Low Alanine Aminotransferase Activity in Older People Is Associated with Greater Long-Term Mortality

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OBJECTIVES: To find possible association between liver enzymes and mortality in older people.

DESIGN: A prospective cohort study.

SETTING: Jerusalem.

PARTICIPANTS: A systematically selected representative sample of 455 70-year-old ambulatory individuals was prospectively followed for 12 years.

MEASUREMENTS: An extensive social and medical profile was developed at age 70 using a detailed interview and physical and ancillary examination. Information on mortality was obtained annually. Differences in survival between subjects stratified according to liver enzyme levels were assessed using the Kaplan–Meier method. Multivariable survival analyses using a Cox proportional hazards model were performed to determine the association between liver enzyme levels at age 70 and mortality over 12 years.

RESULTS: Median alanine aminotransferase (ALT) activity of the study population was 11.00 U/L for women and 13.00 U/L for men. Twelve-year survival rates for women with ALT below and above the median levels were similar (78%). For men, these rates were 54% and 65%, respectively ($P < .001$). Proportional hazards models demonstrated that this greater mortality risk was independent of numerous common risk factors for mortality (hazard ratio (HR) = 1.5, 95% confidence interval (CI) = 1.08–2.19). Adding an interaction between sex and low ALT to the model demonstrated a higher risk of mortality for men with low ALT levels (HR = 2.42, 95% CI = 1.15–5.08). No such risk was demonstrated for the other liver enzymes.

CONCLUSION: ALT activity represents a strong and independent surrogate marker for mortality in community-dwelling elderly men. **J Am Geriatr Soc 54:1719–1724, 2006.**

Key words: alanine aminotransferase; mortality; aging population.

The aging population is the greatest user of health resources in Western societies. Reliable clinical and laboratory markers that can predict tendencies for morbidity and mortality in this age group are needed to facilitate evaluation, follow-up, and treatment. Risk factors for mortality in older people include the presence of hypertension, diabetes mellitus, ischemic heart disease (IHD), chronic renal failure (CRF), physical disability, smoking, and sedentary life style.[1–8] Suggested markers for risk for all-cause mortality include high resting heart rate and low serum albumin levels.[9–12] It has also been suggested that low serum cholesterol levels may be associated with adverse outcomes in this age group, but this association is still controversial.[13–18]

The aging liver undergoes profound morphological and functional changes.[19–24] Alanine aminotransferase (ALT) activity is the most specific and widely used screening test in the evaluation of hepatic disease. It has been suggested that age, body mass index (BMI), obesity, and serum cholesterol levels influence ALT activity, yet no clear guidelines for changes in ALT activity with age have been constructed.[25–28] The possible association between ALT activity and mortality has not been previously studied in older people.

In this study, information from a large, prospective cohort of 70-year-old subjects was used to evaluate the relationship between liver enzyme activity and future mortality.

METHODS

Study Participants

The Jerusalem Longitudinal Study follows a representative sample of West Jerusalem residents born between June 1920 and May 1921, all at age 70 at the beginning of the study. The study instrument was a two-part questionnaire offering respondents graded multiple-choice answers and including detailed demographic, personal history, lifestyle, health services utilization, and functional and cognitive status

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questions and a thorough medical history and examination. Standard clinical laboratory tests, including blood and urine tests, electrocardiograms, and pulmonary function test, were also performed. Details of the cohort have been previously published.[29] Complete information was available for 455 subjects, which constituted the study population. Participants were found to be representative of the 70-year-old Jerusalem population with regard to general hospital utilization rates and total and disease-specific mortality rates during the postsurvey period.[30]

Mortality Data

Mortality data were obtained annually for 12 years of follow-up (1990–2002) from the records of the Ministry of Interior based on copies of all death certificates issued in Israel.

