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## Normal serum aminotransferase concentration and risk of mortality from liver diseases: prospective cohort study

Hyeon Chang Kim, Chung Mo Nam, Sun Ha Jee, Kwang Hyub Han, Dae Kyu Oh, Il Suh

### Abstract

**Objective** To examine the relation between the normal range of serum aminotransferase concentration and mortality from liver disease.

**Design** Prospective cohort study.

**Setting** Korea Medical Insurance Corporation study with eight years' follow up.

**Participants** 94 533 men and 47 522 women aged 35-59 years.

**Main outcome measure** Mortality from liver diseases according to death certificate.

**Results** There was a positive association between the aminotransferase concentration, even within normal range (35-40 IU/l), and mortality from liver disease. Compared with the concentration < 20 IU/l, the adjusted relative risks for an aspartate aminotransferase concentration of 20-29 IU/l and 30-39 IU/l were 2.5 (95% confidence interval 2.0 to

3.0) and 8.0 (6.6 to 9.8) in men and 3.3 (1.7 to 6.4) and 18.2 (8.1 to 40.4) in women, respectively. The corresponding risks for alanine aminotransferase were 2.9 (2.4 to 3.5) and 9.5 (7.9 to 11.5) in men and 3.8 (1.9 to 7.7) and 6.6 (1.5 to 25.6) in women, respectively. According to receiver operating characteristic curves the best cut-off values for the prediction of liver disease in men were 31 IU/l for aspartate aminotransferase and 30 IU/l for alanine aminotransferase.

**Conclusion** People with slightly increased aminotransferase activity, but still within the normal range, should be closely observed and further investigated for liver diseases.

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## Introduction

Serum aminotransferase assays are the most common laboratory tests for the detection of liver diseases. Because the enzyme concentration in a population forms a continuous distribution, the cut-off concentration that discriminates between healthy and diseased livers is not clearly defined. The normal range is calculated from a supposedly healthy reference population. However, reference populations probably include people with mild to moderate chronic liver diseases.<sup>1 2</sup> The normal range may also be determined from prospective studies on the association between enzyme concentration and long term mortality. However, there is little information on the association between serum aminotransferase concentration and mortality from liver diseases, especially for relatively low concentrations of aminotransferase.

## Methods

### Study population

We selected participants from the cohort used in the Korea Medical Insurance Corporation study. The corporation provides health insurance to government and private school employees and their dependents. In 1990, the corporation insured 1 213 594 workers and 3 389 767 dependents, about 11% of the total Korean

population. The corporation required all insured workers to take a biennial health examination. The study cohort consisted of 115 200 men and 67 932 women, aged 35-59 years in 1990, who underwent health examinations in 1990 and 1992. We had data on serum aminotransferase assay and smoking and alcohol intake for 102 741 men and 51 180 women. We excluded 162 men and 21 women who died before 1993 and 8046 men and 3637 women who had any known diseases at baseline and enrolled 94 533 men and 47 522 women for the analysis.

**Data collection**—We obtained baseline information from the health examinations in 1990 and 1992 and the self reported questionnaire in 1992. The outcome variable was mortality from death certificates. The follow up period was eight years (1993-2000). In the survival analyses, of the deaths from liver diseases as recorded on the death certificates, we used data only for those patients who had previously been admitted to hospital with liver disease. Information on hospital admissions was obtained from the health insurance claim data.

**Statistical analysis**—We classified participants according to body mass index; serum total cholesterol concentration; plasma glucose concentration; blood pressure; smoking; alcohol consumption; and family history of liver disease. Cox proportional hazard regression analysis was used to control for age and the above variables. We plotted the receiver operating characteristic curve of the serum aminotransferase concentration for the detection of future mortality from liver disease.

## Results

During the eight years' follow up 3392 men and 394 women died. The mortality per 100 000 person years was 456 for men and 104 for women. The number of deaths from liver disease was 690, and 524 were confirmed by the previous admission history. Mortality from liver disease was positively associated with baseline age, serum aminotransferase concentration, and blood pressure in both sexes. Family history of liver diseases, high fasting plasma glucose concentration, low total serum cholesterol concentration, and heavy drinking were also correlated with mortality from liver disease in men (table 1).

