Relationship between serum aminotransferase level and mortality from all causes and liver diseases in middle-aged men

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ABSTRACT

Chronic liver diseases constitute an enormous global burden. Worldwide about 350 million people are chronic carriers of the hepatitis B virus (HBV), and 170million people are affected by hepatitis C virus (HCV). These infections are responsible for a large proportion of mortality from end-stage liver disease and liver cancer. Morbidity and mortality from liver diseases are especially high in some African and Asian countries including Korea.

Serum aspartate and alanine aminotransferase (AST and ALT) levels are most commonly measured to screen acute and chronic liver disease. However, the widely used normal limits (40 IU/L for men) sometimes fail to identify people with chronic liver disease. And little is known about the serum aminotransferase level in relation with mortality. This study was performed to investigate the relationship between serum aminotransferase level and mortality in general population.

This is a prospective study using the KMIC (Korea Medical Insurance Corporation) Study cohort. The study population consisted of 95,459 men who were aged 35 to 59 years at baseline, had participated both health examinations in 1990 and 1992, and answered that they had no known disease. Primary outcomes were deaths from all causes and deaths from liver diseases during the follow-up period between 1993 and 2000. Independent association between serum aminotransferase level and mortality was assessed after adjusting for age, body mass index, blood pressure, smoking, alcohol consumption, serum glucose and cholesterol level, and family history

of liver disease using Cox proportional hazard regression models.

During the follow-up period, 3,370 deaths were reported, and liver diseases accounted for 19% of all mortality. There was significant positive relationship between serum aminotransferase level and mortality from all causes and liver diseases. When compared to the lowest level (<20 IU/L), enzyme levels of 20 to 39 IU/L were also related to increased risk of mortality. Adjusted risk ratio (95% CI) for all-cause mortality of serum AST of 20-29 IU/L and 30-39 IU/L were 1.3 (1.2-1.4) and 1.8 (1.6-2.0), respectively. Corresponding risk ratio (95% CI) of serum ALT of 20-29 IU/L and 30-39 IU/L were 1.2 (1.1-1.3) and 1.7 (1.5-2.9), respectively. Relationship between liver disease mortality and serum aminotransferase level was more prominent; corresponding risk ratio (95% CI) were 2.6 (1.8-3.9) and 7.9 (5.3-11.8) for AST, and 2.4 (1.8-3.3) and 7.7 (5.8-10.4) for ALT, respectively.

The best cutoff values of AST and ALT tests in identifying men at high risk for liver disease mortality were estimated to 31 IU/L and 30 IU/L, respectively using receiver-operating characteristic curves. If this new cutoff values were used instead of current normal limits (40 IU/L), the sensitivity could be increased from 52% to 70% for AST and from 44% to 66% for ALT. The related tradeoff in specificity was acceptable (AST, 92% to 82%; ALT, 91% to 79%). These results suggest the need to revise the current normal limits for serum aminotransferase levels.

Keywords: Aminotransferase, AST, ALT, Mortality, Liver disease, Liver cancer

1. INTRODUCTION

Chronic liver disease, such as chronic viral hepatitis, cirrhosis and primary liver cancer, constitutes an enormous global burden. It is estimated that over 350 million people live with a chronic hepatitis B virus (HBV) infection, claiming over one million deaths per year due to progress of the disease to cirrhosis and/or liver cancer (Kane, 1995; Kao and Chen, 2002). Hepatitis C virus (HCV) infection also affects 170 million people worldwide and it is responsible for a large proportion of patients with cirrhosis and liver cancer (Kim, 2002; WHO, 1997; WHO, 1999). Liver cancer is the third most common cause of cancer death in the world. In 2000, liver cancer accounted for 8.7% (10.7% for men and 6.2% for women) of total cancer mortality (Shibuya et al, 2002).

Prevalence of HBV infection and mortality from liver diseases are very high in some African and Asian countries. In Korea, chronic liver diseases are the most serious health problem, especially in men. The liver cancer mortality in Korea is the highest in the world at 21.3 (32.5 for men and 10.0 for women) per 100,000 population (National Statistical Office, 2001). The burden of liver cancer was estimated to be the largest among all malignancies (529 person-years per 100,000 population), based on DALY (disability adjusted life year) measurement (Yoon et al, 2002). Recent epidemiologic studies indicate that 5-10 % of men and 1-5 % of women are HBV carriers (Ahn, 1999; Chun et al, 1992; Yang et al, 2001). The overall prevalence of HCV infection was estimated to 2-6% among Korean adults (Jung et al, 1993; Kim et al, 1992; Shin et al, 2000).

Measurements of serum aspartate aminotransferase (AST, formerly called as GOT: glutamic oxaloacetic transaminase) and alanine aminotransferase (ALT, formerly called as GPT: glutamic pyruvic transaminase) levels are common laboratory tests, which are used to help clinical diagnosis and to screen acute and chronic liver diseases in general population (Craxi and Almasio, 1996; Pratt and Kaplan, 2000; Scheig, 1996; Sorbi et al, 1999). AST catalyzes the transfer of the amino group of aspartic acid to ketoglutaric acid, forming glutamic acid and oxaloacetic acid. Elevated serum AST level is a marker for liver damage or cardiac muscle damage. ALT catalyzes the transfer of the amino group of alanine to glutaric acid, forming glutamic acid and pyruvic acid. Elevated serum ALT specifically indicates liver damage. The ALT activity is a more sensitive indicator of hepatic dysfunction than the AST activity. Serum levels of AST and ALT are elevated to some extent in almost all liver diseases. The highest elevations occur in severe viral hepatitis, drug-induced or toxin-induced hepatic necrosis, and circulatory shock (Friedman et al, 1996; Sherman, 1991).

Serum AST and ALT levels are known as very sensitive measures in detecting liver damage, but their specificity in healthy population is not sufficient. Because the distribution of serum aminotransferase level is in the form of a continuous rather than a discrete variable, there is no clear cutoff level that discriminates between healthy liver and diseased liver. Current normal limit of serum aminotransferase activity is rather arbitrary (Sherman, 1991; Siest et al, 1975). The most common methods of obtaining normal limits of a continuous variable in medical field are to employing the mean $\pm$ 2 standard deviations, and to take percentile cutoffs from reference population (Herrera,

1958). However, the normal ranges obtained with these methods vary with gender, age, race and socio-economic characteristics of the reference population. Methods and equipments used for the assay also may affect the normal range (Bailey, 1974; Jarvisalo et al, 1989; Kahn et al, 1982; Kundrotas and Clement, 1993; Lai et al, 2001; Manolio et al, 1992; Prati et al, 2002). For these reasons, many laboratories are trying to set their own reference values for serum aminotransferase tests. There is another approach to finding normal range of laboratory tests; the use of prospective studies. Normal (or healthy) range may also be defined as levels with the lowest morbidity or mortality in the long run. Therefore, we need cohort studies of enough follow-up length and large representative population. Several prospective studies have tried to find upper normal limit of serum aminotransferase level. The purpose of many of those studies were selecting people with normal (or disease-free) liver for blood donation or liver transplantation (Alter et al, 1981; Dubois et al, 1994; Hung et al, 1997; Kahn et al, 1982; Kundrotas and Clement, 1993; Piton et al, 1998; Prati et al, 2002; Shakil et al, 1995; Tsai et al, 1997; Widell et al, 1988).

There is no universal consensus on the normal range of serum aminotransferase levels. Current upper normal limits for serum AST and ALT level were set, on average, at 40 IU/L (ranged 30 to 50 IU/L) in studies conducted over the decades (Angulo, 1999; Daniel et al, 1999; Prati et al, 2002; Pratt and Kaplan, 2000). However, several studies repeatedly revealed that considerable proportion of HCV carriers have serum aminotransferase levels less than 40 IU/L. Moreover the reference populations likely included many persons with nonalcoholic fatty liver disease, which is recognized as an important cause of chronic liver disease in developed countries (Angulo, 1999; Daniel

et al, 1999). Therefore the use of current normal range may lead to underestimation of the frequency of chronic liver disease. Nevertheless, persistence for longer than six months of AST or ALT elevation (40IU/L or more) is a usual indication to begin further investigation in asymptomatic individuals (Daniel et al, 1999; Friedman et al, 1996; Gholson et al, 1997).

Recently, many studies assessed the significance of mild elevation of serum aminotransferase level in an asymptomatic person. Several results discovered pathologic evidence of liver disease, such as fatty liver, chronic hepatitis and cirrhosis, in asymptomatic patients with moderately elevated aminotransferase activity (Hay et al, 1989; Hutcrantz et al, 1986; Mathiesen et al, 1999; Meyer et al, 1990). However, there is little information on the relationship between serum aminotransferase and mortality from and liver diseases and all causes, especially within normal range of serum aminotransferase.

The detection of liver disease at pre-clinical stage and the prevention of severe complications or early death are important in middle-aged male Korean population. Therefore a review of the significance of serum aminotransferase level in relation with mortality is needed, since it is not yet been fully investigated in general population.

2. OBJECTIVES

This study was performed to evaluate the relationship between serum aminotransferase levels and mortality in a healthy middle-aged male population.