Serum Liver Enzyme Levels

Serum for ALT, aspartate aminotransferase (AST), alkaline phosphatase (AP), and gamma-glutamyl transpeptidase (γGTP) measurement was obtained in glass tubes, centrifuged, and analyzed on the day of sampling using a Kone Progress Selective Chemistry Analyzer (Kone Instruments, Espoo, Finland). All serum samples were processed in the same laboratory using the same methods and the same reference values.

Study Variables

The *International Classification of Diseases, Ninth Edition,* provided the basis for grouping disease. The groups included were malignant neoplasm, smoking, diabetes mellitus, hypertension, alcohol consumption, anemia, IHD, and CRF. High education level was defined as the completion of 10 or more years of formal education. Subjects were asked to define their health status subjectively as being healthy or not. Exercise was defined as the performance of at least 4 hours of aerobic exercise weekly. Functional independence was assessed based on the activity of daily living (ADL) and instrumental activity of daily living (IADL) scales of Katz[31] and Lawton.[32] Independence in ADLs was defined as ease in performing four or more ADL tasks, as previously described.[33] Independence in IADLs was defined as ease in performing four or more of the following IADL tasks: cleaning, cooking, laundry, phone use, and shopping.

BMI was calculated as weight (kg) divided by height (m) squared. Smoking was quantified in pack years (one pack year = one pack of cigarettes smoked daily for a year).

Data Analysis

Data analysis was performed using SAS software version 8.1 (SAS Institute, Inc., Cary, NC). The dependent variable of the study was mortality during a 12-year follow-up period (1990–2002). The major independent variable was each of the four tested liver enzymes (ALT, AST, AP, and γGTP) analyzed at 1990 as explained above. Chi-square or Wilcoxon tests were performed, where appropriate, to estimate possible association between each of the liver enzymes and potentially confounding variables. Significance level was defined as $P < .05$. Kaplan–Meier analysis and log rank test were used for primary analysis of survival. Cox proportional hazards models were used to evaluate the effect of liver enzyme levels on 12-year survival after adjustment for potential confounders. These included median ALT level, sex, education level, BMI, physical activity, health perception, smoking, albumin level, ADLs, and comorbid conditions including diabetes mellitus, hypertension, IHD, malignancy, anemia, CRF, and hypercholesterolemia. To achieve the final model, backward elimination was performed with $P > .1$ as a removal level. An interaction term between sex and median ALT was added to the final model.

RESULTS

Characteristics of the Study Population

Baseline characteristics of the study population are shown in Table 1. A high ratio of individuals reported being in

Table 1. Baseline Characteristics of the Study Population at Age 70

Characteristic	All (N = 455)	Women (n = 210; 46.2%)	Men (n = 245; 53.8%)
≥10 years of education, %	73.6	69.5	77.1
Perception of good health, %	71.6	67.3	75.2
Employed/volunteer, %	47.4	41.0	52. 9
Active physically, %	53.3	50.5	55.7
Independent in activities of daily living, %	87.5	85.4	89.4
Diabetes mellitus, %	15.9	12.4	18.8
Hypertension, %	38.3	43.1	34.3
Ischemic heart disease, %	26.6	20.6	31.8
Neoplastic disease, %	3.7	4.3	3.3
Anemia, %	12.1	14.3	10.2
Chronic renal failure, %	14.8	4.3	23.7
Smoking (pack years), % (mean ± SD)*	42.4 (33.9 ± 22.6)	29 (29.91 ± 22.7)	53.9 (35.8 ± 22.4)
Body mass index, kg/m^2, mean ± SD	27.2 ± 4.0	26.7 ± 3.5	27.7 ± 4.4
Total cholesterol, mmol/L, mean ± SD†	5.9 ± 1.1	5.7 ± 1.1	6.3 ± 1.1

* For smokers only.
† Total of 57 women and 130 men.
SD = standard deviation.

