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Elevation of Serum Aminotransferase Levels and Future Risk of Death from External Causes: A Prospective Cohort Study in Korea

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Purpose: The association between liver enzymes and death from external causes has not been examined. We investigated the association between serum aminotransferase levels and external-cause mortality in a large prospective cohort study.

Materials and Methods: A total of 142322 subjects of 35–59 years of age who completed baseline examinations in 1990 and 1992 were enrolled. Mortalities were identified using death certificates. Serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels were categorized into quintiles. Sub-distribution hazards ratios and 95% confidence intervals (CIs) were estimated using a competing risks regression model in which deaths from other causes were treated as competing risks.

Results: Of 8808 deaths, 1111 (12.6%) were due to external causes. Injury accounted for 256 deaths, and suicide accounted for 255. After adjusting for covariates, elevated ALT and AST were significantly associated with an increased risk of all external-cause mortalities, as well as suicide and injury. Sub-distribution hazards ratios (95% CIs) of the highest versus the lowest quintiles of serum ALT and AST were, respectively, 1.57 (1.26–1.95) and 1.45 (1.20–1.76) for all external causes, 2.73 (1.68–4.46) and 1.75 (1.15–2.66) for suicide, and 1.79 (1.10–2.90) and 1.85 (1.21–2.82) for injury. The risk of external-cause mortality was also significantly higher in the fourth quintile of ALT (21.6–27.5 IU/L) than in its first quintile.

Conclusion: Elevated aminotransferase levels, even within the normal range, were significantly associated with increased risk of all external-cause mortalities, including suicide, and injury.

Key Words: Liver enzymes, external-cause mortality, cardiovascular disease, hepatic disease

INTRODUCTION

External-cause mortality is one of the leading causes of death worldwide.[1] These deaths, including suicide, homicide, accidents, and injuries, account for 12.8% (65.6/100000 persons) of all deaths in the Republic of Korea, and are the third leading cause of death, following cancer (144.4/100000 persons) and cardiovascular disease (112.5/100000 persons), according to 2010 data.[2]

The possible association between death from external causes and serum total cholesterol has been suggested since the 1990s.[3] Although findings on cardiovascular risk factors are still contradictory, numerous studies report an association between cardiovascular risk factors, such as diabetes, obesity, and serum total cholesterol, and the risk of external-cause mortalities, such as suicide.[4,5]

Clinical and epidemiological studies have reported an association between elevated liver enzymes, such as gamma-glutamyltransferase, alkaline phosphatase, alanine aminotransfer-

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ase (ALT), and aspartate aminotransferase (AST), with non-liver-related mortality and morbidity, including cardiovascular disease.[6,7] Although elevated liver enzymes are also associated with several factors, such as alcohol intake, viral hepatitis, and non-alcoholic fatty liver disease (NAFLD),[8,9] they are strong predictors of cardiovascular disease, and are a hepatic manifestation of metabolic syndrome.[10,11] Since cardiovascular risk factors are associated with external-cause mortalities, elevation of liver enzymes may also be associated with these deaths.

This study investigated the effect of elevated serum aminotransferase on overall and specific subtypes of external-cause mortality in a large, population-based cohort study in Korea by applying a competing risks regression analysis.

MATERIALS AND METHODS

Study subjects

In Korea, all workers and their dependents are required to join compulsory National Health Insurance service and participate in biennial medical examinations performed by the National Health Insurance Corporation. A total of 94.5% and 94.4% of these individuals completed the biennial examinations in 1990 and 1992, respectively. Our cohort consisted of all female workers aged 35–59 years and a 25% systematic random sample of all insured male workers aged 35–59 years who completed a health examination in 1990 and 1992.[12] After excluding cases of death before January 1, 1993, 108637 males and 64149 females were included in this study.

Data collection

Biennial examinations, including measurements of blood pressure, serum total cholesterol, fasting blood glucose, ALT, AST, weight, and height, were conducted following a standardized protocol at 416 hospitals located throughout the Republic of Korea in 1990 and 1992. Each hospital adhered to internal and external quality control procedures directed by the Korean Association of Laboratory Quality Control. Self-reported surveys on smoking habits, alcohol intake, marital status, and subjective health status were conducted in 1992. This study was approved by the Institutional Review Board of Yonsei University Health System, Seoul, Korea (4-2004-0105), and the requirement for informed consent was waived because we used secondary data containing randomly generated identification numbers to mask the identities of the subjects.

