Loss of Life Expectancy by 10 Years or More From Elevated Aspartate Aminotransferase: Finding Aspartate Aminotransferase a Better Mortality Predictor for All-Cause and Liver-Related than Alanine Aminotransferase

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OBJECTIVES: **Serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST) are 2 commonly ordered liver function tests, and ALT has long been considered more liver-specific than AST. Between the 2, the one which is better in predicting liver or non–liver-related mortality remains unsettled.**

METHODS: **The cohort, 416,122 adults, came from a self-paying comprehensive health surveillance program during 1994–2008 and was followed up till 2008. Mortality came from National Death Index, with 10,412 deaths identified. Hazard ratios (HRs), computed by Cox model, and life expectancy, by life table method, were presented for 5 levels of AST and ALT with elevated AST or ALT defined as ≥40 IU/L. Liver disease included liver cancer and other liver conditions.**

RESULTS: **There were 3 times more elevated ALT (15.4%) than AST (5.7%). However, those with elevated AST had higher mortality for all-cause (HR = 2.44), for liver disease (HR = 27.2), and for liver cancer (HR = 47.6) than its ALT counterparts (HR = 1.69, 10.8, and 20.2, respectively). Elevated AST also lost more years of life expectancy (10.2) than those lost by ALT (5.2) and larger than most common risks. Elevated AST had increased mortality from all cancers (HR = 3.57), stroke (HR = 1.36), respiratory diseases (HR = 1.34), and injuries (HR = 1.82), other than just liver disease. All-cause mortality remained significantly increased, when high risk groups were excluded, such as frequent drinkers, hepatitis carriers, those died from nonmedical conditions, those died in the first 3 years, or advanced fibrosis index based on 4 factors or aspartate transaminase-to-platelet ratio index. Results were consistent between those returned for second visits and those analyzed in initial visits.**

DISCUSSION: **Those with elevated AST (≥40 IU/L) had life expectancy cut short by 10.2 years, doubled the number of years lost with elevated ALT. For all-cause and for liver-related mortality, AST was an important predictor, better than ALT.**

SUPPLEMENTARY MATERIAL accompanies this paper at http://links.lww.com/AJG/B248

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INTRODUCTION

Aspartate aminotransferase (AST), a marker of hepatocyte injuries, is generally known to be less specific to the liver than alanine aminotransferase (ALT), resulting in ALT a preferred clinical test to detect liver diseases. This is because AST originated from sources more than the liver, including heart, skeletal muscle, kidney, brain, or red blood cells (1–3).

Another aspect of these aminotransferases was that neither AST nor ALT was routinely considered in clinical practice to assess conditions outside of liver (2,3). That elevated AST or ALT could increase all-cause mortality has been reported, but its clinical significance remained unresolved (4–9). Increased all-cause mortality would have shortened life expectancy, but with unknown magnitude. Furthermore, the relative predictive ability for mortality between AST and ALT has yet been settled. Whether ALT is more specific to the liver and AST more specific outside of liver in terms of clinical outcome is a hypothesis as yet to be verified (7,10–13). Some studies, finding increased mortality from elevated aminotransferases, focused on the high-risk group with preexisting conditions, and the presence of these conditions would have confounded the results (8,14). With the high frequency of liver function tests conducted in clinical settings, particularly among Asian countries, significant implications of elevated values are obvious.

With cohort data on AST and ALT values for nearly half a million individuals in Taiwan, prospectively followed up for a median of 8.1 years (15), we examined the mortality risks and life expectancy of different levels of serum AST and ALT activity. The objectives of this study were to (i) quantify and compare relative risks of AST and ALT for all-cause, liver-related, and non–liver-related mortality, after controlling for confounders, and (ii) calculate the loss in life expectancy at different levels of elevated AST and ALT. Sensitivity analyses were conducted by excluding high risk subjects who were frequent drinker, carrier of hepatitis B or C, positive history of liver disease, deaths from external injuries, deaths within the first 3 years, or those with advanced fibrosis index based on 4 factors (FIB-4) or aspartate transaminase-to-platelet ratio index (APRI) (16–18).

METHODS

Study population

The cohort consisted of participants aged 20 years or older who participated in a standard medical screening program by MJ Health Management Institution, Taiwan. From 1994 to 2008, a total of 416,122 participants without cancer history at baseline were included in the analysis. Details of this cohort have been published previously (19,20). Briefly, this is a prospective study in which every participant reported personal health history and lifestyle information through questionnaire. Medical tests for blood, urine, physical examination, body measurements, blood pressure, and functional test were conducted. This study was reviewed and approved by the National Health Research Institutes, Zhunan, Taiwan. All participants have signed a consent form.

