5	
Regular exercise[b]	17.1	15.9	0.311
History of heart disease	5.0	5.4	0.567
History of stroke	0.4	2.3	<0.001
Diabetes	4.0	16.5	<0.001
Hypertension	17.5	42.3	<0.001
Metabolic syndrome[c]	16.8	31.0	<0.001
Fatty liver			0.108
No	73.7	71.3	
Yes	26.3	28.7	
NAFLD or AFLD			0.045
NAFLD	21.6	23.3	
AFLD	4.9	6.6	

[a] Data are mean (SD), median (IQR), or %. To convert glucose in mg/dL to mmol/L, multiply by 0.05551; to convert cholesterol in mg/dL to mmol/L, multiply by 0.02586; to convert bilirubin in mg/dL to μmol/L, multiply by 17.10.
[b] More than 3 times/week.
[c] For estimating metabolic syndrome, waist circumference was available in only 58% of the whole cohort. Therefore the denominators for calculating metabolic syndrome in the group who were alive was 45 757, and in the group who had died, 386.

ercise, or fatty liver (Table 6 and online Supplementary Tables 1 and 2).

For comparison with the data for GGT serum enzyme activities and mortality outcomes, and because ALT enzyme activities are often increased with fatty liver disease, we compared associations between another liver enzyme, ALT, and mortality outcomes (see online Supplementary Tables 6–8). These data showed a different

Table 2. Baseline GGT serum enzyme activity levels according to different patient characteristics.[a]

Characteristic	GGT, IU/L
Never smoker	14 (10–22)
Former smoker	27 (17–44)
Current smoker	30 (19–51)
Alcohol use, g/day	
0	13 (10–21)
<20	22 (14–36)
≥20	42 (26–71)
Regular exercise	19 (12–32)
No regular exercise	19 (12–34)
No metabolic syndrome	17 (11–29)
Metabolic syndrome	36 (22–61)
No diabetes	19 (12–33)
Diabetes	33 (20–60)
No hypertension	18 (11–30)
Hypertension	29 (17–51)
No fatty liver	16 (11–26)
Fatty liver	34 (22–55)
NAFLD	30 (20–47)
AFLD	57 (38–92)

[a] Data are HR (95% CI).

direction of associations between ALT and each of the mortality outcomes compared with those observed for GGT levels. For all-cause mortality, in the fully adjusted model, there was a borderline significant inverse association between ALT and all-cause mortality, and for cancer mortality there was a significant inverse association with ALT.

Discussion

Our data obtained in a large occupational cohort of approximately 250 000 people show that higher levels of GGT were strongly associated with increased risk of death from all causes and from cancer, independently of fatty liver and other important potential confounders including age, sex, smoking status, alcohol intake, exercise, BMI, hypertension, diabetes, history of heart disease, and history of stroke.

In a narrative review of studies that have investigated the relationship between GGT enzyme activity results and mortality, it was noted that adjustment for confounders is often incomplete *(13)*. Previously, increased GGT levels have been shown to be associated with increased cardiovascular mortality in 163 944 Austrian adults followed for up to 17 years *(14)*, whereas others have failed to show an association between increased GGT and cardiovascular mortality in a death certificate–based 12-year follow-up of 14 950 adult participants in the third US National Health and Nutrition Examination Survey *(15)*. The role of ultrasound in people with increased GGT has been investigated, and it has been shown previously that liver ultrasound improves risk stratification in individuals with increased GGT levels *(16)*. In our relatively young cohort, we did not observe an increase in all-cause, cancer, or CVD mortality with fatty liver per se that was attributable to NAFLD or AFLD (data not shown). Such a finding may reflect the fact that our cohort was relatively young (at baseline, the mean age of our individuals who were alive at follow-up was 40 years; that of those who died during follow-up was 53 years). Thus nonalcoholic steatohepatitis, which is well known to be associated with increased risk of CVD, and which cannot be diagnosed specifically by ultrasound, may be rare in our cohort. Similarly, steatohepatitis due to alcohol, which is known to be associated with