Outcome measurements

Mortality from external causes was identified using death certificate data from the National Statistical Office from 1993 to 2006. Deaths from external causes were classified into the following groups according to the International Classification of Diseases, 10th Revision: deaths from all internal causes (A00-R99), deaths from all external causes (S00-Y98), and injury [fall (W00–W19), fires (X00–X09), poisonings (X40–X49), drowning (W65–W74), unintentional injuries (V90–V99, W20–W64, W75–W99, X10–X39, X50–X59)], and suicide (X60–X84).

Statistical analysis

After excluding cases lacking smoking, alcohol intake, marital status, and subjective health status data (30258), 142322 individuals who completed biennial examinations in 1990 and in 1992 were included in the analysis. Characteristics of the excluded and included subjects are shown in Supplementary Table 1 (only online). With the exception of smoking status, alcohol intake, marital status, and subjective health status (which were measured in 1992 only), the average of two baseline measurements was used for analysis.

Smoking status was defined as nonsmoker, ex-smoker, and current smoker. Alcohol intake was defined as non-drinker and quartiles according to grams of alcohol per day (<10.3, 10.3–20.5, 20.6–30.8, or ≥30.9 g/day). Blood pressure was classified according to the guidelines of the Seventh Joint National Committee for the Detection, Evaluation, and Treatment of High Blood Pressure: normal [systolic blood pressure (SBP) <120 and diastolic blood pressure (DBP) <80 mm Hg], prehypertension (120≤SBP<140 or 80≤DBP<90 mm Hg), stage 1 hypertension (140≤SBP<160 or 90≤DBP<100 mm Hg), or stage 2 hypertension (160≤SBP or 100≤DBP mm Hg).[13]

To investigate the association of serum aminotransferase levels with each specific type of death from external causes, we used competing risk regression analysis, which treated deaths from all other causes (e.g., deaths from internal causes) as competing risks.[14] We estimated cumulative incidences, sub-distribution hazard ratios (SHRs), and 95% confidence intervals (CIs) of SHRs of all external-cause mortalities, as well as the suicide and injury subtypes.[15] In the competing risk regression model, all potential confounding variables, such as age, sex, marital status, subjective health status, smoking status, alcohol intake, body mass index, blood pressure (JNC 7 classification), serum total cholesterol, and fasting blood glucose, were included. Due to potential effect modification between serum aminotransferase level and alcohol intake on external cause mortality, subjects were divided into three groups based on alcohol intake: never or light (<10.3 g/day), moderate (≥10.3 and <30.9 g/day), or heavy (≥30.9 g/day). Interaction effects were also examined after including the interaction term (quintiles of serum aminotransferase level and alcohol intake) in the competing risk regression model.

Since ALT and AST were closely correlated each other, all analyses were done separately. Due to relatively small numbers of deaths from external causes and no interaction effect between sex and serum aminotransferase level on external cause mortalities, analyses were not stratified by sex.

The 'cmprsk' package version 2.2-1 (R software version 2.13.0) and SAS version 9.3 (SAS Institute, Cary, NC, USA) were used for analysis.

Table 1. Baseline Characteristics of the Subjects According to Specific Causes of Death