Covariates definition

Fasting morning serum samples were collected for transaminase determination, and participants with AST or ALT divided into 5 groups: <15, 15–24, 25–39, 40–69, and ≥ 70 IU/L, with ≥ 40 IU/L defined as elevated and 15–24 as the reference group.

Diabetes or hypertension was defined as self-reported history, use of medications, or screened abnormal values, with fasting plasma glucose ≥ 126 mg/dL for diabetes and either systolic ≥ 140 mm Hg or diastolic ≥ 90 mm Hg for hypertension. Education was classified by middle school or lower (9 years of schooling or less), high school or junior college (10–14 years of schooling), and college or higher (15 or more years). Exercise volume was a product of exercise duration/frequency and intensity, with intensity based on metabolic equivalent value (MET; 1 MET = 1 kcal per hour per kg of bodyweight), and duration, expressed as hours within a week. Status of physical activity was based on exercise volume, categorized as inactive (<3.75 MET-hr/week), moderately active (3.75–7.49 MET-hr/week), with 15 min/d or more, and fully active (≥7.5 MET-hr/week), with 30 min/d or more with moderate intensity (19). Frequent drinkers were those with 6 drinks or more per week, and occasional drinkers, 1–5 drinks/wk. Carriers of hepatitis B surface antigen or hepatitis C virus antibody were expressed as (HBV+) or (HCV+), respectively.

Follow-up for mortality

The cohort participants were followed up to December 31, 2008, with 3.4 million person-years, by linking individual ID to the Taiwan National Cancer Registry or Taiwan National Death File. Causes of death were coded according to International Classification of Diseases (ICD)-9. The ICD codes for liver disease were a combination of liver cancer (ICD-9 155), acute or chronic hepatitis or necrosis (ICD-9 070, 570), and liver cirrhosis (ICD-9 571). The median follow-up time was 96.9 months or 8.1 years.

Statistical analysis

Cox proportional hazards models were used for the multivariate analysis controlling for 11 variables: age, sex, education, body mass index, smoking status, drinking status, physical activity, hypertension, diabetes, FIB-4, and APRI. The life table method was used to calculate shortening of life expectancy (21). The FIB-4 score was based on Stirling's formula as age (years) × AST (IU/L)/platelet count (expressed as platelets × 10^9) × ALT $^{1/2}$ (IU/L) (22). The APRI score was based on Wai's formula as (AST/upper limit of normal considered as 40 IU/L)/platelet count (expressed as platelets × 10^9) × 100 (23).

RESULTS

Baseline host characteristics

There were 5.7% (23,697) of AST ≥40 IU/L but 15.4% (64,075) of ALT, with ALT 3 times more than ALT (Table 1 and see Supplemental Table 1, Supplementary Digital Content 1, http://links.lww.com/AJG/B248). Women were lower than men for both AST and ALT, but more so for ALT. The effect of age on these 2 was limited, particularly with AST (see Supplemental Figure 1, Supplementary Digital Content 1, http://links.lww.com/AJG/B248). Specifically, ALT increased at early age, more pronounced in men than in women, but decreased after age 60, while AST slightly increased with age in women at younger age, but remained flat at old age for both gender.

Mortality risk

AST values had a strong dose response relationship with all-cause mortality above 25 IU/L (Table 2 and see Supplemental Figure 2, Supplementary Digital Content 1, http://links.lww.com/AJG/B248), when compared with those 15–24 IU/L, but, for ALT, the

Table 1. Distribution of serum AST (IU/L) by selected characteristics of the cohort