Specifically,

(1) To investigate the relationship between serum aminotransferase (AST and ALT) levels and mortality from all causes, all liver disease, and liver cancer

(2) To find the safe range of serum aminotransferase (AST and ALT) level in relation with mortality

3. METHODS

Study Population

The study population was selected among members of the Korea Medical Insurance Corporation (KMIC) Study cohort. The KMIC provided health insurance to government employees, private school teachers and staffs, and their dependents. In 1990, out of a total Korean population of 43 million, 4,603,361 (11%) were insured by the KMIC, including 1,213,594 workers and 3,389,767 dependants. All insured workers are

required to have their general health assessed every two years by the KMIC. In 1990 and 1992, 95% and 94% of insured workers, respectively, had these assessments. The KMIC Study cohort consists of 115,200 men and 67,932 women aged 35-59, who attended both 1990 and 1992 examinations. The cohort was 25% systematic random sample of male workers and all of female workers, drawn from insured members ordered by national identification number. This study restricted analyses to men, because the number of deaths related with liver diseases in women was insufficient to evaluate the relationship between serum aminotransferase activity and mortality.

For the analyses of this study, subjects were selected based on the following inclusion criteria.

(1) Male cohort members who were aged 35 to 59 years in 1990

(2) Those who have data on AST and ALT levels both in 1990 and 1992

(3) Those who have data on average alcohol consumption in 1992

(4) Those who survived until December 31, 1992

(5) Those who answered that they had no previously diagnosed diseases in 1992

Of the 115,200 members, 108,714 men had adequate serum AST and ALT results at the two examinations. After exclusion of 1,087 men without information on alcohol consumption and 172 men who died before year 1993 (1,087), 107,455 men were left on. In order to eliminate the possible confounding effects of concurrent illness on mortality, I excluded 11,996 men who answered that they had known diagnosed

diseases. Ultimately 95,459 men were selected for the analyses. The subgroup of relatively low aminotransferase level was defined as men who had serum AST less than 50 IU/L and ALT level less than 50 IU/L. The number of subgroup of relatively low aminotransferase level was 90,176.

Data Collection

Baseline information were obtained from KMIC health assessments in 1990 and 1992 and self-reported questionnaire in 1992. The KMIC health assessments are undertaken every two years in a standardized way by medical staff at local hospitals. In 1990, assessments were done at 416 hospitals. In the 1992 questionnaire, individuals were asked to describe their health habits, including smoking and alcohol consumption and answered that whether they had family history of liver disease, cardiovascular disease, diabetes mellitus or cancer. Trained staff reviewed the completed questionnaires.

At each health assessment, weight and height were measured and body mass index was calculated as weight (kg) per height squared (m^2). Blood pressure was measured in the seated position by a registered nurse or blood pressure technician using a standard mercury sphygmomanometer or automatic manometer. In case of manual manometers, systolic and diastolic blood pressure were measured as the first and fifth Korotkoff sounds, respectively. Fasting blood samples were taken and analyzed for serum total cholesterol, glucose and aminotransferase (AST and ALT) activity. Each

hospital that participated in the assessments followed internal and external quality control procedures as stipulated by the Korean Society of Quality Control in Clinical Pathology (Chung et al, 1991; Kim et al, 1993). In the analyses, blood pressure, body mass index, fasting serum glucose, total cholesterol, and serum aminotransferase activities were the average of two measurements obtained in 1990 and 1992. Meanwhile, data on smoking status, alcohol consumption and family history of liver disease were available only for 1992.

The primary outcome variable was mortality from death certificates, and the follow-up period was eight years, between January 1, 1993 and December 31, 2000. Computerized searches of death certificate data from the National Statistical Office in Korea were performed on each of the KMIC enrollees. For those who died during this period, follow-up time was defined as the interval between Jan 1, 1993, and the date of death on the death certificate. For the calculation of cause-specific mortality, three groups of causes were considered for this report using ICD-9 or ICD-10 code diagnoses on death certificate: all causes, all liver disease including liver cancer, and liver cancer. In order to evaluate the validity of cause of death, hospital admission history due to liver disease was matched for all subjects who died from liver diseases. Information on the primary diagnosis and the date of admission were obtained from health insurance claim data to KMIC. The hospital admission data were available from the year 1993. And the analyses were performed when the cause of death was confirmed by hospital admission history.

Statistical Analysis

Baseline characteristics of the study subjects were displayed according to the level of serum aminotransferase. Distribution of serum AST and ALT was shown in the form of each measurement and the average of the two measurements. Number of death and age-adjusted mortality from all causes, all liver diseases and liver cancer were calculated according to the level of serum AST and ALT. The mortality rate was standardized with direct method using the total study population as the standard, and expressed as the estimated number of death per 100,000 person-year observation. Multivariate adjusted risk ratio for death was also calculated according to the serum AST and ALT level using Cox proportional hazard regression analyses. Age, body mass index, blood pressure, fasting serum glucose and total cholesterol, smoking status, amount of average alcohol consumption, and family history of liver disease were adjusted for the multivariate models. In order to assess the association between change of serum aminotransferase activity and mortality, individuals were classified into four categories: normal (<40 IU/L) both in 1990 and 1992, normal in 1990 but high (≥40 IU/L) in 1992, high in 1990 but normal in 1992, and high both in 1990 and 1992. And to compare the strength of association of AST and ALT to mortality, individuals were classified again into four categories; both normal AST and ALT, normal AST but high ALT, high AST but normal ALT, and both high AST and ALT.

For the relatively low (<50 IU/L) aminotransferase subgroup, further analyses were performed to investigate the relationship between serum AST, ALT levels and mortality. Risk ratio for mortality from all causes, all liver disease, and liver cancer was

estimated according to the level of serum AST and ALT, with 5 IU/L intervals. For this analysis the mean and the higher levels of serum aminotransferase were used for independent variables, separately. And, risk of mortality according to the magnitude of change in serum aminotransferase level between 1990 and 1992 was also estimated. In order to assess the possible confounding effects of concurrent illness, stratified analyses were done by the follow-up periods. And stratified analyses by the presence of family history for liver disease were also done.

In all the above models, body mass index was classified into quartile categories; lower than 21.7 kg/m^2, 21.7-<23.4 kg/m^2, 23.4-<25.0 kg/m^2, and 25.0 kg/m^2 or more. Individuals were classified as 'current smokers' if they smoked during at least the past one year, 'nonsmokers' if they had never smoked, and 'ex-smokers' if they had stopped. Categories for average alcohol consumption divided into a non-drinker group and four drinker groups based on average daily alcohol intake: less than 50 g/day, 50-<100 g/day, 100-<200 g/day, 200 g/day or more. Using National Diabetes Data Group's diagnostic criteria, fasting blood glucose level was classified to three categories; lower than 100mg/dL, 100-<126mg/dL, and 126mg/dL or more (National Diabetes Data Group, 1997). Total serum cholesterol level was classified into quintile categories: lower than 167 mg/dL, 167-<184 mg/dL, 184-<200 mg/dL, 200-<220 mg/dL, and 220 mg/dL or more. Blood pressure was categorized to three levels according to the sixth report of the Joint National Committee on Prevention, Detection, and Treatment of High Blood Pressure: normal (SBP < 130 mmHg and DBP < 85 mmHg), high-normal (SBP 130-139 mmHg or DBP 85-89 mmHg), hypertension (SBP ≥ 140 mmHg or DBP ≥ 90 mmHg).

If the systolic and diastolic pressure readings for a subject were in different categories, the higher of the two categories was used (National Institute of Health, 1997). There was no difference in mortality between men without family history of liver disease and men with unknown history; the two groups were combined together. Therefore, the family history of liver disease was used as dichotomous variable: no/unknown and yes.

One of the best cutoff values for laboratory tests can be obtained from the receiver-operating characteristic (ROC) curve, on the assumption that the false positive cost / false-negative cost ratio was 1/1. The best cutoff value is that which maximizes the sum of the sensitivity and specificity, which is the point nearest the top left-hand corner of ROC curves. ROC curves of serum AST and ALT levels for detecting future mortality from liver disease were plotted. Additionally, the distribution of baseline serum aminotransferase level in men who died from liver disease and in men who still survived or died from other causes.

4. RESULTS

Baseline Characteristics of Study Population

Table 1 displays the baseline characteristics of the study population by the level of serum aminotransferase. The mean age was 44.8 years and the mean body mass index was 23.4 kg/m^2. Mean SBP and DBP were 125.2 and 81.9 mmHg, respectively. Average of the serum aminotransferase levels were 25.6 IU/L for AST and 25.2 IU/L for ALT. Approximately 80 % of the men were current or past smokers, and 70 % were regular alcohol drinkers. And 3.6 % of the population answered that they had family history of liver disease.