	Total (n=142322)	Non-case (n=133514)	Deaths from external causes		
			All causes (n=1111)	Suicide (n=255)	Injury (n=256)
Age (yrs)	43.9±6.60	43.6±6.51	46.1±6.62	46.0±6.63	46.9±6.54
Sex, male (%)	94019 (66.1)	86297 (64.6)	982 (88.4)	221 (86.7)	231 (90.2)
Smoking status					
Non-smoker	67758 (47.6)	65494 (49.1)	308 (27.7)	72 (28.2)	71 (27.7)
Ex-smoker	20152 (14.2)	18639 (14.0)	172 (15.5)	44 (17.3)	43 (16.8)
Current smoker	54412 (38.2)	49381 (37.0)	631 (56.8)	139 (54.5)	142 (55.5)
Marital status					
Married	133435 (93.8)	125134 (93.7)	1048 (94.3)	229 (89.8)	247 (96.5)
Not married	3673 (2.6)	3559 (2.7)	19 (1.7)	10 (3.9)	1 (0.4)
Others	5214 (3.7)	4821 (3.6)	44 (4.0)	16 (6.3)	8 (3.1)
Subjective health status					
Healthy	65254 (45.9)	61643 (46.2)	510 (45.9)	106 (41.6)	120 (46.9)
Unhealthy	51477 (36.2)	48748 (36.5)	359 (32.3)	92 (36.1)	75 (29.3)
Illness	14488 (10.2)	13557 (10.2)	120 (10.8)	25 (9.8)	25 (9.8)
Diseased	11103 (7.8)	9566 (7.2)	122 (11.0)	32 (12.6)	36 (14.1)
Drinking status					
Non-drinker (0 g/day)	71375 (50.2)	68085 (51.0)	361 (32.5)	88 (34.5)	85 (33.2)
Q1 (<10.3 g/day)	15137 (10.6)	14157 (10.6)	132 (11.9)	40 (15.7)	24 (9.4)
Q2 (10.3–20.5 g/day)	17225 (12.1)	15362 (12.0)	165 (14.9)	32 (12.6)	37 (14.5)
Q3 (20.6–30.8 g/day)	21371 (15)	19587 (14.7)	234 (21.1)	47 (18.4)	51 (19.9)
Q4 (≥30.9 g/day)	17214 (12.1)	15723 (11.8)	219 (19.7)	48 (18.8)	59 (23.1)
Blood pressure					
Normal	50674 (35.6)	48888 (36.6)	264 (23.8)	69 (27.1)	54 (21.1)
Pre-hypertension	60721 (42.7)	57007 (42.7)	527 (47.4)	117 (45.9)	117 (45.7)
Stage 1 hypertension	23938 (16.8)	21640 (16.2)	234 (21.1)	51 (20.0)	59 (23.1)
Stage 2 hypertension	6989 (4.9)	5989 (4.5)	86 (7.7)	18 (7.1)	26 (10.2)
Body mass index (kg/m^2)	23.1±2.49	23.0±2.48	23.2±2.58	22.9±2.59	23.1 (2.71)
Serum total cholesterol (mg/L)	190.7±37.88	190.5±37.56	191.6±39.24	191.7±34.85	194.8±43.81
Fasting plasma glucose (mg/L)	90.4±20.86	89.8±19.25	96.1±29.65	95.8±30.37	100.6±40.81
ALT (IU/L)	22.4±19.76	21.9±18.50	25.8±20.62	25.7±18.34	26.3±22.55
AST (IU/L)	23.5±15.89	23.0±14.42	27.8±23.88	26.9±15.29	31.1±36.87

AST, aspartate aminotransferase; ALT, alanine aminotransferase.
Values are expressed as number and percentage or mean±standard deviation.

RESULTS

A total of 8808 deaths (7697 from internal causes and 1111 from external causes) were reported during follow-up. Of the 1111 from external causes, 255 (23.0%) died due to suicide and 256 (23.0%) due to injury. The majority of external-cause mortalities occurred in males (88.4%). Table 1 shows the baseline characteristics of the subjects stratified by cause of death at follow-up. The proportions of current smokers, heavy drinkers, and pre-hypertensive or hypertensive patients were higher for subjects who died from external causes than for those who did not.

Cumulative incidences of death from external causes, suicide, or injury, respectively, were significantly higher in the highest quintiles of AST and ALT, compared with the lowest quintile (Fig. 1). After adjustments for covariates, the risk of death from external causes was significantly higher for subjects in the two highest quintiles (quintile 4 and quintile 5, respectively) of ALT and the highest quintile of AST, compared to the lowest respective quintiles (Table 2). The linear trend was also statistically significant for both ALT (p<0.001) and AST (p<0.001). The risk of death from suicide or injury was also significantly increased for individuals in the higher quintiles of ALT and AST, with the highest risks being in quintile 5 for both enzymes.

The SHRs of death from all external causes and injury were significantly higher among heavy drinkers (≥30.9 g/day), compared to non-drinkers, after adjusting for ALT and AST levels with other confounding factors: 1.42 (95% CI, 1.20–1.69) and

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1.36 (95% CI, 1.14–1.62) for all external causes and 1.76 (95% CI, 1.24–2.50) and 1.67 (95% CI, 1.17–2.39) for injury, respectively. However, suicide mortality was not associated with alcohol intake. In the never or light alcohol intake group, the risks of suicide and injury deaths were significantly increased in the highest ALT quintile, although the risk of all external-cause mortality was not associated with ALT (Table 3). In the moderate or heavy alcohol intake group, the risks of external-cause mortality and injury were significantly increased in the high ALT quintiles, and the linear trend of the association between suicide risk and ALT approached significance (p=0.05). The risk of external-cause death was significantly increased in quintile 5 of AST in the never or light and the moderate alcohol intake groups, and linear trends showed a significant association between AST and external-cause mortality in all three alcohol intake groups (Table 4). Although linear trends were observed, the risk of death from suicide and injury was not significantly increased in high AST quintiles, compared to quintile 1. No interaction effects were observed between serum aminotransferase levels and alcohol intake for any type of external-cause death.