	Total	<15		15–24		25–39		40–69		≥70		≥40	
No. of participants	416,122	34,272	(8.2)	269,743	(64.8)	88,410	(21.2)	17,976	(4.3)	5,721	(1.4)	23,697	(5.7)
Age, y													
<40	237,985	26,589	(11.2)	160,791	(67.6)	40,171	(16.9)	8,129	(3.4)	2,305	(1.0)	10,434	(4.4)
40–59	130,049	6,490	(5.0)	81,611	(62.8)	33,082	(25.4)	6,677	(5.1)	2,189	(1.7)	8,866	(6.8)
≥ 60	48,088	1,193	(2.5)	27,341	(56.9)	15,157	(31.5)	3,170	(6.6)	1,227	(2.6)	4,397	(9.1)
Sex													
Men	205,018	7,659	(3.7)	122,160	(59.6)	59,615	(29.1)	12,059	(5.9)	3,525	(1.7)	15,584	(7.6)
Women	211,104	26,613	(12.6)	147,583	(69.9)	28,795	(13.6)	5,917	(2.8)	2,196	(1.0)	8,113	(3.8)
Education													
Middle school or below	99,434	4,200	(4.2)	58,895	(59.2)	27,549	(27.7)	6,340	(6.4)	2,450	(2.5)	8,790	(8.8)
High school	95,534	9,530	(10.0)	62,069	(65.0)	18,809	(19.7)	3,882	(4.1)	1,244	(1.3)	5,126	(5.4)
Junior college	91,974	9,342	(10.2)	61,287	(66.6)	17,152	(18.6)	3,317	(3.6)	876	(1.0)	4,193	(4.6)
College or higher	129,180	11,200	(8.7)	87,492	(67.7)	24,900	(19.3)	4,437	(3.4)	1,151	(0.9)	5,588	(4.3)
BMI (kg/m^2)													
<18.5	35,962	4,466	(12.4)	26,750	(74.4)	3,847	(10.7)	610	(1.7)	289	(0.8)	899	(2.5)
18.5–24.9	269,539	25,556	(9.5)	184,084	(68.3)	48,984	(18.2)	8,015	(3.0)	2,900	(1.1)	10,915	(4.0)
25–29.9	94,702	3,717	(3.9)	52,077	(55.0)	30,072	(31.8)	6,989	(7.4)	1,847	(2.0)	8,836	(9.3)
≥30	15,779	518	(3.3)	6,766	(42.9)	5,466	(34.6)	2,350	(14.9)	679	(4.3)	3,029	(19.2)
Smoking status													
Nonsmoker	293,561	26,795	(9.1)	196,181	(66.8)	56,132	(19.1)	10,987	(3.7)	3,466	(1.2)	14,453	(4.9)
Former smoker	25,636	1,099	(4.3)	14,869	(58.0)	7,644	(29.8)	1,541	(6.0)	483	(1.9)	2,024	(7.9)
Current smoker	96,925	6,378	(6.6)	58,693	(60.6)	24,634	(25.4)	5,448	(5.6)	1,772	(1.8)	7,220	(7.4)
Drinking status													
Nondrinker	327,749	30,012	(9.2)	218,085	(66.5)	63,243	(19.3)	12,578	(3.8)	3,831	(1.2)	16,409	(5.0)
Occasional drinker	58,835	3,033	(5.2)	36,187	(61.5)	15,874	(27.0)	2,938	(5.0)	803	(1.4)	3,741	(6.4)
Frequent drinker	29,538	1,227	(4.2)	15,471	(52.4)	9,293	(31.5)	2,460	(8.3)	1,087	(3.7)	3,547	(12.0)
Physical activity													
Inactive	217,676	21,418	(9.8)	141,141	(64.8)	42,502	(19.5)	9,549	(4.4)	3,066	(1.4)	12,615	(5.8)
Moderately active	95,574	7,700	(8.1)	63,145	(66.1)	19,703	(20.6)	3,839	(4.0)	1,187	(1.2)	5,026	(5.3)
Fully active	102,872	5,154	(5.0)	65,457	(63.6)	26,205	(25.5)	4,588	(4.5)	1,468	(1.4)	6,056	(5.9)
Diabetes													
No	394,183	32,716	(8.3)	258,235	(65.5)	82,534	(20.9)	15,852	(4.0)	4,846	(1.2)	20,698	(5.3)
Yes	20,894	1,418	(6.8)	10,779	(51.6)	5,728	(27.4)	2,099	(10.0)	870	(4.2)	2,969	(14.2)
Hypertension													
No	345,608	31,804	(9.2)	230,373	(66.7)	66,858	(19.3)	12,635	(3.7)	3,938	(1.1)	16,573	(4.8)
Yes	70,415	2,455	(3.5)	39,311	(55.8)	21,528	(30.6)	5,339	(7.6)	1,782	(2.5)	7,121	(10.1)
HBV (+)													
No	340,944	31,378	(9.2)	226,517	(66.4)	66,486	(19.5)	12,925	(3.8)	3,638	(1.1)	16,563	(4.9)
Yes	58,536	1,470	(2.5)	31,951	(54.6)	18,716	(32.0)	4,475	(7.6)	1,924	(3.3)	6,399	(10.9)
HCV (+)													
No	74,999	5,889	(7.9)	48,195	(64.3)	16,542	(22.1)	3,446	(4.6)	927	(1.2)	4,373	(5.8)
Yes	1,815	26	(1.4)	359	(19.8)	618	(34.0)	457	(25.2)	355	(19.6)	812	(44.7)
α-fetoprotein													
<10 ng/mL	411,283	33,935	(8.3)	267,651	(65.1)	87,561	(21.3)	17,402	(4.2)	4,734	(1.2)	22,136	(5.4)