Table 1. Baseline characteristics of the study population

	Serum aminotransferase (AST and ALT) level *			
	Normal at both examination (n=74,801)	High at one examination (n=15,531)	High at both examinations (n=5,127)	Total (n=95,459)
Variables	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD
Age (years)	44.8 ± 6.7	44.6 ± 6.5	44.3 ± 6.4	44.8 ± 6.7
Body mass index (kg/m^2)	23.2 ± 2.3	24.1 ± 2.5	24.5 ± 2.7	23.4 ± 2.3
Systolic blood pressure (mmHg)	124.4 ± 13.6	127.5 ± 14.4	129.2 ± 14.6	125.2 ± 13.9
Diastolic blood pressure (mmHg)	81.4 ± 9.3	83.5 ± 9.7	84.6 ± 9.6	81.9 ± 9.4
Fasting blood sugar (mg/dL)	91.1 ± 16.7	94.5 ± 20.3	98.0 ± 21.7	92.0 ± 17.7
Total serum cholesterol (mg/dL)	192.6 ± 31.7	198.5 ± 34.8	199.6 ± 39.4	193.9 ± 32.8
Serum AST (IU/L)	22.0 ± 5.0	33.2 ± 14.7	52.8 ± 31.2	25.6 ± 13.0
Serum ALT (IU/L)	20.2 ± 5.6	37.1 ± 17.8	61.6 ± 32.3	25.2 ± 15.7
	Number (%)	Number (%)	Number (%)	Number (%)
Smoking status				
Nonsmoker	16,201 (21.8)	3,156 (20.6)	945 (18.7)	20,122 (21.4)
Ex-smoker	15,380 (20.8)	3,118 (20.4)	945 (18.7)	19,443 (20.6)
Current smoker	42,382 (57.4)	9,028 (59.0)	3,154 (62.5)	54,654 (58.0)
Average alcohol consumption				
Non-drinker	22,140 (30.4)	4,059 (26.8)	1,263 (25.3)	27,462 (29.5)
< 50 g/day	44,353 (60.8)	9,081 (60.0)	2,947 (59.1)	56,831 (60.6)
≥ 50 g/day	6,410 (8.8)	1,986 (13.1)	779 (15.6)	9,175 (9.9)
Family history of liver disease				
No or unknown	72,180 (96.5)	14,922 (96.1)	4,890 (95.4)	91,992 (96.4)
Yes	2,621 (3.5)	609 (3.9)	237 (4.6)	3,467 (3.6)

AST, aspartate aminotransferase; ALT, alanine aminotransferase

*Normal serum aminotransferase level is defined as AST<40 IU/L and ALT<40 IU/L

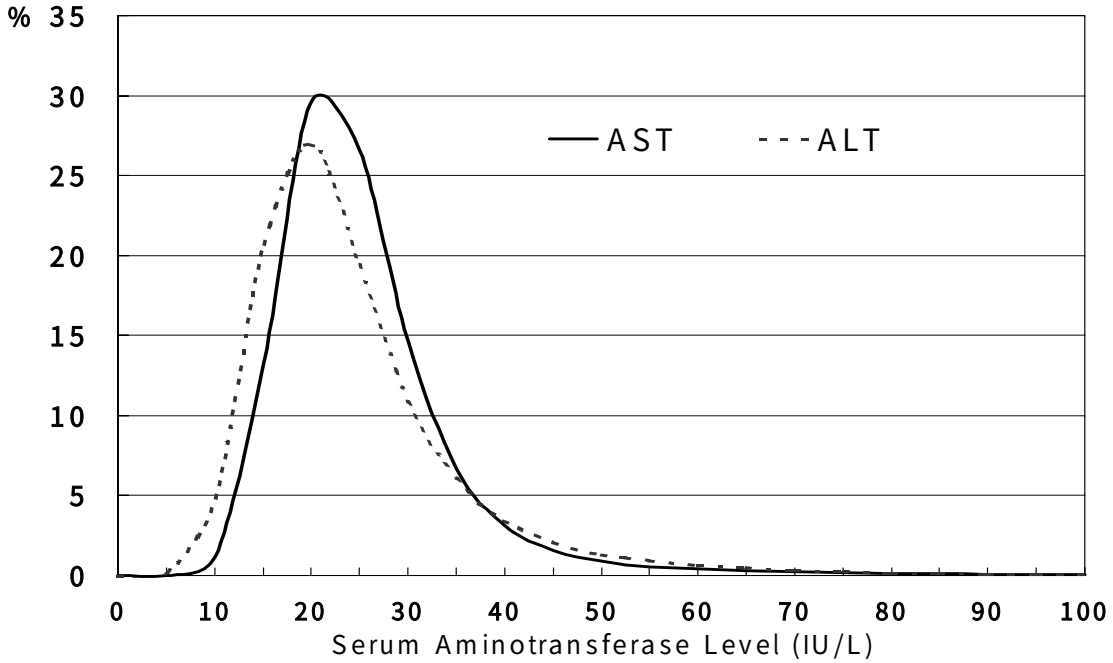
Men with higher serum aminotransferase level tended to weigh more and to have higher level of blood pressure, serum glucose and total cholesterol. In high aminotransferase group, the percentage of current smokers, heavy drinkers and those with family history of liver disease were higher than that in normal aminotransferase group. All these associations were statistically significant.

Table 2 and Figure 1 display the distribution of serum aminotransferase level in the study population. Both AST and ALT levels had rightly skewed distribution, and AST level was slightly higher than ALT. Between the two measurements with two-year interval, mean serum AST and ALT levels increased by 1.4 IU/L and 1.6 IU/L, respectively. Ninety-fifth percentile value, which is frequently used as normal limits, was 42.0 IU/L for AST and 48.5 IU/L for ALT. When compared with data from Korean National Health and Nutrition Examination Survey 1998 (mean 28.8 IU/L and median 25.0 IU/L for AST, mean 28.7 and median 23.0 for ALT in men with 30 years or older), the serum aminotransferase levels of the study population were slightly lower (Ministry of Health and Welfare, 1999).

Table 2. Distribution of serum aminotransferase level in the study population

	AST (IU/L)			ALT (IU/L)		
Value	In 1990	In 1992	Average	In 1990	In 1992	Average
Mean						
Standard	24.9	26.3	25.6	24.4	26.0	25.2
deviation	15.7	16.9	13.2	18.8	20.4	15.9
Percentile						
5 %	12.0	13.0	14.5	10.0	11.0	12.0
25 %	18.0	19.0	19.0	16.0	16.0	17.0
50 %	22.0	24.0	23.0	21.0	22.0	21.5
75 %	28.0	30.0	28.5	28.0	30.0	28.5
95 %	43.0	46.0	42.0	47.0	53.0	48.5

AST, aspartate aminotransferase; ALT, alanine aminotransferase



AST, aspartate aminotransferase; ALT, alanine aminotransferase

Figure 1. Distribution of serum aminotransferase level in the study population

Serum Aminotransferase Level and Mortality

During the follow-up period of eight years (1993 to 2000), 3,370 deaths were reported over 751,552 person-years total survival time. The crude mortality rate was 448.4 per 100,000 person-years. Cancer accounted for 1,504 deaths and was the leading cause of death (45.0% of all death). The number of liver cancer was 393 (11.7% of all death) and number of deaths related non-malignant liver disease was 249 (7.4% of all death). In terms of target organs, liver diseases were the most common cause of death in this population. Deaths from all liver disease accounted for 19.1% of all mortality (Table 3).

Table 3. Number and cause of deaths during the follow-up period (1993 to2000)

	Serum aminotransferase (AST and ALT) level*			
	Normal at both examinations (n=74,801)	High at one examination (n=15,531)	High at both examinations (n=5,127)	Total (n=95,459)
Cause of death	No. of death (%)	No. of death (%)	No. of death (%)	No. of death (%)
All causes	2,136 (2.86)	753 (4.85)	481 (9.38)	3,370 (3.53)
Cancers	975 (1.30)	321 (2.07)	208 (4.06)	1,504 (1.58)
Cardiovascular diseases	442 (0.59)	122 (0.79)	57 (1.11)	621 (0.65)
External causes	399 (0.53)	116 (0.75)	61 (1.19)	576 (0.60)
Disease of digestive system	67 (0.09)	94 (0.61)	120 (2.34)	281 (0.29)
Others	253 (0.34)	100 (0.64)	35 (0.68)	388 (0.41)
Liver disease				
Liver cancer	140 (0.19)	119 (0.77)	134 (2.61)	393 (0.41)
Liver cirrhosis	42 (0.06)	69 (0.44)	96 (1.87)	207 (0.22)
Other liver diseases	10 (0.01)	16 (0.10)	16 (0.31)	42 (0.04)
All liver disease	192 (0.26)	204 (1.31)	246 (4.80)	642 (0.67)

AST, aspartate aminotransferase; ALT, alanine aminotransferase
*Normal serum aminotransferase level is defined as AST<40 IU/L and ALT<40 IU/L

For the surrogate methods to verify the causes of death on certificates, diagnosis on health insurance claim data were used. For all deaths from liver cancer and non-cancer liver disease in year 1995 to 2000, history of hospital admission due to liver disease in year 1993 to 2000 was pursued. In 76.2% (391 over 513) of deaths from liver disease, preceding hospital admissions due to liver disease were found. Of the 306 liver cancer deaths, 77.1% (236 cases) had experiences of admission from liver cancer (Table 4). Small proportion of men who died from liver cancer (19.3%) and non-cancer liver disease (30.4%) did not have records of hospital admission for liver disease. Therefore all reported deaths and cause-confirmed deaths were separately used for outcome (dependent) variables in the following analyses.

Table 4. Verification of cause of death on certificate by health insurance claim data.