DISCUSSION

Until recently, although many clinical and epidemiologic studies have investigated the effect of cardiovascular risk factors on external-cause mortalities (e.g., suicide and injury), the effect of elevated liver enzymes has not been explored. In the present study, we used a large prospective cohort to investigate the association between serum aminotransferase levels and external-cause mortality and found that elevated serum aminotransferase levels, even within normal range, substantially increased the risk of death from all external causes, suicide, and injury.

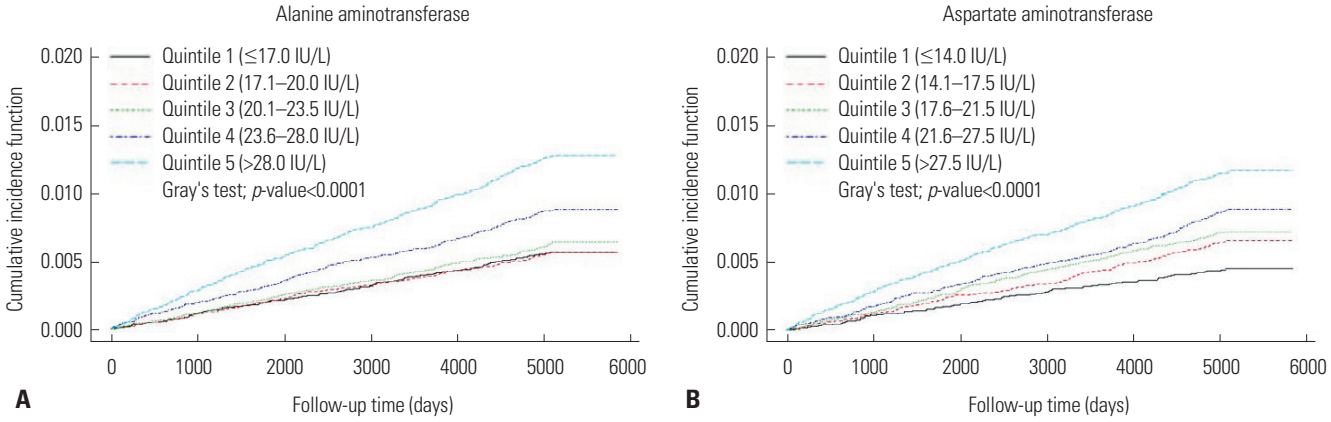

Fig. 1. Cumulative incidences of deaths from external causes based on (A) serum alanine aminotransferase and (B) aspartate aminotransferase stratified into quintiles.

Table 2. Sub-Distribution Hazard Ratios (SHRs) of Death from All External Causes, Suicide, and Injury

	SHR (95% CI)		
	All external causes (n=1111)	Suicide (n=255)	Injury (n=256)
ALT			
Quintile 1 (≤14.0 IU/L)	1.00	1.00	1.00
Quintile 2 (14.1–17.5 IU/L)	1.18 (0.94–1.48)	2.10 (1.26–3.48)	1.07 (0.65–1.77)
Quintile 3 (17.6–21.5 IU/L)	1.14 (0.91–1.42)	1.33 (0.77–2.29)	1.42 (0.89–2.28)
Quintile 4 (21.6–27.5 IU/L)	1.27 (1.08–1.60)	2.13 (1.28–3.57)	1.22 (0.74–2.00)
Quintile 5 (>27.5 IU/L)	1.57 (1.26–1.95)	2.73 (1.68–4.46)	1.79 (1.10–2.90)
p for trend	<0.001	0.001	0.012
AST			
Quintile 1 (≤17.0 IU/L)	1.00	1.00	1.00
Quintile 2 (17.1–20.0 IU/L)	0.89 (0.71–1.11)	1.02 (0.63–1.65)	1.00 (0.61–1.64)
Quintile 3 (20.1–23.5 IU/L)	0.90 (0.73–1.12)	1.22 (0.78–1.91)	1.39 (0.89–2.16)
Quintile 4 (23.6–28.0 IU/L)	1.14 (0.92–1.39)	1.46 (0.93–2.28)	1.15 (0.72–1.83)
Quintile 5 (>28.0 IU/L)	1.45 (1.20–1.76)	1.75 (1.15–2.66)	1.85 (1.21–2.82)
p for trend	<0.001	<0.001	<0.001