Table 1. (*continued*)

	Total	<15		15–24		25–39		40–69		≥70		≥40	
≥10 ng/mL	4,070	248	(6.1)	1,528	(37.5)	755	(18.6)	558	(13.7)	981	(24.1)	1,539	(37.8)
FIB-4													
≤3.25	415,924	34,261	(8.2)	269,680	(64.8)	88,372	(21.2)	17,944	(4.3)	5,667	(1.4)	23,611	(5.7)
>3.25	184	6	(3.3)	55	(29.9)	37	(20.1)	32	(17.4)	54	(29.3)	86	(46.7)
APRI													
≤1.5	413,833	34,266	(8.3)	269,713	(65.2)	88,378	(21.4)	17,804	(4.3)	3,672	(0.9)	21,476	(5.2)
>1.5	2,275	1	(0.0)	22	(1.0)	31	(1.4)	172	(7.6)	2,049	(90.1)	2,221	(97.6)
Platelets													
$<150 \times 10^3/mm^3$	11,699	499	(4.3)	5,629	(48.1)	3,157	(27.0)	1,331	(11.4)	1,083	(9.3)	2,414	(20.6)
150–400 $10^3/mm^3$	400,224	33,221	(8.3)	261,430	(65.3)	84,506	(21.1)	16,467	(4.1)	4,600	(1.1)	21,067	(5.3)
$\geq 400 \times 10^3/mm^3$	4,199	552	(13.1)	2,684	(63.9)	747	(17.8)	178	(4.2)	38	(0.9)	216	(5.1)

APRI, aspartate transaminase-to-platelet ratio index; AST, aspartate aminotransferase; BMI, body mass index; FIB-4, fibrosis index based on 4 factors; HBV, carriers of hepatitis B surface antigen; HCV, hepatitis C carriers.

relationship found only above 40 IU/L. Trends for AST and ALT were both significant for all-cause, liver disease, non-liver disease, and cancer mortality.

The proportion of elevated AST was smaller in women (3.8%) than in men (7.6%); the associated mortality risk was similar between women (hazard ratio [HR] = 2.28) and men (HR = 2.52). The stepwise increase was also similar for women: 1.18, 1.83, and 3.55 for 25–39, 40–69, and >70, as for men, 1.09, 2.02, and 3.93 (see Supplemental Table 2, Supplementary Digital Content 1, http://links.lww.com/AJG/B248). As a result, the same cut point applied to both men and women.

With only 1/3 in the number of subjects of ALT in Figure 1, AST had as many liver cancer deaths, 586 vs 582, or all-cause mortality, 1,846 vs 2,229, as ALT, resulting in larger HR for AST (47.57 and 2.44) than ALT (20.21 and 1.69), respectively. Causes of excess mortality from all causes in AST, other than hepatic origin, came from all cancer (HR, 3.57), non-liver cancer (HR, 1.45), colon cancer (HR, 1.46), stroke (HR, 1.36), respiratory system (HR, 1.34), and injuries (HR, 1.82). Among them, non-liver cancer, particularly colon and lung cancer, and stroke contributed most to the excess mortality (Table 2).

With those below 15 IU/L significantly increased for all-cause mortality (HR = 1.39 for AST and HR = 1.19 for ALT), the dose response relationship for entire spectrum of AST or ALT became a J-shaped one, and the optimal reference group became 15–24 IU/L (Table 2, see Supplemental Figure 2 and Supplemental Table 3, Supplementary Digital Content 1, http://links.lww.com/AJG/B248).

Kaplan-Meier survival curve for all-cause mortality by different levels of AST and ALT showed much lower survival for AST 25–39, 40–69 and >70 IU/L than their ALT counterparts (Figure 2). This relationship was an actual one without risk adjustment.