The association between aminotransferase concentration and mortality in men was continuous and positive (table 2). The association between the aminotransferase concentration and mortality from liver disease was significant, even within the current normal limits. Compared with the lowest concentration (< 20 IU/l), the risks for mortality from liver disease for aspartate and alanine aminotransferase concentrations at 20-29 IU/l (only in men) and 30-39 IU/l were significantly increased (table 2).

We estimated that the best cut-off values for identifying men who are risk of death from liver disease were 31 IU/l for aspartate aminotransferase and 30 IU/l for alanine aminotransferase. The areas under the receiver operating characteristic curve were 0.83 and 0.78, respectively (figure). We could not establish the cut-off value in women, but we would expect it to be lower than in men.

**Table 1** Association between baseline characteristics and risk of mortality from liver diseases. Figures are relative risks (95% confidence intervals)

Baseline characteristics	Men	Women
Age (per one year increase)	1.05 (1.04 to 1.06)	1.14 (1.07 to 1.21)
Raised AST ( $\geq 40$ IU/l)	18.17 (15.24 to 21.66)	22.53 (8.36 to 60.67)
Raised ALT ( $\geq 40$ IU/l)	8.93 (7.49 to 10.64)	27.32 (11.24 to 66.40)
Family history of liver disease	2.62 (1.93 to 3.56)	—
Body mass index* (kg/m <sup>2</sup> ):		
<21.75 (<20.51)	1.00	1.00
21.75-23.38 (20.51-22.06)	0.87 (0.68 to 1.10)	0.76 (0.17 to 3.37)
23.39-25.0 (22.07-23.72)	0.82 (0.64 to 1.05)	0.25 (0.03 to 2.27)
$\geq 25.01$ ( $\geq 23.75$ )	0.83 (0.65 to 1.06)	3.83 (1.27 to 11.55)
Blood pressure:		
Normal	1.00	1.00
Prehypertension	1.11 (0.89 to 1.39)	2.99 (1.21 to 7.41)
Hypertension	1.91 (1.46 to 2.49)	3.63 (0.75 to 17.45)
Fasting plasma glucose (mmol/l):		
<6.1	1.00	1.00
6.1-6.9	2.10 (1.77 to 2.57)	0.68 (0.09 to 5.04)
$\geq 7.0$	3.18 (2.29 to 4.42)	—
Total serum cholesterol* (mmol/l):		
<4.4 (<4.3)	1.00	1.00
4.4-4.8 (4.3-4.7)	0.63 (0.50 to 0.79)	1.32 (0.46 to 3.80)
4.9-5.4 (4.8-5.3)	0.49 (0.38 to 0.62)	0.97 (0.31 to 3.01)
$\geq 5.5$ ( $\geq 5.4$ )	0.48 (0.37 to 0.61)	0.50 (0.13 to 2.01)
Smoking:		
Non-smoker	1.00	1.00
Past smoker	1.07 (0.81 to 1.42)	—
Current smoker	1.20 (0.95 to 1.51)	—
Ever smoked	—	5.53 (0.75 to 41.04)
Alcohol consumption (g/day):		
Non-drinker	1.00	1.00
<50	0.78 (0.64 to 0.94)	—
50-99	0.96 (0.68 to 1.35)	—
100-199	1.09 (0.58 to 2.06)	—
$\geq 200$	3.33 (1.64 to 6.76)	—
Drinker	—	1.66 (0.39 to 7.08)

AST=aspartate aminotransferase, ALT=alanine aminotransferase.  
\*Figures in parentheses are ranges for women.