Cause of death on certificate during 1995 to 2000	Hospital admission history of liver disease during 1993 to 2000		
		Verified	
	Primary diagnosis	Number	Proportion
All liver disease	**All liver disease**	**391**	**76.2 %**
	No data for liver disease	122	23.8 %
	Total	513	100.0 %
Liver cancer	All liver disease	247	80.7 %
	Liver cancer	**236**	**77.1 %**
	Non-cancer liver diseases	63	20.6 %
	No data for liver disease	59	19.3 %
	Total	306	100.0 %
Non-cancer liver disease	All liver disease	144	69.6 %
	Liver cancer	17	8.2 %
	Non-cancer liver diseases	**136**	**65.7 %**
	No data for liver disease	81	30.4 %
	Total	207	100.0 %

Table 5 displays number of death and age-adjusted mortality according to the serum aminotransferase level. Table 6 shows relative risk for mortality from all causes, all liver diseases and liver cancer by the serum aminotransferase level. When compared with the lowest aminotransferase level (< 20 IU/L), higher aminotransferase level was significantly related to higher mortality from all causes, all liver diseases and liver cancer. The association between serum aminotransferase level and mortality was continuous and positive, except the highest level (150IU/L or more). Slight decrease in mortality at the very high aminotransferase level can be observed, because the highest enzyme activity usually results from acute liver damage rather than severe chronic liver dysfunction.

Table 5. Age-adjusted mortality by the serum aminotransferase level

Serum amino-transferase level	Number of men	Age-adjusted mortality per 1,000 person-year (number of death)*					
		Death from all causes		Death from all liver diseases		Death from liver cancer	
				All reported	Cause-confirmed	All reported	Cause-confirmed
AST (IU/L)							
<20	26,840	2.99	(621)	0.16 (34)	0.12 (25)	0.10 (21)	0.07 (14)
20-<30	48,654	3.84	(1481)	0.38 (187)	0.26 (101)	0.28 (109)	0.19 (75)
30-<40	14,033	5.34	(597)	1.13 (127)	0.88 (99)	0.72 (81)	0.57 (64)
40-<50	3,139	8.94	(217)	3.71 (90)	2.89 (70)	2.23 (54)	1.78 (43)
50-<100	2,363	19.17	(345)	9.93 (178)	8.01 (143)	5.94 (107)	4.78 (86)
100-<150	378	34.20	(76)	22.53 (50)	16.13 (35)	7.54 (17)	5.41 (12)
≥ 150	55	32.77	(33)	15.25 (15)	12.05 (12)	4.57 (4)	3.20 (3)
ALT (IU/L)							
<20	37,940	3.47	(1052)	0.24 (72)	0.14 (43)	0.15 (46)	0.09 (27)
20-<30	36,859	4.06	(1197)	0.50 (148)	0.37 (109)	0.35 (102)	0.27 (79)
30-<40	12,068	5.54	(509)	1.48 (137)	1.18 (110)	0.90 (83)	0.70 (65)
40-<50	4,110	7.76	(231)	3.04 (92)	2.42 (75)	1.73 (53)	1.35 (43)
50-<100	3,901	10.48	(299)	5.12 (145)	3.84 (110)	2.88 (81)	2.27 (64)
100-<150	420	18.79	(57)	11.74 (36)	9.67 (30)	7.18 (21)	4.80 (14)
≥ 150	161	20.90	(25)	10.04 (12)	7.48 (9)	5.87 (7)	4.18 (5)

AST, aspartate aminotransferase; ALT, alanine aminotransferase

*Adjusted with direct method using the total study population as the standard

Table 6. Risk ratio for mortality by the serum aminotransferase level

Serum amino-transferase level	Risk ratio (95% confidence interval) for mortality*				
	Death from all causes	Death from all liver diseases		Death from liver cancer	
		All reported	Cause-confirmed	All reported	Cause-confirmed
AST (IU/L)					
<20	1.0	1.0	1.0	1.0	1.0
20-<30	1.3 (1.2-1.4)	2.6 (1.8-3.9)	2.5 (1.6-4.0)	3.0 (1.8-4.8)	3.2 (1.8-5.7)
30-<40	1.8 (1.6-2.0)	7.9 (5.3-11.8)	8.7 (5.5-13.9)	7.8 (4.8-12.9)	9.5 (5.2-17.4)
40-<50	2.7 (2.3-3.2)	25.9 (17.1-39.1)	29.1 (17.9-47.2)	25.0 (14.9-42.0)	31.2 (16.6-58.3)
50-<100	5.3 (4.6-6.1)	62.4 (42.3-91.9)	72.8 (46.1-114.7)	60.9 (37.5-98.8)	76.9 (42.6-138.7)
100-<150	9.1 (7.1-11.7)	131.4 (83.3-207.4)	138.8 (80.8-238.4)	73.2 (38.2-140.5)	81.5 (37.0-179.5)
≥ 150	8.5 (5.9-12.3)	80.6 (42.6-152.3)	103.5 (50.9-210.5)	27.8 (8.2-94.1)	42.6 (12.0-150.8)
ALT (IU/L)					
<20	1.0	1.0	1.0	1.0	1.0
20-<30	1.2 (1.1-1.3)	2.4 (1.8-3.3)	3.0 (2.1-4.4)	2.5 (1.7-3.6)	3.4 (2.2-5.3)
30-<40	1.7 (1.5-1.9)	7.7 (5.8-10.4)	10.5 (7.3-15.2)	7.1 (4.9-10.3)	9.6 (6.0-15.3)
40-<50	2.2 (1.8-2.5)	14.9 (10.7-20.6)	19.8 (13.3-29.5)	12.9 (8.5-19.5)	18.0 (10.8-29.8)
50-<100	3.0 (2.6-3.5)	25.5 (19.0-34.3)	32.4 (22.3-46.9)	22.1 (15.2-32.1)	30.0 (18.8-47.8)
100-<150	5.1 (3.9-6.8)	50.3 (33.4-75.8)	70.9 (43.9-114.5)	44.0 (26.0-74.4)	49.1 (25.4-94.9)
≥ 150	5.6 (3.7-8.5)	33.7 (17.3-65.6)	50.6 (24.5-104.6)	28.3 (12.0-66.7)	39.5 (15.1-103.2)

AST, aspartate aminotransferase; ALT, alanine aminotransferase

*Adjusted for age, body mass index, smoking status, alcohol consumption, serum glucose and total cholesterol, blood pressure, and family history of liver disease

Table 7 shows combined effects of serum AST and ALT levels on mortality. The men with both low enzymes activity (AST <40IU/L and ALT <40IU/L) were the reference group. Compared to the reference group, all the other groups were at significantly higher risk for mortality from all causes, all liver diseases and liver cancer. The men with high AST and high ALT level had the highest mortality, and men with high AST and low ALT had higher mortality than men with low AST and high ALT. Table 8 shows the effects of each aminotransferase measurements on mortality. High aminotransferase level at any one of the two examinations was related to increased risk for mortality. The men with repeatedly high aminotransferase level had the highest mortality from all causes, all liver diseases and liver cancer.

All the above associations between serum aminotransferase level and mortality were observed, even when the outcome events of liver disease mortality were limited to cause-confirmed death.

Table 7. Risk ratio for mortality by the mean level of serum aspartate and alanine aminotransferase

Mean serum aminotransferase level*		Risk ratio (95% confidence interval) for mortality†				
		Death from all causes	Death from all liver diseases		Death from liver cancer	
AST	ALT		All reported	Cause-confirmed	All reported	All reported
Low	Low	1.0	1.0	1.0	1.0	1.0
Low	High	1.2 (1.0-1.4)	2.4 (1.6-3.5)	2.5 (1.6-4.0)	2.2 (1.4-3.7)	2.1 (1.2-3.9)
High	Low	3.1 (2.6-3.6)	12.7 (9.8-16.5)	15.0 (11.1-20.2)	10.2 (7.2-14.4)	12.0 (8.1-17.8)
High	High	3.4 (3.1-3.8)	18.7 (15.6-22.4)	20.6 (16.7-25.3)	15.8 (12.5-19.8)	17.3 (13.2-22.5)

AST, aspartate aminotransferase; ALT, alanine aminotransferase
*Low level is defined as less than 40 IU/L
†Adjusted for age, body mass index, smoking status, alcohol consumption, serum glucose and total cholesterol, blood pressure, and family history of liver disease

Table 8. Risk ratio for mortality by the level of serum aminotransferase at each examination

Serum amino-transferase level*		Risk ratio (95% confidence interval) for mortality†				
		Death from all causes	Death from all liver diseases		Death from liver cancer	
In 1990	In 1992		All reported	Cause-confirmed	All reported	Cause-confirmed
Low	Low	1.0	1.0	1.0	1.0	1.0
Low	High	1.7 (1.6-1.9)	6.4 (5.1-8.1)	7.3 (5.6-9.5)	5.0 (3.7-6.6)	5.4 (4.0-7.5)
High	Low	1.7 (1.5-1.9)	4.6 (3.5-6.1)	4.7 (3.4-6.6)	3.9 (2.7-5.5)	3.7 (2.4-5.6)
High	High	3.3 (2.9-3.6)	20.4 (16.7-25.0)	22.55 (17.8-28.5)	15.5 (12.1-20.0)	16.6 (12.5-22.2)

*Low level is defined as less than 40 IU/L

†Adjusted for age, body mass index, smoking status, alcohol consumption, serum glucose and total cholesterol, blood pressure, and family history of liver disease

Relatively Low Serum Aminotransferase Level and Mortality

From the table 9, analyses were focused on the relatively low aminotransferase group. The relatively low aminotransferase group was defined as men with serum AST and ALT level less than 50 IU/L at both examinations, because currently used upper normal limits are ranged from 30 to 50 IU/L. For the independent variables, mean level and higher value of the two measurements in 1990 and 1992 were used separately. Even under the level of 50 IU/L, the positive association between serum AST or ALT level and mortality was statistically significant. The association was similar, regardless of using average or higher value of the two measurements. In general, the magnitude of association was greater in AST than in ALT, while the confidence interval was narrower in ALT (Table 9 and 10).