Sensitivity analyses

We assessed the AST relationship with all-cause mortality by excluding a number of different conditions: (i) liver related: HBV(+) or HCV(+) (n = 62,147), self-reported liver disease (n = 15,541), FIB-4 > 3.25 (n = 184) or APRI > 1.5 (n = 2,275), AFP (alpha-fetoprotein) > 10 ng/mL (n = 4,070); (ii) deaths related: first 3 years of death, deaths from injury, and suicide; (iii) lifestyle related: drinking frequently; (iv) among repeated visit participants; (v) different age groups: for age 20–59 and age 60 or above. The findings (Table 3) were generally consistent with the original table and statistical significance remained for all-cause, liver, and non-liver diseases in elevated AST.

A forest plot in Supplemental Figure 3 (see Supplementary Digital Content 1, http://links.lww.com/AJG/B248) compared relative risks between AST ≥ 40 IU/L and AST 15–24 IU/L for subgroups in the cohort. Higher risks for ≥40 IU/L were found in all subgroups, including men, women, young (age 20–59), old (60 or above), ever smoker, frequent drinker, obese individuals, and inactive individuals.

Life expectancy

Relative to 15–24 IU/L, participants with AST 25–39 IU/L, 40–69 IU/L, ≥40 IU/L, or ≥70 IU/L had shortened life expectancies by 1.17 year, 7.45 years, 10.2 years, or 16.7 years, respectively, for men (Figure 3). The number of life years lost by AST, 10.2 years, was twice the size of the loss from the ALT counterparts (5.2 years). Similar relationship was found for women with 8.2 years of loss for AST and 5.4 years for ALT (see Supplemental Figure 4, Supplementary Digital Content 1, http://links.lww.com/AJG/B248). By fitting a line for the dose response with loss of life years, a 2-month shortening for every unit of AST increase above 25 IU/L was found, whereas only 1-month shortening for ALT counterpart (data not shown).

Fully active individuals, with >7.5 MET-hr/wk, when compared to inactive individuals, were associated with gains in life expectancy. For those elevated AST, if active, a gain of 3.5 years could be achieved (see Supplemental Figure 5, Supplementary Digital Content 1, http://links.lww.com/AJG/B248).

DISCUSSION

In this study, we demonstrated that elevated AST was better than ALT in identifying and predicting subjects with increased risks for both all-cause and liver-related mortality. Those with AST ≥ 40 units in this cohort showed their life span cut short by 10.2

Table 2. Adjusted mortality risks of serum AST (IU/L), with 15–24 as reference, by all-cause and selected cause-specific deaths