**Table 2** Relative risk (RR) of mortality from all causes and from liver disease by the serum aminotransferase concentration at baseline (expressed as floating absolute risks)

	Total No of participants	All causes		Liver diseases	
		No of deaths	RR* (95% CI)	No of deaths	RR* (95% CI)
<b>Men</b>					
Aspartate aminotransferase (IU/l):					
<20	26 416	619	1.0 (0.9 to 1.1)	25	1.0 (0.7 to 1.5)
20-29	48 185	1494	1.3 (1.2 to 1.4)	108	2.5 (2.0 to 3.0)
30-39	13 964	590	1.7 (1.6 to 1.9)	98	8.0 (6.6 to 9.8)
40-49	3 127	219	2.7 (2.4 to 3.1)	70	25.7 (20.3 to 32.5)
50-99	2 397	358	5.4 (4.9 to 6.0)	149	65.7 (55.8 to 77.4)
≥100	444	112	8.6 (7.2 to 10.4)	51	111.3 (84.0 to 147.4)
Alanine aminotransferase (IU/l):					
<20	37 425	1061	1.0 (0.9 to 1.1)	45	1.0 (0.7 to 1.4)
20-39	36 589	1197	1.2 (1.1 to 1.3)	113	2.9 (2.4 to 3.5)
30-39	11 975	516	1.7 (1.5 to 1.8)	110	9.5 (7.9 to 11.5)
40-49	4 068	225	2.2 (1.9 to 2.5)	74	19.2 (15.3 to 24.2)
50-99	3 887	310	3.0 (2.7 to 3.4)	117	30.0 (25.0 to 36.1)
≥100	589	83	5.2 (4.2 to 6.4)	42	59.0 (43.4 to 80.1)
<b>Women</b>					
Aspartate aminotransferase (IU/l):					
<20	25 362	185	1.0 (0.9 to 1.2)	3	1.0 (0.3 to 3.2)
20-29	19 463	174	1.0 (0.9 to 1.2)	9	3.3 (1.7 to 6.4)
30-39	2 114	24	1.2 (0.7 to 1.6)	6	18.2 (8.1 to 40.4)
40-49	336	3	0.8 (0.3 to 2.5)	3	46.1 (14.9 to 147.4)
≥50	247	8	2.9 (1.4 to 5.8)	2	46.2 (11.0 to 180.4)
Alanine aminotransferase (IU/l):					
<20	35 187	257	1.0 (0.9 to 1.2)	6	1.0 (0.4 to 2.3)
20-29	10 201	103	1.2 (1.0 to 1.4)	8	3.8 (1.9 to 7.7)
30-39	1 380	19	1.4 (0.9 to 2.2)	2	6.6 (1.5 to 25.6)
40-49	365	10	3.0 (1.6 to 5.6)	5	68.3 (27.4 to 162.0)
≥50	389	5	1.2 (0.5 to 3.0)	2	21.5 (5.3 to 85.6)

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

## Discussion

We found a strong relation between aminotransferase concentrations and long term mortality. We also found that a slightly increased but still normal aminotransferase concentration is related to increased risk of death from liver disease.

### Mortality from liver disease and normal serum aminotransferase concentration

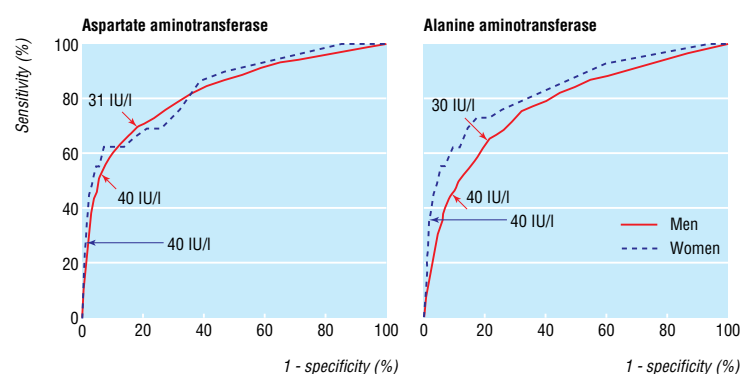
There could be several explanations for the increased risk of mortality in men with slightly increased but still normal enzyme concentrations. Firstly, mortality may be due to unrecognised liver diseases. Secondly, the relation may be due to other risk factors for liver disease such as obesity, alcohol consumption, serum cholesterol concentration, and plasma glucose concentration.<sup>3-5</sup> Even after we adjusted for such risk factors, we observed an independent association between the aminotransferase concentration and mortality from liver disease. Thirdly, advanced chronic liver diseases with relatively low enzyme activity may contribute to the association. This is unlikely, however, as we excluded men with known liver diseases and used the average of two enzyme measurements at two year intervals.