Table 3. Risk of death from all causes by GGT quartile.[a]

	Person-years	Deaths, n	Mortality rate (per 10 000 person-years)	Age · sex-adjusted HR (95% CI)	Multivariate HR (95% CI)[b]		
					Model 1	Model 2	Model 3
GGT quartile, IU/L							
1–12	291 168.4	136	4.7	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
13–19	260 717.4	167	6.4	0.90 (0.72–1.14)	1.04 (0.81–1.34)	1.02 (0.80–1.31)	1.03 (0.80–1.33)
20–34	275 813.7	265	9.6	1.11 (0.88–1.38)	1.29 (1.00–1.65)	1.24 (0.97–1.59)	1.28 (1.00–1.65)
≥35	273 610.3	342	12.5	1.38 (1.10–1.72)	1.53 (1.18–2.00)	1.43 (1.09–1.86)	1.50 (1.15–1.96)
P for trend				<0.001	<0.001	0.002	<0.001

[a] Cox proportional hazard models were used to estimate HRs and 95% CIs.
[b] Model 1: adjusted for age, sex, smoking status, alcohol intake, regular exercise, BMI, LDL cholesterol, HDL cholesterol, and triglycerides. Model 2: model 1 plus adjustment for hypertension, diabetes, history of heart disease, and history of stroke. Model 3: model 2 plus fatty liver.

Table 4. Risk of death from cancer by GGT quartile.[a]

	Person-years	Events, n	Mortality rate (per 10 000 person-years)	Age · sex-adjusted HR (95% CI)	Multivariate HR (95% CI)[b]		
					Model 1	Model 2	Model 3
GGT quartile, IU/L							
1–12	291 168.4	64	2.2	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
13–19	260 717.4	78	3.0	0.92 (0.66–1.30)	1.10 (0.76–1.59)	1.11 (0.77–1.60)	1.13 (0.78–1.63)
20–34	275 813.7	117	4.2	1.10 (0.79–1.53)	1.37 (0.95–1.98)	1.38 (0.95–1.99)	1.46 (1.01–2.11)
≥35	273 610.3	131	4.8	1.24 (0.89–1.73)	1.44 (0.97–2.15)	1.44 (0.98–2.15)	1.57 (1.05–2.35)
P for trend				0.084	0.041	0.042	0.013

[a] Cox proportional hazard models were used to estimate HRs and 95% CIs.
[b] Model 1: adjusted for age, sex, smoking status, alcohol intake, regular exercise, BMI, LDL cholesterol, HDL cholesterol, and triglycerides. Model 2: model 1 plus adjustment for hypertension, diabetes, history of heart disease, and history of stroke. Model 3: model 2 plus fatty liver.

mortality outcomes such as liver cancer, may also be rare in this cohort.

To assess the effect of age in the study participants, we examined the association between GGT and CVD mortality, stratified by age <50 or ≥50 years. Similar to Ghouri et al. *(13)*, we also observed a trend toward a stronger positive association between GGT and CVD mortality in the younger age group, although it should be noted that the 95% CIs were wide and included overlap between the 2 age groups (see online Supplementary Table 2). Previously, it has been shown that there is a greater effect of moderate alcohol consumption to increase liver enzymes with increasing BMI *(17)*, and in men, synergism has been demonstrated between smoking and alcohol use to increase GGT levels *(18)*. Interestingly, our data demonstrated a strong association between GGT and cancer mortality in nonsmokers and also showed a significant interaction between smoking status and GGT enzyme activity levels (in the association between GGT and cancer mortality). Our results also showed borderline nonsignificant trends for the interaction between alcohol consumption and GGT levels for both all-cause and cancer mortality, and there was an interaction between GGT and BMI when we investigated the association between GGT and all-cause mortality (Table 6) and cancer mortality (see online Supplementary Table 1). Although we cannot be certain of the cause of death in those currently abstinent of alcohol, we noted a marked increase in the HR for death in people who were abstinent of alcohol and also in the highest GGT quartile. Thus these data serve to emphasize that people in the highest quartile of GGT are not dying from alcohol-induced liver disease. There was also a trend toward an increase in HR for CVD mortality in individuals who did not have fatty liver, so it is plausible that the association between increased GGT and CVD reflects another cause that is responsible for increasing GGT, rather than fatty liver. As has been suggested previously, it is plausible that increased GGT levels in people who do not have liver disease and who do