Cause of death	Total deaths	<15			15–24		25–39			40–69			≥70			≥40			*P* trend
		Deaths	HR	95% CI	Deaths	HR	Deaths	HR	95% CI	Deaths	HR	95% CI	Deaths	HR	95% CI	Deaths	HR	95% CI	
All-cause mortality	10,412	484	1.39	(1.27, 1.53)	5,148	1.00	2,934	1.12	(1.07, 1.17)	1,088	1.96	(1.84, 2.10)	758	3.79	(3.51, 4.10)	1,846	2.44	(2.31, 2.58)	***
Liver disease, including liver cancer	1,355	4	0.36	(0.13, 0.97)	154	1.00	353	4.75	(3.92, 5.74)	414	26.72	(22.14, 32.25)	430	73.15	(60.55, 88.38)	844	39.18	(32.85, 46.72)	***
Non-liver disease	9,057	480	1.43	(1.30, 1.57)	4,994	1.00	2,581	1.01	(0.96, 1.06)	674	1.24	(1.15, 1.35)	328	1.70	(1.52, 1.91)	1,002	1.36	(1.27, 1.46)	***
Cancer	4,240	170	1.27	(1.09, 1.49)	1,974	1.00	1,146	1.18	(1.10, 1.27)	550	2.81	(2.55, 3.09)	400	5.75	(5.15, 6.41)	950	3.57	(3.30, 3.87)	***
Liver cancer	912	2	0.32	(0.08, 1.29)	91	1.00	233	5.26	(4.11, 6.71)	297	33.13	(26.09, 42.06)	289	88.10	(69.23, 112.13)	586	47.57	(37.95, 59.62)	***
Non-liver cancer	3,328	168	1.33	(1.13, 1.56)	1,883	1.00	913	0.99	(0.91, 1.07)	253	1.36	(1.19, 1.55)	111	1.71	(1.41, 2.07)	364	1.45	(1.29, 1.62)	***
Lung cancer	890	48	1.50	(1.11, 2.02)	532	1.00	223	0.82	(0.70, 0.96)	60	1.14	(0.87, 1.48)	27	1.45	(0.98, 2.14)	87	1.21	(0.96, 1.52)	0.74
Colon cancer	435	24	1.43	(0.93, 2.18)	254	1.00	106	0.84	(0.67, 1.06)	37	1.43	(1.01, 2.02)	14	1.58	(0.92, 2.72)	51	1.46	(1.08, 1.99)	0.18
Stomach cancer	273	14	1.29	(0.74, 2.24)	176	1.00	69	0.77	(0.58, 1.02)	11	0.63	(0.34, 1.16)	3	0.50	(0.16, 1.57)	14	0.60	(0.35, 1.04)	*
Breast cancer (women)	169	15	1.06	(0.61, 1.85)	101	1.00	43	1.52	(1.05, 2.20)	8	1.23	(0.59, 2.55)	2	0.84	(0.21, 3.42)	10	1.10	(0.56, 2.16)	0.18
Diabetes	628	64	2.18	(1.72, 2.77)	344	1.00	134	0.60	(0.48, 0.76)	51	0.68	(0.48, 0.97)	35	3.90	(3.02, 5.02)	86	1.04	(0.81, 1.34)	0.25
Cardiovascular disease	2,001	83	1.30	(1.04, 1.62)	1,097	1.00	622	1.04	(0.94, 1.15)	143	1.10	(0.92, 1.31)	56	1.25	(0.95, 1.64)	199	1.13	(0.97, 1.32)	0.07
Ischemic heart	558	23	1.14	(0.75, 1.75)	328	1.00	164	0.91	(0.75, 1.10)	30	0.75	(0.52, 1.10)	13	0.94	(0.54, 1.64)	43	0.81	(0.58, 1.11)	0.17
Stroke	830	32	1.25	(0.87, 1.79)	442	1.00	259	1.07	(0.92, 1.25)	71	1.38	(1.07, 1.77)	26	1.41	(0.94, 2.11)	97	1.36	(1.08, 1.70)	**
Respiratory system	601	23	1.42	(0.93, 2.18)	313	1.00	207	1.14	(0.96, 1.36)	36	1.10	(0.78, 1.56)	22	1.93	(1.25, 2.99)	58	1.34	(1.01, 1.77)	*
Genitourinary system	331	31	2.75	(1.86, 4.06)	167	1.00	97	1.07	(0.83, 1.37)	28	1.38	(0.92, 2.07)	8	1.12	(0.55, 2.29)	36	1.30	(0.90, 1.87)	0.21
Acute/chronic liver disease	443	2	0.40	(0.10, 1.66)	63	1.00	120	4.02	(2.96, 5.47)	117	17.66	(12.93, 24.12)	141	51.97	(38.17, 70.76)	258	27.24	(20.49, 36.21)	***
Injury	644	28	1.03	(0.70, 1.52)	345	1.00	183	1.10	(0.92, 1.32)	57	1.58	(1.19, 2.10)	31	2.40	(1.65, 3.49)	88	1.82	(1.43, 2.32)	***
Suicide	286	19	0.97	(0.60 ,1.58)	167	1.00	79	1.25	(0.95, 1.65)	14	1.03	(0.59, 1.79)	7	1.45	(0.68, 3.11)	21	1.19	(0.75, 1.90)	0.23

Adjusted for 11 variables: age, sex, education, body mass index, smoking status, drinking status, physical activity, hypertension, diabetes, fibrosis index 4, and aspartate transaminase-to-platelet ratio index.
AST, aspartate aminotransferase; CI, confidence index.
*$P < 0.05$; **$P < 0.01$; ***$P < 0.001$.