Table 9. Risk ratio for mortality by the level of serum aspartate aminotransferase in men with relatively low (<50 IU/L) aminotransferase level

Serum AST level	Risk ratio (95% confidence interval) for mortality*				
	Death from all causes	Death from all liver diseases		Death from liver cancer	
		All reported	Cause-confirmed	All reported	Cause-confirmed
Mean level†					
<20	1.0	1.0	1.0	1.0	1.0
20-<25	1.2 (1.1-1.3)	1.8 (1.2-2.8)	1.6 (1.0-2.7)	2.1 (1.2-3.5)	2.2 (1.2-4.3)
25-<30	1.4 (1.2-1.6)	3.7 (2.5-5.7)	3.8 (2.3-6.2)	4.2 (2.5-7.0)	4.5 (2.4-8.4)
30-<35	1.6 (1.4-1.9)	6.3 (4.1-9.7)	7.0 (4.3-11.6)	6.3 (3.7-10.7)	7.8 (4.1-14.8)
35-<40	2.0 (1.7-2.3)	11.6 (7.4-18.3)	12.4 (7.2-21.2)	11.5 (6.5-20.4)	12.5 (6.2-25.0)
40-<45	2.9 (2.4-3.6)	24.5 (15.2-39.2)	28.8 (16.7-49.7)	20.4 (11.0-37.6)	27.9 (13.6-56.9)
45-<50	3.1 (2.4-4.2)	33.5 (19.5-57.5)	38.3 (20.3-71.8)	32.1 (16.0-64.0)	40.5 (18.0-91.2)
Higher level‡					
<20	1.0	1.0	1.0	1.0	1.0
20-<25	1.1 (1.0-1.3)	2.0 (1.0-3.7)	2.0 (0.9-4.5)	2.1 (0.9-4.6)	2.4 (0.9-6.4)
25-<30	1.2 (1.0-1.4)	3.4 (1.8-6.3)	3.6 (1.7-7.7)	3.8 (1.8-8.1)	4.6 (1.8-11.7)
30-<35	1.6 (1.3-1.8)	4.2 (2.2-7.8)	4.3 (2.0-9.2)	4.3 (2.0-9.3)	4.7 (1.8-12.4)
35-<40	1.6 (1.4-1.9)	8.1 (4.3-15.1)	9.2 (4.3-19.6)	8.5 (4.0-18.3)	10.4 (4.0-27.0)
40-<45	2.0 (1.7-2.4)	14.2 (7.5-26.6)	15.8 (7.3-34.1)	12.5 (5.7-27.3)	12.4 (4.6-33.7)
45-<50	2.3 (2.0-2.8)	24.1 (13.1-44.3)	29.7 (14.1-62.1)	20.6 (9.7-43.7)	27.7 (10.8-70.5)

AST, aspartate aminotransferase

* Adjusted for age, body mass index, smoking status, alcohol consumption, serum glucose and total cholesterol, blood pressure, and family history of liver disease

† Mean and ‡higher level of the two measurements (1990 and 1992)

Table 10. Risk ratio for mortality by the level of serum alanine aminotransferase in men with relatively low (<50 IU/L) aminotransferase level

Serum ALT level	Risk ratio (95% confidence interval) for mortality*				
	Death from all causes	Death from all liver diseases		Death from liver cancer	
		All reported	Cause-confirmed	All reported	Cause-confirmed
Mean level†					
<20	1.0	1.0	1.0	1.0	1.0
20-<25	1.1 (1.0-1.3)	1.8 (1.3-2.5)	2.3 (1.5-3.5)	2.1 (1.4-3.2)	2.8 (1.7-4.6)
25-<30	1.3 (1.2-1.4)	3.0 (2.1-4.3)	3.7 (2.4-5.7)	2.5 (1.6-3.9)	3.5 (2.0-5.9)
30-<35	1.5 (1.3-1.7)	6.7 (4.7-9.3)	8.9 (5.9-13.5)	6.0 (3.9-9.1)	8.0 (4.8-13.5)
35-<40	1.5 (1.3-1.8)	5.8 (3.8-8.8)	7.6 (4.6-12.5)	6.4 (3.9-10.4)	8.5 (4.6-15.4)
40-<45	1.6 (1.3-2.0)	9.6 (6.2-14.8)	11.9 (7.0-20.1)	8.6 (5.0-14.9)	10.9 (5.6-21.2)
45-<50	1.3 (0.9-1.8)	5.0 (2.5-10.1)	8.4 (4.1-17.6)	5.8 (2.6-12.8)	9.8 (4.2-23.0)
Higher level‡					
<20	1.0	1.0	1.0	1.0	1.0
20-<25	1.1 (0.9-1.2)	1.6 (1.1-2.4)	2.7 (1.5-4.6)	2.1 (1.3-3.6)	3.6 (1.8-7.3)
25-<30	1.2 (1.0-1.3)	2.1 (1.4-3.2)	3.0 (1.7-5.3)	2.6 (1.5-4.4)	3.9 (1.9-8.0)
30-<35	1.2 (1.1-1.4)	2.8 (1.8-4.3)	4.2 (2.4-7.6)	3.4 (2.0-5.8)	5.7 (2.7-12.0)
35-<40	1.5 (1.2-1.7)	4.6 (3.0-7.2)	8.3 (4.7-14.6)	4.8 (2.7-8.6)	8.6 (4.1-18.3)
40-<45	1.6 (1.4-1.9)	8.3 (5.5-12.4)	12.9 (7.4-22.3)	7.6 (4.4-13.0)	12.1 (5.7-25.3)
45-<50	1.6 (1.3-1.8)	6.5 (4.3-10.0)	10.6 (6.1-18.6)	6.9 (4.0-12.0)	12.3 (5.9-25.5)

ALT, alanine aminotransferase

* Adjusted for age, body mass index, smoking status, alcohol consumption, serum glucose and total cholesterol, blood pressure, and family history of liver disease

† Mean and ‡higher level of the two measurements (1990 and 1992)

The relationship between the magnitude of change in serum aminotransferase level and mortality were also evaluated. Increase in serum AST or ALT level by 5 units or more was related to increasing mortality from all causes, all liver diseases and liver cancer. Decrease by 5 units or more in serum AST was related to decreasing mortality. However, decrease by 5 to 9 units in serum ALT could not decrease the risk of death. In general, increase of serum aminotransferase activities during the interval of two years indicated increasing risk of future death from all-cause and liver disease. And the greater increase of serum enzyme levels was related to greater increase of mortality (Table 11).

Table 11. Risk ratio for mortality by the magnitude of change in serum aminotransferase level in men with relatively low (<50 IU/L) aminotransferase level

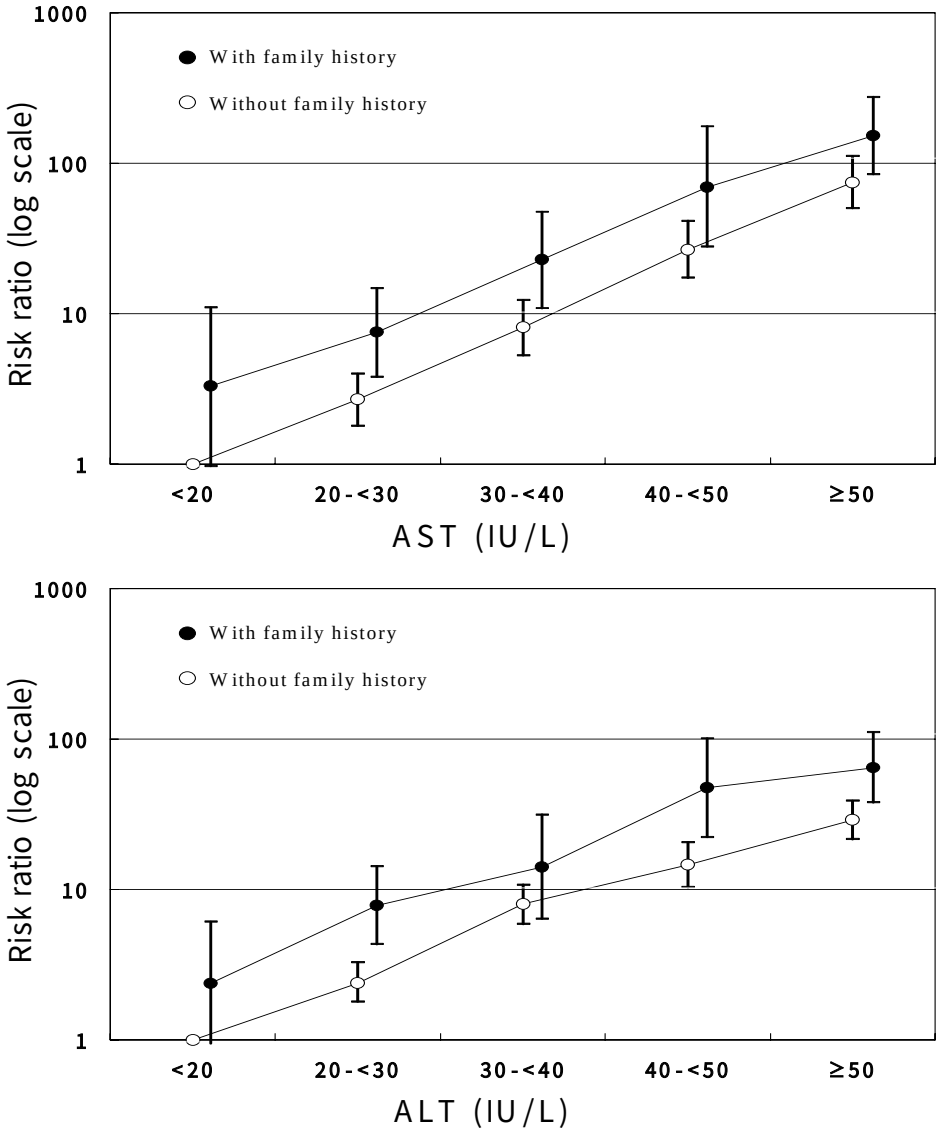
Change of serum aminotransferase level (IU/L)	Risk ratio (95% confidence interval) for mortality*		
	All causes	All liver disease	Liver cancer
	Risk ratio*(95%CI)	Risk ratio*(95%CI)	Risk ratio*(95%CI)
AST (IU/L)			
Decrease by 10 or more	0.74 (0.64-0.86)	0.35 (0.23-0.54)	0.23 (0.14-0.40)
Decrease by 5 to 9	0.85 (0.75-0.97)	0.72 (0.50-1.05)	0.62 (0.40-0.98)
Change within 5	1.00	1.00	1.00
Increase by 5 to 9	1.12 (1.00-1.25)	1.62 (1.16-2.28)	1.60 (1.08-2.36)
Increase by 10 or more	1.43 (1.28-1.59)	3.65 (2.76-4.82)	2.72 (1.94-3.83)
ALT (IU/L)			
Decrease by 10 or more	0.98 (0.77-1.02)	0.49 (0.32-0.73)	0.39 (0.23-0.64)
Decrease by 5 to 9	1.10 (0.97-1.24)	0.97 (0.67-1.38)	0.87 (0.56-1.35)
Change within 5	1.00	1.00	1.00
Increase by 5 to 9	1.16 (1.04-1.31)	1.46 (1.04-2.05)	1.58 (1.07-2.35)
Increase by 10 or more	1.32 (1.19-1.47)	2.43 (1.84-3.22)	2.14 (1.52-3.02)