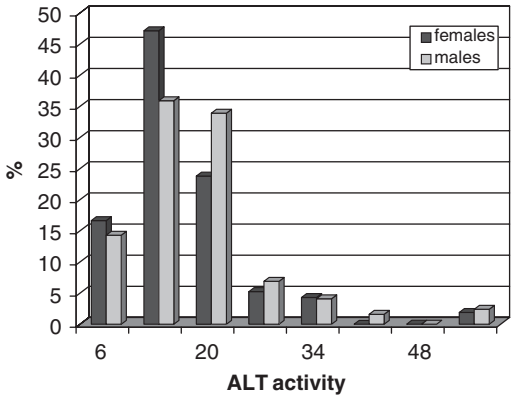

Figure 1. Distribution of alanine aminotransferase (ALT) activity at age 70 in the study population.

good health and demonstrated independence in ADLs and IADLs. Mean BMI levels were in the overweight range, and hypercholesterolemia was prevalent. Only a minority of the subjects was hypertensive or had diabetes mellitus or IHD.

Liver Enzyme Levels of the Study Population

The distribution of ALT activity of the study population at age 70 is shown in Figure 1. Mean and median activity of the various liver enzymes is shown in Table 2. Mean and median ALT activity were low (mean ALT activity 15.48 ± 23 U/L (15.59 ± 14.35 U/L in men, 15.34 ± 30.1 U/L in women, $P = .02$); median ALT activity 13.00 for men and 11.00 for women). Most of the study population (96%) demonstrated ALT activity levels that ranged within the currently regarded normal values (<40 U/L for men, <30 U/L for women). The majority of the study population (84% of men, 74% of women) had extremely low ALT activity, ranging in the lower two quartiles of the currently regarded normal ranges.

Association Between Liver Enzyme Activity and Baseline Clinical Variables

When dichotomizing ALT activity above and below the median level (Table 3), higher ALT activity was significantly and positively associated with diabetes mellitus ($P = .04$), hypercholesterolemia ($P = .02$), high BMI ($P = .002$), and smoking status ($P = .02$). No association was found between ALT activity and any other demographic, clinical, or laboratory variables (Table 3). Using ALT as a continuous variable, in addition to sex differences, statistical significance was found by the two levels of BMI ($P < .001$). No significant association was found between other clinical variables and ALT.

Association Between Liver Enzyme Levels and Survival

Of 455 participants at age 70, 309 were still alive at the 12-year follow-up. Kaplan–Meier methods demonstrated that low ALT activity at age 70 was associated with low survival in men. This effect on survival was already evident after 4 years of follow-up. Twelve-year survival rates for women with ALT below and above the median levels were similar (78%). For men, these rates were 54% and 65%, respectively ($P < .001$, Figure 2).

The Cox proportional hazards model was used with the potentially confounding variables mentioned above. The proportional hazard assumption was checked by adding time-dependent variables to the model, demonstrating that none of them were significant (collectively or individually), thus supporting the assumption.

After backward elimination, sex, median ALT level, physical activity, health perception, diabetes mellitus, IHD, malignancy, CRF, anemia, and smoking were found to be associated with mortality. Low ALT activity was significantly associated with high 12-year mortality (hazard ratio (HR) = 1.5, 95% confidence interval (CI) = 1.08–2.19). To control for a modification effect by sex, an interaction between level below the median ALT and male sex was entered into the model. Results (Table 4) demonstrate a higher risk for mortality in men with low ALT levels (HR = 2.42, 95% CI = 1.15–5.08). Using the same analysis for the other liver enzymes, neither AST activity (HR = 0.96, 95% CI = 0.69–1.36), AP levels (HR = 1.22, 95% CI = 0.87–1.7), nor γGTP levels (HR = 1.03, 95% CI = 0.72–1.47) were significantly associated with mortality. When analyzing ALT and the other liver enzyme levels as continuous variables, no association was found with mortality using the Cox proportional hazards model.