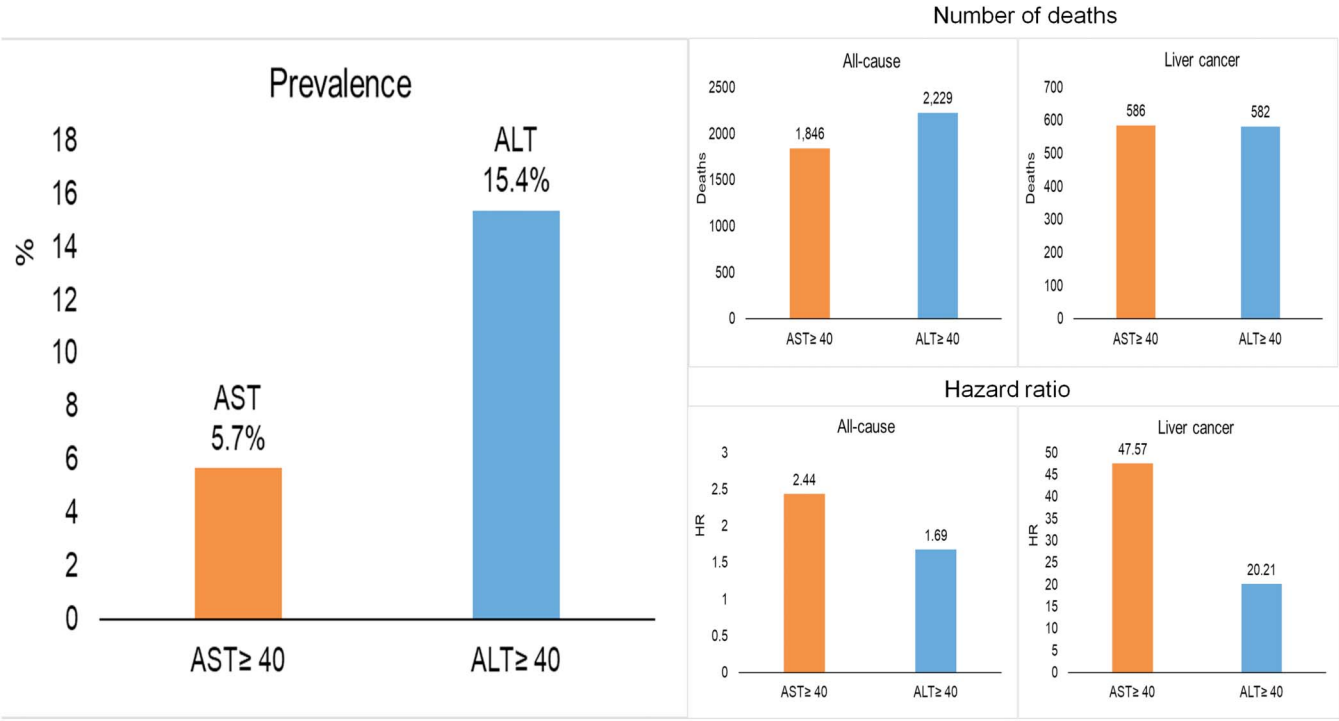


Figure 1. Prevalence, number of deaths, and adjusted HRs for all-cause and liver cancer mortality with elevated AST or ALT. ALT, alanine aminotransferase; AST, aspartate aminotransferase; HR, hazard ratio.

years, and at ≥70 IU/L by 16.7 years, doubling those with ALT, 5.2 and 8.7 years, respectively. Indeed, with every unit increase above 25 IU/L, a 2-month shortening was expected for AST but only 1 month for ALT. They reflected a larger systemic risk for AST (HR = 2.44) than its ALT counterpart (HR = 1.69). We were the first to discover that AST was a better predictor of liver cancer than ALT in a previous report (15), and now, AST was superior to ALT in predicting all-cause mortality. The 10.2 years of life loss by AST was large and ranked high among 30 common health risks, with its size larger than diabetes (8.9 years), hypertension (systolic 4.4 years) or metabolic syndrome (2.4 years) (see Supplemental Figure 6, Supplementary Digital Content 1, http://links.lww.com/AJG/B248) (24).

Given that ALT is commonly known to be more liver-specific and valued more for assessing liver conditions than AST (2,3), our findings of AST to be a better predictor for both liver and non-liver mortality may seem puzzling. However, realizing the differences in the distribution of elevated aminotransferase present