AST, aspartate aminotransferase; ALT, alanine aminotransferase; CI, confidence interval.
The competing regression model included age, sex, marital status, subjective health status, smoking status, alcohol intake, blood pressure (JNC 7 classification), body mass index, serum total cholesterol, fasting blood glucose, ALT (or AST), and AST-ALT ratio (≤2 or >2).

Table 3. Sub-Distribution Hazard Ratios (SHRs) of All External-Cause Mortality, Suicide, and Injury Stratified by Alcohol Intake

ALT	Alcohol intake			*p* for interaction
	Never or light (<10.3 g/day)	Moderate (10.3–30.8 g/day)	Heavy (≥30.9 g/day)	
All external causes				
Quintile 1 (≤14.0 IU/L)	1.00	1.00	1.00	<0.001
Quintile 2 (14.1–17.5 IU/L)	1.16 (0.86–1.55)	1.43 (0.92–2.24)	0.90 (0.48–1.68)	
Quintile 3 (17.6–21.5 IU/L)	0.92 (0.67–1.25)	1.62 (1.06–2.48)	1.12 (0.63–2.01)	
Quintile 4 (21.6–27.5 IU/L)	1.08 (0.79–1.48)	1.67 (1.10–2.55)	1.29 (0.74–2.26)	
Quintile 5 (>27.5 IU/L)	1.25 (0.91–1.71)	2.10 (1.39–3.19)	1.62 (0.94–2.78)	
p for trend	0.291	<0.001	0.007	
Suicide				
Quintile 1 (≤14.0 IU/L)	1.00	1.00	1.00	0.192
Quintile 2 (14.1–17.5 IU/L)	2.52 (1.30–4.87)	1.20 (0.47–3.07)	3.00 (0.65–13.79)	
Quintile 3 (17.6–21.5 IU/L)	1.39 (0.66–2.91)	1.02 (0.40–2.58)	1.86 (0.37–9.26)	
Quintile 4 (21.6–27.5 IU/L)	2.73 (1.40–5.35)	1.30 (0.52–3.21)	2.35 (0.51–10.89)	
Quintile 5 (>27.5 IU/L)	2.42 (1.23–4.76)	2.05 (0.87–4.80)	4.64 (1.12–19.18)	
p for trend	0.026	0.055	0.028	
Injury				
Quintile 1 (≤14.0 IU/L)	1.00	1.00	-	0.049
Quintile 2 (14.1–17.5 IU/L)	0.83 (0.43–1.61)	3.87 (1.13–13.3)	-	
Quintile 3 (17.6–21.5 IU/L)	0.98 (0.52–1.85)	3.93 (1.16–13.3)	-	
Quintile 4 (21.6–27.5 IU/L)	0.92 (0.46–1.82)	2.46 (0.69–8.77)	-	
Quintile 5 (>27.5 IU/L)	1.35 (0.69–2.63)	5.12 (1.49–17.6)	-	
p for trend	0.319	0.041	-	

-, non-calculable.
Alanine aminotransferase (ALT) levels were divided into quintiles. Competing regression model included age, sex, marital status, subjective health status, smoking status, blood pressure (JNC 7 classification), body mass index, serum total cholesterol, fasting blood glucose, and ALT.