DISCUSSION

This prospective study demonstrates that low ALT activity is a strong and independent marker of mortality in older people, an association not previously documented in the medical literature. Male subjects with low ALT activity have an approximately doubled risk of long-term mortality. The significant association between low ALT activity and high mortality persisted after adjusting for the effects of multiple potentially confounding factors. No such risk was demonstrated for the other less-specific liver enzymes AST, AP, and γGTP.

Elderly persons often have multiple illnesses, each contributing to the overall risk of adverse outcomes. Markers that signal a tendency toward all-cause mortality may be of special value in this population, by leading to a more-careful evaluation and treatment of susceptible individuals. Unfortunately, the multitude of illnesses in older individuals results in a small probability that a single parameter will solely predict all-cause mortality.[1–4,34]

One possible explanation for the observed association between low ALT activity and high mortality in older people relates to its role as a surrogate marker of exaggerated hepatic aging processes. The normal aging liver has been shown to decrease progressively in size and blood flow, accumulate lipofuscin, have decreasing numbers of mitochondria and endoplasmic reticuli, decline in protein-synthesizing capacity, have an increase in the number of lysosomes, and have greater susceptibility to toxins.[20–22] In addition, profound changes are noted during aging in the hepatic sinusoidal epithelium, including endothelial thickening, a reduction in the number of fenestrations in the epithelium, and collagen deposition in the space of Disse.[19,35,36]

Hepatic aging is also associated with greater production of free radicals, leading to significantly greater oxidative stress.[21,22,37] This, in turn, results in alteration in

Table 2. Liver Enzyme Levels of the Study Population

Enzyme	Sex	Median (Units/L)	Mean (Units/L)	Standard Deviation
Alanine aminotransferase	Female	11	15.3	30.1
	Male	13	15.6	14.3
Aspartate aminotransferase	Female	31	32.4	14.1
	Male	29	31.1	9.2
Alkaline phosphatase	Female	177	196.2	82.8
	Male	173	186.9	71.0
Gamma glutamyl transpeptidase	Female	15	25.4	36.2
	Male	19	26.2	22.6

deoxyribonucleic acid structure and cellular membrane fluidity, leading to greater hepatic cell apoptosis.[38–41] When exaggerated, these processes may lead to a decrease in total hepatocyte number, reflected by lower ALT activity. Unrecognized disease states or processes may cause such enhanced oxidative stress, which may affect multiple extrahepatic systems and result in greater mortality.[42]

An alternate explanation for the negative association between ALT activity and mortality is that individuals with high-normal ALT activity might have already died by the time the study had started, as a result of chronic liver disease (such as nonalcoholic fatty liver disease), congestive heart failure, excessive alcohol abuse, or diabetes mellitus. Survivors who reach old age despite high-normal ALT activity may feature an inherent resistance to the deleterious effect of their advancing age and chronic medical conditions.

A significant direct association was noted between ALT activity and BMI. The lower BMI levels in individuals with low ALT activity may reflect worse nutritional status, which may be related to their occult predisposition for increased mortality. Occult pyridoxine deficiency as part of malnutrition can result in lowered ALT activity, because its active form (pyridoxal-5′-phosphate) serves as a coenzyme for transaminases.[43] The relatively high AST:ALT ratio noted in the study population may support this hypothesis (ALT being more sensitive to pyridoxal-5′-phosphate deficiency than AST). Yet it should be noted that, even after the inclusion of multiple variables, including BMI, in the Cox regression model, ALT activity remained a strong and independent predictor of mortality throughout the study period.

The majority of the study population featured average and median ALT activity that remained in the lower two quartiles of the currently regarded normal range. This finding, supported by similar results from a recent retrospective study of healthy blood donors,[25] highlights the need for a reevaluation of normal ALT activity in the elderly population. If the maximal normal value of ALT activity is indeed lower in the elderly population, the threshold of screening for occult liver disorders should be lowered accordingly.