Though we consistently observed an association between serum aminotransferase concentration and mortality from liver disease in men, we could not do so in women because mortality from liver diseases in woman is low.

### Application of results

Recently, Prati et al proposed that the upper normal limit of serum alanine aminotransferase should be revised to 30 IU/L.<sup>2</sup> The outcome of the application of the updated normal upper limit is increased sensitivity (76.3%) with acceptable specificity (88.5%) in identifying active C viral hepatitis during six month follow up.<sup>2</sup> Our data agree with this report.

However, updating the current normal range remains controversial. Lowering the upper normal limits will increase the number of asymptomatic patients with abnormal aminotransferase concentration, which may increase the healthcare costs. The



Receiver operating characteristic (ROC) curves of serum aminotransferase concentration for identification of people at risk of death from liver diseases

lower upper limit will limit blood supplies.<sup>6</sup> People who repeatedly show increased aminotransferase concentrations according to the lowered normal upper limit should be further investigated by serum biochemistry, viral marker tests, and ultrasonography. The cost effectiveness of this approach still needs to be evaluated prospectively in various settings.

#### Strength and weakness

This study has several strong points. Firstly, it was performed with a large population (142 055 people) and had a long follow up period (eight years). Previous studies have had a cross sectional design or short follow up period, and they failed to investigate the association between serum aminotransferase concentration and long term mortality.<sup>2-7-9</sup> Secondly, the results can be generalised to the broader Korean population and, perhaps, to other populations as well. While previous studies investigated special populations, such as blood donors and haemodialysis patients, our study cohort was recruited from the nationwide general population.<sup>2-7-9</sup> Thirdly, the use of repeated measurements of variables decreased the possibility of measurement error or misclassification bias. Finally, to increase the validity of the causes of death, we verified mortality from liver diseases by reviewing data on hospital admissions.

Potential limitations of this study include the brief information on pre-existing diseases, lack of other laboratory tests for liver diseases, and non-standardised aminotransferase assays. Firstly, as the objective medical history of the study population was not available, we used the information provided by participants. We excluded people who indicated that they had any previously known diseases. We also assessed the confounding effects of unknown pre-existing disease by comparing the results by different follow up periods and found no association. Secondly, we did not study viral marker or perform liver function tests other than aminotransferase assays in the baseline examination. Individuals with family history of liver disease are at high risk of the chronic hepatitis B virus infection because the infection is common in Korea, 5-10% in men and 1-5% in women, and transmitted horizontally in high frequency.<sup>10-11</sup> We assessed the effects of the family history of liver disease using a stratified analysis. The results showed that family history of liver diseases did not alter the outcome of the study. Thirdly, 419 hospitals over the country conducted the health examination and the serum aminotransferase assay was not standardised. All hospitals, however, followed the internal and external quality control procedures as stipulated by the Korean Society of Quality Control in Clinical Pathology. The misclassification bias, if any, is likely to be non-differential reduction of the relative risk. Hence, the results are unlikely to be distorted by measurement error.

#### Conclusion

Our findings indicate that serum aminotransferase concentration is associated with mortality from liver disease, even within the current normal range. The adjustment of the normal limit of serum aminotransferase may be necessary, especially in populations in which liver diseases are common.

#### What is already known on this topic

The serum aminotransferase test with upper normal limit of 40 IU/l can identify liver damage

Little is known about the association between the normal range of the serum aminotransferase concentration and mortality

#### What this study adds

Serum aminotransferase concentration, even under 40 IU/l, is positively associated with mortality from liver disease

The sensitivity of the serum aminotransferase test with the current normal range is low in identifying individuals at risk of death from liver disease

Lowering the normal range of the serum aminotransferase concentration is advisable in populations in which liver diseases are common

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#### Endpiece

#### Many a true word spoken in jest

I am only a small cigarette,  
But my work I will get in, you bet,  
For the stern coffin maker  
And the grim undertaker  
Will declare I bring fish to their net.

*Everybody's book of jokes*. London, 1890

Michael Warner, retired, Canterbury