AST, aspartate aminotransferase; ALT, alanine aminotransferase

* Adjusted for age, body mass index, smoking status, alcohol consumption, serum glucose and total cholesterol, blood pressure, and family history of liver disease

Figure 2 shows the results of stratified analyses by the presence of family history of liver disease. Men with family history of liver disease showed higher mortality than men without family history, but there was no interaction effect between

family history and serum aminotransferase level on liver diseases mortality.



AST, aspartate aminotransferase; ALT, alanine aminotransferase

Figure 2. Relationship between serum aminotransferase level and liver disease mortality by the presence of family history of liver diseases

In order to eliminate the confounding effects of concurrent disease at baseline, men with previously known disease in 1992 were not included in this study. However, more detailed information on objective health status or disease history was not available. To assess the amount of residual confounding effects due to previous or concurrent illness, further analyses were performed using different follow-up period. The follow-up length did not seriously affect the relationship between serum aminotransferase level and mortality. (Table 12)

Table 12. Relationship between serum aminotransferase level and liver disease mortality by the follow-up period.

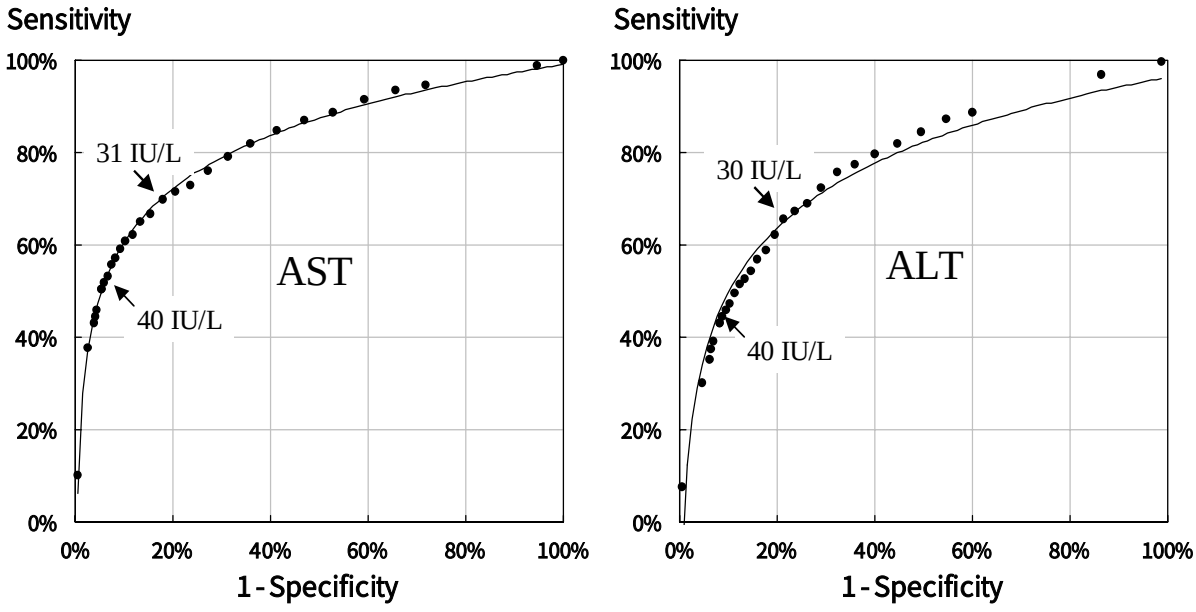
Serum aminotransferase level	Risk ratio (95% confidence interval) for mortality*			
	Death from all causes		Death from all liver diseases	
	Year1993 to 1996	Year 1997 to 2000	Year1993 to 1996	Year 1997 to 2000
AST (IU/L)				
<20	1.0	1.0	1.0	1.0
20-<25	1.3 (1.1-1.5)	1.1 (1.0-1.3)	1.8 (1.0-3.5)	1.8 (1.0-3.3)
25-<30	1.5 (1.2-1.8)	1.3 (1.1-1.5)	3.7 (2.0-6.9)	3.8 (2.2-6.6)
30-<35	1.8 (1.5-2.2)	1.5 (1.3-1.8)	7.2 (3.9-13.6)	5.6 (3.1-10.1)
35-<40	2.2 (1.7-2.8)	1.8 (1.5-2.3)	13.4 (6.9-26.1)	10.2 (5.4-19.1)
40-<45	3.4 (2.5-4.6)	2.5 (1.9-3.4)	29.0 (14.7-57.1)	20.6 (10.6-40.0)
45-<50	2.7 (1.7-4.3)	3.4 (2.4-4.9)	25.0 (10.4-60.0)	40.3 (20.1-80.8)
ALT (IU/L)				
<20	1.0	1.0	1.0	1.0
20-<25	1.2 (1.0-1.4)	1.1 (1.0-1.3)	1.7 (1.0-2.9)	1.8 (1.2-2.9)
25-<30	1.4 (1.2-1.7)	1.2 (1.0-1.4)	2.9 (1.7-4.8)	3.2 (2.0-5.0)
30-<35	1.8 (1.5-2.2)	1.3 (1.1-1.6)	7.8 (4.8-12.8)	5.7 (3.6-9.1)
35-<40	1.9 (1.5-2.4)	1.3 (1.0-1.6)	8.7 (5.0-15.2)	3.6 (1.8-6.9)
40-<45	1.8 (1.3-2.5)	1.5 (1.1-2.0)	10.4 (5.5-19.7)	8.8 (4.8-16.0)
45-<50	1.2 (0.7-2.0)	1.4 (0.9-2.1)	2.5 (0.6-10.7)	7.0 (3.1-15.8)

AST, aspartate aminotransferase; ALT, alanine aminotransferase

*Adjusted for age, body mass index, smoking status, alcohol consumption, serum glucose and total cholesterol, blood pressure, and family history of liver disease

Normal Limits of Serum Aminotransferase Level

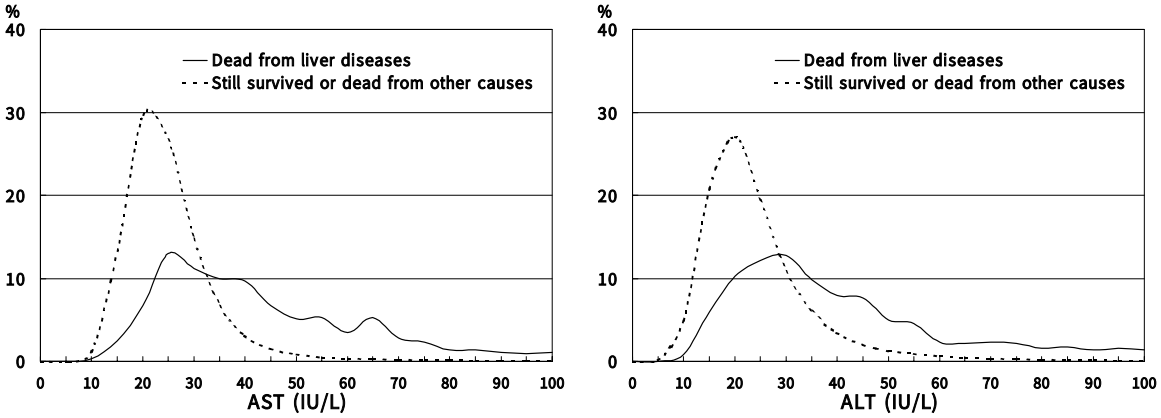
In the ROC plotting curves, the performance of different cutoff values in the identification of men with risk for death from liver disease (Figure 3). The best cutoff values were estimated as 31 IU/L for AST and 30 IU/L for ALT, and the area under the curve were 0.83 (95% CI, 0.81 to 0.85) and 0.78 (95% CI, 0.76 to 0.80), respectively. When the current upper normal limits (40 IU/L) were applied, the tests had fairly high specificity (94.1% for AST and 91.2% for ALT) but relatively low sensitivity (51.9% for AST and 44.4% for ALT). With cutoff value of 31 IU/L, AST test had increased sensitivity (69.9%) with acceptable tradeoff in specificity (82.1%). And with 30 IU/L, ALT test had also superior sensitivity (65.7%) and acceptable specificity (78.7%).