One limitation of this study is the lack of differentiation between ALT as a marker of mortality due to unrecognized liver disease or a marker of global aging and overall mortality. Another limitation is the use of all-cause mortality as

Table 3. Association Between Alanine Aminotransferase (ALT) Activity and Study Variables

Characteristic	ALT Activity < Median Level (%)	ALT Activity > Median Level (%)	*P*-value
Female	47.0	42.3	.71
> 10 years of education	73.3	73.7	.86
Not active physically	47.8	44.4	.61
Low perception of health	30.0	26.8	.45
Diabetes mellitus	12.5	19.4	.04
Hypertension	35.8	41.0	.25
Ischemic heart disease	25.9	27.5	.69
Malignant disease	3.9	3.8	.87
Chronic renal failure	12.5	17.1	.16
Activity of daily living dependence	14.3	10.6	.24
Instrumental activity of daily living dependence	26.7	33.3	.17
Cholesterol > 5.17 mmol/L	70.7	79.6	.02
Body mass index > 25 kg/m^2	64.4	77.8	.002
Current smoker	16.6	8.2	.02

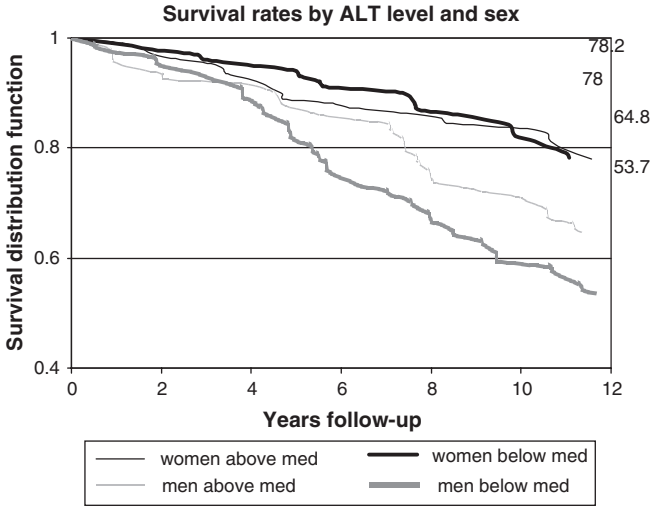

Figure 2. Survival rates by alanine aminotransferase (ALT) activity and sex. med=median.

the primary end point, due to great variations in fulfillment of causes of death in death certificates. The lack of information on specific causes of death in individuals with low ALT activity precludes recommendations for the possible interventions to prevent the excess mortality.

Despite these limitations, this prospective study is the first to assess the prognostic importance of ALT activity in a large, population-based cohort of elderly subjects. It revealed that older people, especially men, whose ALT levels are lower than 13 U/L have approximately double the risk of long-term mortality. The study introduces a new, inexpensive, and widely available clinical tool that, if proven in further studies, may aid in the prognostic assessment of individuals who often suffer from multiple comorbidities and are major users of health resources.

Further studies are needed to verify the cause-and-effect relationship between ALT activity and mortality, to evaluate the cost effectiveness of ALT activity as a screening tool in the older population, to redefine the normal range of ALT activity with advancing age, and to construct recommendations for further evaluation of these individuals. In the meanwhile, low ALT activity in elderly male individuals should be considered a marker of risk for all-cause mortality.

Table 4. Risk Factors for 12-Year Mortality by Cox Proportional Hazard Model

Variable	Hazard Ratio	95% Confidence Interval
Male	1.15	0.6–2.0
<Median ALT	0.85	0.5–1.5
Male and <median ALT	2.4	1.1–5.1
Physically active	0.7	0.5–1.0
Perception of good health	0.6	0.4–0.9
Diabetes mellitus	2.7	1.8–3.9
Ischemic heart disease	1.35	0.9–1.9
Malignancy	2.4	1.2–4.9
Chronic renal failure	1.9	1.2–2.9
Anemia	1.6	1.1–2.6
Smoking (pack years)	1.0	1.00–1.02

ALT = alanine aminotransferase.

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