Table 5. Risk of death from CVD by GGT quartile.[a]

	Person-years	Events, n	Mortality rate (per 10 000 person-years)	Age · sex-adjusted HR (95% CI)	Multivariate HR (95% CI)[b]		
					Model 1	Model 2	Model 3
GGT quartile, IU/L							
1–12	291 168.4	22	0.8	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
13–19	260 717.4	31	1.2	1.01 (0.58–1.76)	0.98 (0.53–1.81)	0.92 (0.50–1.69)	0.92 (0.50–1.70)
20–34	275 813.7	55	2.0	1.35 (0.79–2.31)	1.33 (0.73–2.39)	1.18 (0.65–2.14)	1.21 (0.67–2.20)
≥35	273 610.3	70	2.6	1.66 (0.97–2.83)	1.57 (0.84–2.94)	1.30 (0.69–2.44)	1.35 (0.72–2.56)
P for trend				0.016	0.069	0.243	0.194

[a] Cox proportional hazard models were used to estimate HRs and 95% CIs.
[b] Model 1: adjusted for age, sex, smoking status, alcohol intake, regular exercise, BMI, LDL cholesterol, HDL cholesterol, and triglycerides. Model 2: model 1 plus adjustment for hypertension, diabetes, history of heart disease, and history of stroke. Model 3: model 2 plus fatty liver.

Table 6. Associations between GGT serum enzyme activity levels and all-cause mortality in clinically relevant subgroups.[a]