Serum aminotransferase has been used since 1955 to diagnose liver diseases, such as viral hepatitis, and it is used today to screen for alcohol abuse or determine liver and pancreatic function in primary care settings. Recently, the majority of liver test abnormalities are attributed to the presence of alcoholic or NAFLD.[16] Although liver enzyme measurements show relatively low sensitivity and may therefore underestimate the prevalence of NAFLD, ALT is closely related to fat accumulation in the liver and visceral adipose tissue in both Western and Asian countries.[17,18]

In the present study, higher ALT and AST levels were associated with increased external-cause mortality, suicide, and injury in a dose-dependent manner. Even though ALT was within the normal range in quintile 4 (21.7–27.5 IU/L), the risk of death from external causes (SHR, 1.27; 95% CI, 1.08–1.60) and suicide (SHR, 2.13; 95% CI, 1.28–3.57) was significantly increased, compared to the lowest quintile (≤14.0 IU/L). Although the observational nature of our study makes it difficult to fully explain our results, increased external-cause mortality risk may be attributed to the morbidity of cardiovascular disease, diabetes mellitus (DM), or cancer in association with liver enzyme elevations. Many epidemiologic and clinical studies have shown that elevated liver enzymes, even within the normal range, are associated with increased risks of coronary artery disease, atherosclerosis, hypertension, insulin resistance, and type 2 DM, as well as overall mortality, and that they may serve as surrogates for morbidity or mortality.[19-21] Our previous study also highlighted an association between elevated liver enzymes and the risks of all-cause and cause-specific mortalities, such as cancer and cardiovascular diseases.[7] Many studies have also suggested an association between death from external causes, (suicide and injury) with cardiovascular disease and related risk factors.[4,5]

Among the elderly, physical illnesses, such as DM and cardiovascular diseases, are significantly associated with the risk of hospitalization or death from falls, suicide, or suicide attempts,[22-24] with stroke in particular being an important risk factor for suicide.[25,26] Although biological mechanisms for these associations are not fully understood, cardiovascular disease, DM, and metabolic syndrome are frequently accompanied by brain dysfunction, such as depression, cognitive decline, and other psychiatric illness.[27-30] Other mechanisms, such as inflammation, hypoperfusion, and disconnection of neural connectivity due to focal vascular damage, have been proposed in the pathogenesis of cognitive impairment, depression, and endothelial damage in regional cerebral blood flow.[31,32] Depression is a major risk factor of suicide mortality, and cognitive decline is significantly associated with high risk of injury, including falls.[33-35] As liver enzyme elevation is associated with morbidity related to cardiovascular diseases, DM, insulin resistance, and cancer, it may also be associated with increased risk of external-cause mortality.

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Table 4. Sub-Distribution Hazard Ratios (SHRs) of Death from All External Causes, Suicide, and Injury Stratified by Alcohol Intake

AST	Alcohol intake			*p* for interaction
	Never or light (<10.3 g/day)	Moderate (10.3–30.8 g/day)	Heavy (≥30.9 g/day)	
All external causes				
Quintile 1 (≤17.0 IU/L)	1.00	1.00	1.00	0.006
Quintile 2 (17.1–20.0 IU/L)	0.89 (0.66–1.19)	0.81 (0.54–1.21)	1.13 (0.62–2.08)	
Quintile 3 (20.1–23.5 IU/L)	0.91 (0.68–1.21)	0.80 (0.54–1.17)	1.19 (0.68–2.10)	
Quintile 4 (23.6–28.0 IU/L)	1.01 (0.75–1.36)	1.37 (0.97–1.93)	1.05 (0.60–1.84)	
Quintile 5 (>28.0 IU/L)	1.37 (1.04–1.81)	1.49 (1.06–2.09)	1.63 (0.98–2.71)	
p for trend	0.022	<0.001	0.031	
Suicide				
Quintile 1 (≤17.0 IU/L)	1.00	1.00	1.00	0.243
Quintile 2 (17.1–20.0 IU/L)	1.20 (0.64–2.22)	0.61 (0.24–1.52)	1.49 (0.36–6.19)	
Quintile 3 (20.1–23.5 IU/L)	1.51 (0.84–2.70)	0.77 (0.34–1.74)	1.33 (0.33–5.34)	
Quintile 4 (23.6–28.0 IU/L)	1.56 (0.85–2.86)	1.11 (0.51–2.40)	1.94 (0.54–7.04)	
Quintile 5 (>28.0 IU/L)	1.67 (0.94–2.98)	1.29 (0.62–2.68)	2.75 (0.82–9.27)	
p for trend	0.047	0.138	0.041	
Injury				
Quintile 1 (≤17.0 IU/L)	1.00	1.00		0.141
Quintile 2 (17.1–20.0 IU/L)	0.70 (0.36–1.37)	1.29 (0.50–3.34)	-	
Quintile 3 (20.1–23.5 IU/L)	1.24 (0.70–2.18)	1.55 (0.64–3.79)	-	
Quintile 4 (23.6–28.0 IU/L)	0.62 (0.30–1.28)	2.17 (0.93–5.11)	-	
Quintile 5 (>28.0 IU/L)	1.80 (1.03–3.16)	2.09 (0.90–4.86)	-	
p for trend	0.066	0.027	-	

-, non-calculable.
Aspartate aminotransferase (AST) levels were divided into quintiles. Competing regression model included age, sex, marital status, subjective health status, smoking status, blood pressure (JNC 7 classification), body mass index, serum total cholesterol, fasting blood glucose, and AST.