AST, aspartate aminotransferase; ALT, alanine aminotransferase

Figure 3. Receiver-operating characteristic (ROC) curves of serum aminotransferase level in identifying men who died from liver diseases

The usefulness of current upper normal limits can be estimated from Figure 4. Majority of men who died from liver diseases during the follow-up period, had serum AST and ALT level less than 40 IU/L at baseline. The distribution of baseline enzyme levels of men who died from liver disease and that of men who did not die from liver disease, overlap each other in considerable portion. However, the reference value around 30 IU/L has the largest power to discriminate the men who are at high risk from those who are not.



AST, aspartate aminotransferase; ALT, alanine aminotransferase

Figure 4. Distribution of baseline serum aminotransferase level in men who died from liver disease and in men who still survived or died from other causes

5. DISCUSSION

These results suggest a positive and statistically significant relationship between serum aminotransferase level and mortality (from all causes, all liver disease and liver cancer) in middle-aged Korean men. And this relationship could be observed in relatively low serum aminotransferase level (20 to 50 IU/L). It proposes that slight increase of serum AST or ALT level, but still under normal limits, is also related to high risk for death from chronic liver disease. Serum aminotransferase levels are widely used laboratory tests and very useful indicators of acute and chronic liver diseases. The strong association between serum aminotransferase level and the prevalence of liver disease is well known. And several studies were done on the significance of slightly elevated enzyme activity. However, little is known about the direct relationship of aminotransferase level to mortality. This study could assess the relationship between serum aminotransferase level and mortality from all causes and liver diseases, in general population with prospective design and enough follow-up length.

Serum aminotransferase level is associated with several other factors, which are risk factors for morbidity or mortality from chronic disease. Body mass index, alcohol consumption, serum cholesterol level, and blood glucose level are most frequently associated with increased liver aminotransferase level (Bailey wt al, 1974; Lai et al, 2001; Lee et al, 2001; Piton et al, 1998; Porikos et al, 1983; Salvaggio et al, 1991; Steffensen et al, 1997). All these variables are positively related with serum AST and ALT levels in this study. Body mass index and serum cholesterol level had negative

association with liver disease mortality, while blood glucose level had positive association. Amount of alcohol consumption showed U-shaped association with liver disease mortality. I tried to control the effects of above mentioned variables and some others in statistical models. The results found a strong correlation between serum aminotransferase level and mortality, even after adjustment for such potential confounders as age, body mass index, smoking status, alcohol consumption, blood pressure, serum glucose and cholesterol level, and family history of liver disease. Nevertheless, serum aminotransferase level is unlikely to have causal relation with future death from liver disease. Increased serum aminotransferase are rather results of liver disease. Repeatedly high level of liver enzyme is a clear sign of liver cell damage, and is also a risk factor of death related with liver disease.

However, for the relatively low level of these enzymes, little is known related with morbidity and mortality. There could be several explanations for the high risk of mortality in men with increased but still under normal enzyme level (20 to 40 IU/L). At first, sub-clinical liver disease can mediate this association. Minimal increase of liver enzyme activity may indicate early stage of chronic liver disease, and may be a cause of death in the long run. Several studies demonstrated that the presence of patholgy-confirmed liver diseases such as chronic active or persistent hepatitis and even cirrhosis, in men with aminotransferase level less than 40 IU/L. Chronic carriers of hepatitis virus, especially HCV may be another explanation. Many studies reported chronic asymptomatic HCV infection with persistently normal aminotransferase levels (PNAL) as a common form of HCV infection (Alter et al, 1997; Gholson et al, 1997; Jamal et al, 1999; Jensen et al, 1987; Martinot-Peignoux et al, 2001; Naito et al, 1994;

Persico et al, 2000; Pradat et al, 2002; Shin et al, 2000). Kim et al. reported prevalence of Anti-HCV and HBsAg in relation with aminotransferase level. In men with low AST (<25 IU/L) and ALT (<29 IU/L) level, prevalence of Anti-HCV and HBsAg positivity were 1.4 % and 4.6 %, respectively. In men with slight elevated AST (25-<50 IU/L) and ALT (29-<58 IU/L) level, corresponding rates were 2.2 % and 11.6 % (Kim et al, 1992). And co-infection of HCV is known as an important risk factor for hepatocellular carcinoma, in HBV endemic area including Korea.

Advanced chronic liver disease may be another explanation for the association. Men with extensive liver damage have relatively low serum enzyme activity (Friedman et al, 1996). However, the possibility is not considerable, because men with previously known disease were not included for this study, and the average value of the two measurements with two-year interval was used.

Finally, other risk factors for chronic liver disease such as obesity, alcohol consumption, and smoking may cause the relationship. Serum aminotransferase level is positively associated with body mass index and obesity is the most frequent cause of non-alcoholic non-viral hepatitis (Guzzaloni et al, 2000; Porikos et al, 1983; Salvaggio et al, 1991). Smoking and alcohol consumption can increase the risk of liver cancer, chronic hepatitis, or liver cirrhosis (Lee et al, 2001; Nakamura et al, 1998). In the study popualtion, elevated aminotransferase levels were associated with current smoking and heavy drinking ($\geq$ 50g of alcohol per day). These variables were effectively adjusted with statistical methods, but the possibility of residual confounding could not be eliminated.

There were several studies that review the normal limits of serum aminotransferase levels. However, these studies were mainly done with special population such as blood donors and continuous peritoneal dialysis (CAPD) patients. It is known that risk of HBV or HCV infection after transfusion is directly related with serum aminotransferase level of blood donor. Adoption of lower limits for serum aminotransferase value can decrease the risk of post-transfusion infection (Alter et al, 1981; Kakov et al, 1991; Tsai et al, 1996; Widell et al, 1988). Because CAPD patients have higher risk for viral hepatitis and have usually lower aminotransferase activity than healthy population, lower cut-off values of serum aminotransferase level (24 IU/L for AST and 17 to 27 IU/L for ALT) were suggested (Espinosa et al, 2000; Hung et al, 1997).

Recently, Prati et al. suggested a revised normal limit for serum ALT levels with a retrospective study. Their updated upper limits (30 IU/L for men) showed increased sensitivity (76.3%) with acceptable specificity (88.5%) to detect chronic HCV infection or nonalcoholic fatty liver disease during 6-month follow-up. However they commented that this is a new “healthy range” rather than generic update of “normal range”, because it is not an optimal solution to be widely updated (Prati et al, 2002; Pratt and Kaplan, 2000). The results of the KMIC Study also propose that men who demonstrate repeated increase of aminotransferase level (AST ≥ 30 IU/L or ALT ≥ 31 IU/L) should be further investigated for liver disease, even if the aminotransferase level is still under the current normal limit (40 IU/L). With these new guidelines, sensitivity in identifying men who are at risk for death from liver disease can be markedly increased (52% to 70% for AST and 44% to 66% for ALT). And the related tradeoff in

specificity was acceptable (94% to 82% for AST and 91% to 79% for ALT). Morbidity and mortality from liver disease are important health problem in middle-aged Korean men, and revision of normal limits for serum aminotransferase has great implications. Because the percentage of men with serum AST and ALT level of 30 to 39 IU/L is high (18.5% in this study), population attributable risk (PAR) of this level for liver disease mortality is estimated to unexpectedly high (34.5%). Therefore, men with slightly increased but still under normal enzyme level (30 to 39 IU/L) may be an important target population to prevent early death from liver diseases.

In spite of many evidences, update of current normal limits for AST and ALT level is still controversial. There are several undesirable effects of decreasing the upper normal limits. It would increase the number of asymptomatic patients found with abnormal aminotransferase level, and it can cause increase of direct and indirect health care cost. And the lower cutoff value can adversely affect blood supply shortage (Kaplan, 2002). For these reasons, it can be a practical solution to add a new conception of “healthy or optimal range (<30 IU/L)” rather than to revise current “normal range (< 40IU/L)”. Men with the “borderline or high-normal (30 to 39 IU/L)” serum aminotransferase level should be closely observed, and further investigations should be performed by using serum biochemistry tests, viral marker tests, and ultrasonography if needed. Widespread adoption of other laboratory tests, such as viral marker study and nucleic acid study, for health screening examinations can be another alternative.