Subgroup	n	GGT quartile, IU/L				*P* for trend	*P* for interaction
		1–12 IU/L	13–19 IU/L	20–34	≥35		
Sex							0.6965
Male	145 611	1.00 (reference)	1.08 (0.72–1.61)	1.38 (0.94–2.02)	1.56 (1.06–2.31)	0.002	
Female	114 649	1.00 (reference)	1.06 (0.76–1.49)	1.20 (0.80–1.80)	1.77 (1.12–2.82)	0.031	
Age, years							0.6192
<50	216 915	1.00 (reference)	1.02 (0.70–1.48)	1.26 (0.85–1.88)	1.39 (0.90–2.14)	0.078	
≥50	43 345	1.00 (reference)	1.18 (0.83–1.67)	1.55 (1.11–2.18)	1.76 (1.23–2.52)	<0.001	
BMI, kg/m^2							0.0358
<25	180 634	1.00 (reference)	0.92 (0.69–1.22)	1.06 (0.79–1.42)	1.52 (1.12–2.07)	0.002	
≥25	79 604	1.00 (reference)	1.46 (0.83–2.57)	1.87 (1.08–3.23)	1.59 (0.90–2.83)	0.245	
Abdominal obesity							0.3179
No	116 528	1.00 (reference)	1.07 (0.70–1.63)	1.19 (0.78–1.83)	1.49 (0.95–2.34)	0.049	
Yes	34 781	1.00 (reference)	2.14 (0.97–4.74)	1.75 (0.78–3.91)	1.88 (0.82–4.34)	0.424	
Metabolic syndrome							
No	216 221	1.00 (reference)	1.01 (0.76–1.33)	1.19 (0.90–1.57)	1.48 (1.10–2.00)	0.003	0.6257
Yes	43 916	1.00 (reference)	1.06 (0.57–1.95)	1.29 (0.72–2.32)	1.24 (0.68–2.27)	0.421	
Smoking							0.4438
No	182 898	1.00 (reference)	1.02 (0.77–1.35)	1.29 (0.97–1.72)	1.64 (1.20–2.24)	0.001	
Former or current	72 630	1.00 (reference)	1.05 (0.59–1.85)	1.24 (0.72–2.12)	1.31 (0.75–2.28)	0.193	
Drinking							0.0992
No	101 426	1.00 (reference)	1.13 (0.82–1.55)	1.43 (1.02–1.99)	2.05 (1.42–2.96)	<0.001	
Yes	151 374	1.00 (reference)	0.86 (0.57–1.30)	1.06 (0.71–1.57)	1.18 (0.79–1.76)	0.076	
Regular exercise							0.2883
Yes	44 066	1.00 (reference)	0.64 (0.34–1.19)	0.96 (0.53–1.75)	1.25 (0.66–2.37)	0.187	
No	213 053	1.00 (reference)	1.13 (0.86–1.49)	1.37 (1.04–1.80)	1.58 (1.17–2.12)	0.001	
Fatty liver							0.2106
No	191 656	1.00 (reference)	1.01 (0.77–1.32)	1.26 (0.96–1.66)	1.68 (1.26–2.26)	<0.001	
Yes	68 534	1.00 (reference)	0.98 (0.49–1.96)	1.01 (0.52–1.95)	0.95 (0.48–1.85)	0.762	
NAFLD or AFLD							
NAFLD	54 498	1.00 (reference)	0.95 (0.47–1.89)	0.92 (0.47–1.78)	0.83 (0.41–1.65)	0.472	
AFLD	12 357	–	1.00 (reference)	2.05 (0.26–16.09)	2.00 (0.27–14.75)	0.581	
Diabetes							0.6804
No	249 856	1.00 (reference)	1.02 (0.79–1.33)	1.28 (0.98–1.67)	1.39 (1.04–1.86)	0.007	
Yes	10 402	1.00 (reference)	1.16 (0.50–2.67)	1.38 (0.62–3.05)	2.20 (0.99–4.89)	0.007	
History of CVD							0.1947
No	246 497	1.00 (reference)	0.99 (0.77–1.28)	1.21 (0.94–1.57)	1.38 (1.05–1.82)	0.005	
Yes	13 763	1.00 (reference)	3.72 (0.81–17.0)	5.10 (1.15–22.60)	7.85 (1.73–35.56)	0.002	

[a] Data are adjusted HR (95% CI). Adjusted for age, sex, smoking status, alcohol intake, regular exercise, BMI, hypertension, diabetes, history of stroke, history of heart disease, fatty liver, LDL cholesterol, HDL cholesterol, and triglycerides.

not consume alcohol may be a marker of oxidative stress *(19–21)*.

A very recent systematic review and metaanalysis has been undertaken of the association between GGT and ALT enzyme activities and risk (incidence and/or mortality of overall and site-specific cancers) *(22)*. Comparing top vs bottom thirds of baseline circulating GGT levels, pooled risk ratios (95% CIs) were 1.32 (1.15–1.52) for overall cancer, 1.09 (0.95–1.24) for breast cancer and cancers of female genital organs, 1.09 (1.02–1.16) for cancers of male genital organs, 1.94 (1.35–2.79) for cancers of digestive organs, and 1.33 (0.94–1.89) for cancers of respiratory and intrathoracic organs. In contrast to these authors' data for GGT, for ALT, they showed variable associations and also geographic differences in the associations between ALT and overall cancer risk. Our data, on the other hand, showed a significant trend across quartiles

of the hazard for cancer mortality; importantly, this hazard was independent of fatty liver and other potential confounders. Additionally, in this predominantly single-ethnicity Korean cohort, we show a strong independent inverse association between ALT and cancer mortality in the fully adjusted model [HR 0.62 (95% CI 0.42–0.90)] (see online Supplementary Table 7).