The risk of external-cause mortality, especially suicide, may be associated with antiviral treatment, as interferon-α treatment has been shown to be associated with increased risk of suicide or major depression in patients with hepatitis,[36] and most trials report a 10% to 40% incidence of major depression during antiviral therapy.[37] Hepatitis B virus infection is highly prevalent in Asia and Africa, and nationwide vaccination strategies have been adopted to eliminate hepatitis B virus infection in Korea. According to 1998 data, the prevalence of hepatitis B in Korea was estimated at 5.1% in males and 4.1% in females.[38] Hepatic encephalopathy is also directly associated with cognitive impairment in patients with viral hepatitis or alcoholic liver disease.[39] Of the 1111 deaths from external causes in our study, 41 (3.7%) and 47 (4.2%) had been hospitalized for liver diseases and cancer, respectively, from 1993–2003, and two of these individuals had been hospitalized for concurrent liver disease and cancer. However, the actual number of patients who received antiviral treatment may be larger than our hospitalization records indicate, because patients usually receive antiviral treatment in an outpatient clinic. Nevertheless, our results may at least partly reflect the effect of antiviral treatment on external-cause mortality.

Alcohol intake is a major risk factor for both suicide and injury.[24,40] Compared to non-drinkers, heavy drinkers (>30.9 g/day) showed an increased risk of external-cause mortality in our study. Due to the possibility of effect modification of alcohol intake on the association between liver enzymes and death from external causes, we further stratified subjects according to alcohol intake. In the never or light alcohol intake group, subjects with high AST demonstrated an increased risk of death from external cause, and those with high ALT showed an elevated risk of death from suicide and injury. However, no interaction effect of alcohol intake and serum aminotransferase levels on any external-cause mortality was observed. Regardless of alcohol intake, elevated liver enzymes may increase the risk of death from external causes.

Although we used a large population-based cohort, our study has some limitations. First, the relatively small number of deaths reported from external causes may limit the power of our study to correlate liver enzyme levels with external-cause mortality. Thus, the association of potential risk factors with death from specific external causes may have been unintentionally overlooked due to insufficient statistical power. Second, liver enzyme elevation also reflects comorbid conditions that are associated with cognitive or motor impairment, and may increase the risk of external-cause mortality, such as drug intoxication, cirrhosis, viral hepatitis, and hepatocellular carcinoma. We could not account for potentially confounding variables such as socioeconomic status and the use of substances other than tobacco and alcohol. However, because the study enrollees consisted of civil servants and private teachers, substance use and variability in socioeconomic status

would be relatively low. Finally, reverse causation by preexisting illness (e.g., psychiatric disorders) may affect study results, although we included subjective health status in the model to minimize this effect.

In conclusion, we analyzed the effects of serum aminotransferase levels on the risk of external-cause mortalities using a competing risk regression analysis. Elevated serum aminotransferase levels, even within the normal range, substantially increased the risk of death from external causes, suicide, and injury, and this association was not influenced by alcohol intake. As elevations in liver enzyme are associated with metabolic syndrome,[10,11] we included confounding variables related to metabolic syndrome in the model and found that the elevated liver enzymes were still significantly associated with external-causes mortality. These finding suggests that liver enzyme elevation could potentially be an early manifestation of external-causes mortality and clinically indicative of subtle brain dysfunction, which underscores a need to consider both cardiovascular and neuropsychiatric risks in individuals with elevated liver enzymes. Although serum aminotransferases are traditional markers with imperfect sensitivity and specificity, they could be taken as proxy indicators for the general population, as assay of aminotransferases is cheap and widely available. Nonetheless, to confirm the noted relationship between liver enzymes and the risk of external-cause mortalities, a large prospective study that includes extensive information on blood chemistry and imaging (e.g., ultrasound for diagnosis of NAFLD) will be helpful.

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