There are several important strengths of this study compared to previous ones. At first, the KMIC Study has large sample size and the large number of events during

the eight year follow-up. Several previous studies assessed the relationship between serum aminotransferase level and Hepatitis C Virus (HCV) positivity or histologic abnormality in liver biopsy (Gholson et al, 1997; Herve et al, 2000; Hultcrantz et al, 1986; Pradat et al, 2002; Prieto et al, 1995; Shakil et al, 1995) However, these studies had cross-sectional designs or short follow-up lengths, and failed to investigate the effects of increasing serum aminotransferase on long-term morbidity or mortality. Meanwhile, this large prospective study investigated the relationship between serum aminotransferase level and future mortality from all causes, all liver disease and liver cancer. Secondly, the results could be generalized to the broader Korean population, and likely other populations. While many of the previous studies were done with special population such as blood donors and CAPD (continuous ambulatory peritoneal dialysis) patients (Espinosa et al, 2000; Hung et al, 1999), the KMIC Study Cohort was recruited from a nation-wide general population. Another strength of this study is high follow-up rate. Because a unique identification number did computerized matching between baseline data and death certificate data, nearly all deaths of the cohort members could be confirmed. Finally, repeated measures of exposure variables can be one of the strengths of this study. Serum aminotransferase activity and several other risk factors for mortality including body mass index, blood pressure, and serum glucose and cholesterol level were measured at two baseline examinations (in 1990 and 1992). Average of the two measurements was used for each variable in analyses, and the possibility of measurement error or misclassification bias could be diminished.

Potential limitations of this study include brief information on preexisting

diseases, non-standardized aminotransferase assays, and the validity of cause of death. All the cohort members were asked whether they had some known diseases at the time of examination; however, more detailed information about specific diseases was not available. For this reason, all who answered that they had known diseases were not included for the analyses, but as in all observational studies, there is the potential for confounding. Additionally I tried to test the residual confounding effects of preexisting disease, with comparison of the results by the follow-up length. The association between serum aminotransferase level and mortality was slightly attenuated in later follow-up period, but still existed. In spite of these efforts, effects of HBV or HCV infection could not be controlled effectively. Koreans are known to have high prevalence of chronic viral hepatitis. HBV and HCV infection was found to be associated with liver cancer in HBV endemic area (Chuang et al, 1992). Infection of these viruses could confound the relationship between serum aminotransferase level and liver disease mortality. In this study, no viral marker test was performed. Instead, family history of liver disease was included in the analyses, because possibility of chronic HBV infection is high in case of congenital infection. The stratified analyses showed no interaction effect between family history of liver disease and serum aminotransferase level on liver disease mortality. Chronic asymptomatic infection of HBV or HCV did not seem to affect the results seriously. Although the effects of chronic viral infection was not controlled, this study have practical meaning because majority of health screening examinations do not include viral studies for the first line tests.

Because 419 hospitals over the country conducted the health examinations, techniques and equipments for serum aminotransferase measurements were not well

standardized. However, all these hospitals followed internal and external quality control procedures as stipulated by the Korean Society of Quality Control in Clinical Pathology. The variation index score (VIS) of serum AST and ALT measurements in 1992 were 107 and 109, respectively. VIS is a widely used index of quality control with value of less than 100 indicating excellent quality and less than 150 good quality (Kim et al, 1993; Chung et al, 1991). Additionally, using mean of two measurements with two year interval and large sample size had great advantage, comparing with previous studies.

Causes of death used in this study were abstracted from death certificate. The validity of diagnoses on death certificate is not as good as that on medical records. For the alternate method to verify the causes of death on certificates, diagnosis on health insurance claim data were matched. For all deaths from liver disease in year 1995 to 2000, experience of hospital admission due to liver disease in year 1993 to 2000 were pursued. Majority (76.2%) of men who died from liver disease had history of hospital admission for same reason. And the analyses were performed with two types of liver disease mortality for outcome variable: all reported deaths and cause-confirmed deaths by hospital admission history. The results were almost same, regardless of types of outcome variables.

6. CONCLUSIONS

In this study, statistically significant and positive relationship was observed between serum aminotransferase level and mortality from all causes, all liver diseases and liver cancer. This association was also observed within the current normal range. And it was independent from health status or other risk factors of chronic disease at baseline.

In order to screen men with pre-clinical liver disease and prevent them from early death related with liver disease, currently used upper normal limits may not be adequate. With current cutoff value (40 IU/L) of AST and ALT in identifying liver disease mortality in following eight years, yielded sensitivity of only 51.9% and 44.4% respectively. Meanwhile, cutoff values of 31 IU/L for AST and 30 IU/L for ALT had superior sensitivities (69.9% for AST and 65.7% for ALT) with acceptable tradeoff in specificities (82.1% and 78.7%). The men with slightly increased but still under normal serum aminotransferase level (30 to 40 IU/L) should be further investigated for liver disease.

These results strongly suggest the need to review the current normal limits for serum aminotransferase tests. It can be a practical solution to divide the current normal range into two categories: “healthy or optimal range (<30 IU/L)” and “borderline or high-normal range (30-39 IU/L)”. Inclusion of other laboratory tests, such as viral marker and nucleic acid study, for health screening examinations can be considered.

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Abstract in Korean

중년남성에서 혈청 아미노산전환효소 (AST, ALT) 농도와 전체 사망률 및 간질환 사망률과의 관계

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전세계적으로 만성 B형 간염과 C형 간염 유병률은 각각 6%와 3% 정도로 추정되며, 이들은 간경변 및 간암으로 진행되어 많은 사망의 원인이 되기도 한다. 특히, 아프리카와 아시아 지역은 간질환 유병률 및 사망률이 높은 지역으로 알려져 있으며, 우리 나라에서도 간질환은 단일 장기에 의한 사망으로 1위를 차지하고 있는 중요한 질환이다. 혈청 아미노산전환효소 (AST 및 ALT) 검사는 간질환의 진단과 조기검진에 가장 널리 사용되는 생화학 검사이다. 헌재 혈청 AST 및 ALT 농도의 정상 상한값으로는 40 IU/L를 가장 많이 사용되고 있다. 하지만, 혈청 AST 및 ALT 농도에 따른 간질환 발생 또는 사망에 대한 전향적 연구 결과는 거의 없는 실정이며, 현재 사용되는 정상 상한값을 간질환 환자의 조기 발견에 이용할 경우 민감도가 낮아서 이를 고쳐야 한다는 주장도 제기되고 있다. 따라서 본 연구는 일반 성인 남성 인구에서 혈청 아미노산전환효소 농도와 간질환 및 전체 사망률과의 관계를 밝히고, 현재 사용되고 있는 정상 범위의 적절성을 평가하기 위하여 시행하기 위하여 시행되었다.

본 연구는 의료보험관리공단 (Korea Medical Insurance Corporation, KIMC) 코호트 자료를 이용하였다. 연구 대상은 1990년과 1992년 두 차례의 건강검진에 모두 참여한 35-59세 남성이었으며, 1992년 당시에 이미 질병을 가지고 있다고 응답한 사람은 대상에서 제외되었다. 연구 대상자들은

1993년부터 2000년까지 8년 동안 사망여부와 사망 원인에 대하여 추적관찰 되었다. 독립변수인 혈청 아미노산 전환효소 농도와 종속변수인 사망률과의 관계는 콕스의 비례위험 회귀모형을 통하여 분석하였으며, 연령, 체질량지수 (body mass index), 혈압, 흡연, 음주, 혈청 포도당 및 콜레스테롤 농도, 간질환 가족력 등의 변수는 통계적 방법으로 보정하였다.

연구 대상자 95,459명 가운데 추적기간 동안 3,370명의 사망이 관찰되었으며 이 가운데 19%는 간암 또는 간질환이 사망 원인이었다. 다른 변수의 영향을 보정한 상태에서 혈청 AST 및 ALT 농도는 전체 사망 및 간질환으로 인한 사망과 통계적으로 유의한 양의 상관관계를 보였다. 매우 낮은 수준(<20 IU/L)의 혈청 효소 농도와 비교하면, 20-39 IU/L 범위의 효소 농도에서 통계적으로 의미 있게 사망 위험이 증가하였다. 혈청 AST 농도 20-29 IU/L 와 30-39 IU/L의 전체 사망에 대한 비교위험도(95% 신뢰구간)는 각각 1.3 (1.2-1.4)과 1.8 (1.6-2.0)이었으며, 혈청 ALT 농도에서는 비교위험도가 각각 1.2 (1.1-1.3)와 1.7 (1.5-2.9)이었다. 간질환으로 인한 사망 위험은 더 크게 증가하여, 혈청 AST의 비교위험도는 2.6 (1.8-3.9)과 7.9 (5.3-11.8), ALT의 비교위험도는 2.4 (1.8-3.3)와 7.7 (5.8-10.4)이었다.

혈청 AST 및 ALT 검사를 이용하여 향후 8년간 간질환 사망을 예측하는데 최적의 기준치를 ROC 곡선(receiver-operating characteristic curves)을 이용하여 추정한 결과, AST는 31 IU/L 그리고 ALT 는 30 IU/L으로 계산되었다. 기존의 정상 상한값 대신 이 값을 사용할 경우 검사의 민감도가 AST는 52%에서 70%로 ALT는 44%에서 66%로 크게 향상된 반면, 특이도는 각각 94%에서 82%, 91%에서 79%로 감소하였다. 이 결과는 현재 사용되고 있는 정상 상한값이 간질환의 조기 발견에 적절하지 않음을 보여주며, 정상범위를 재설정하여야 할 필요성을 제기하는 것이다.

핵심되는 말: 아미노산전환효소, AST, ALT, 사망률, 간질환, 간암