For cardiovascular and all-cause mortality, a recent metaanalysis of 7 studies with 273 141 participants showed a pooled relative risk for highest vs lowest GGT quartile of 1.52 (95% CI 1.36–1.70) for cardiovascular mortality and 1.56 (1.34–1.83) for all-cause mortality. Importantly, there was considerable heterogeneity in the thresholds of GGT enzyme activity level that defined the highest GGT quartile, and these ranged from >22 to >56 IU/L. Furthermore, subgroup analyses on the basis of ethnicity, sex, follow-up duration, and sample size showed inconsistent results, and the summary estimates were different for the Asian subgroup *(4)*. Our data in a predominantly single-ethnicity Korean cohort, therefore, add to these findings and also add to the findings from the pooled analysis of results from the British Women's Heart and Health Study *(23)*. In the latter study, involving 10 prospective studies, a change of 1 IU/L GGT was shown to be associated with a fully adjusted HR of 1.20 (95% CI 1.02–1.40) for coronary heart disease and 1.54 (1.20–2.00) for stroke *(23)*. However, once again, heterogeneity was noted between studies; there also was considerable uncertainty about variable effects resulting from inclusion of different ethnicities, as the HRs were substantially decreased when 2 studies in Asian populations were excluded from the analyses.

Limitations to our study need to be considered. Because we have assessed only the presence or absence of fatty liver disease defined by ultrasound and FLI (and not liver histology obtained by biopsy), we are unable to comment on associations between liver function tests and mortality outcomes in people with more advanced forms of liver disease. Furthermore, recent work from Hart et al. *(24)* shows clearly that only modest alcohol consumption (within the threshold that some use to define NAFLD and below the threshold used to define AFLD) acts synergistically with obesity to increase markedly the risk of developing cirrhosis. Our estimate of alcohol intake is imprecise, as data on alcohol consumption were available only from self-administered questionnaire data. Additionally, people who identified as abstinent of any alcohol consumption at the time of the questionnaire (at the occupational health checkup) may previously have consumed alcohol, and the precise threshold of daily alcohol intake that should be used to define AFLD is uncertain *(25)*. In support of the notion that the positive association between GGT levels and mortality outcomes is unlikely to be confounded by fatty liver, we also examined ALT, as it is often affected by fatty liver disease due to NAFLD or alcoholic liver disease. As can be seen in online Supplementary Tables 6–8, the direction of the association between ALT and mortality outcomes was in the opposite direction from that of GGT with mortality outcomes. There was an inverse trend (not significant) for the association between ALT and all-cause mortality, and there was a significant inverse association between ALT and cancer mortality.

In conclusion, over a 7-year period, there was an increased risk of all-cause and cancer mortality with higher levels of GGT in this Korean cohort. There were similar hazards for all-cause and cancer mortality, whereas the hazard was attenuated for CVD mortality for people in the highest GGT quartile, adjusting for fatty liver (assessed by either ultrasound or FLI). Although we are uncertain as to the mechanism contributing to increased GGT enzyme activity levels and the hazard for mortality outcomes, it is plausible that increased cellular oxidative stress may underpin the association between increased GGT and disease outcomes.

Author Contributions: *All authors confirmed they have contributed to the intellectual content of this paper and have met the following 3 requirements: (a) significant contributions to the conception and design, acquisition of data, or analysis and interpretation of data; (b) drafting or revising the article for intellectual content; and (c) final approval of the published article.*

Authors' Disclosures or Potential Conflicts of Interest: *Upon manuscript submission, all authors completed the author disclosure form. Disclosures and/or potential conflicts of interest:*

Employment or Leadership: None declared.
Consultant or Advisory Role: None declared.
Stock Ownership: None declared.
Honoraria: None declared.
Research Funding: C.D. Byrne, Southampton National Institute for Health Research Biomedical Research Centre, UK.
Expert Testimony: None declared.
Patents: None declared.

Role of Sponsor: The funding organizations played no role in the design of study, choice of enrolled patients, review and interpretation of data, or preparation or approval of manuscript.

Acknowledgments: We acknowledge the efforts of the health screening group at Kangbuk Samsung Hospital, Korea.

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