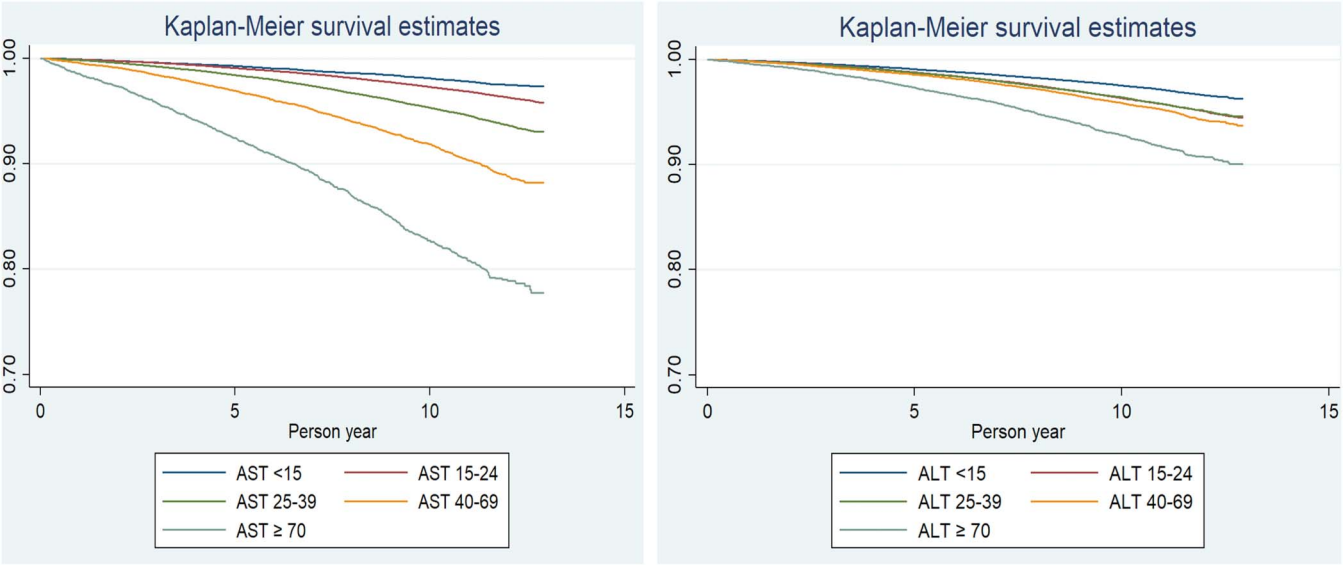
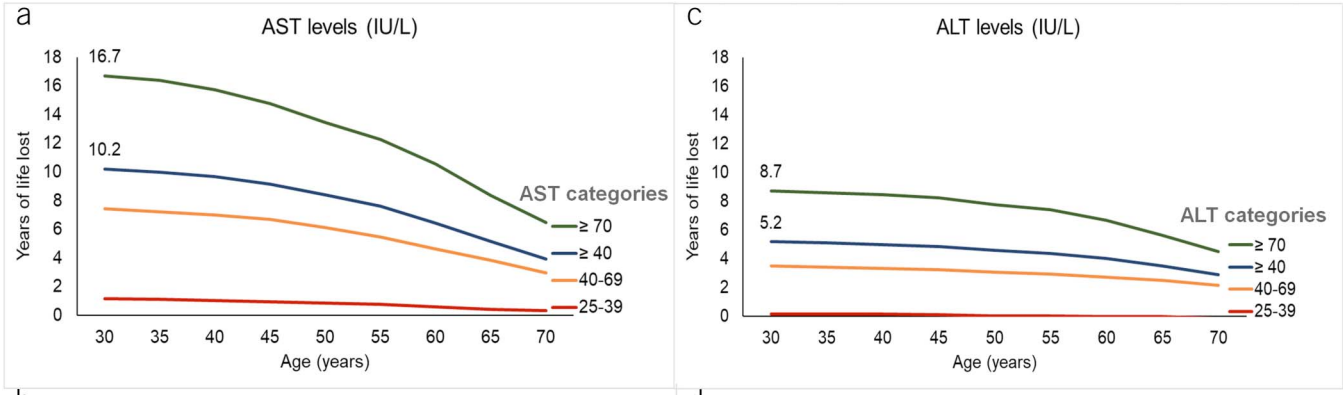


Figure 2. Kaplan-Meier survival curves for all-cause mortality by AST (left) and ALT (right) levels. ALT, alanine aminotransferase; AST, aspartate aminotransferase.

Table 3. Sensitivity analyses for all-cause and liver-related mortality risks of different levels of AST (IU/L) by excluding various risk factors

	15–24			25–39				40–69				≥70				≥ 40			
All-cause mortality	**N**	**Deaths**	**HR**	**N**	**Deaths**	**HR**	**95% CI**	**N**	**Deaths**	**HR**	**95% CI**	**N**	**Deaths**	**HR**	**95% CI**	**N**	**Deaths**	**HR**	**95% CI**
Total cohort	269,743	5,148	1.00	88,410	2,934	1.12	(1.1, 1.2)	17,976	1,088	1.96	(1.8, 2.1)	5,721	758	3.79	(3.5, 4.1)	23,697	1,846	2.44	(2.3, 2.6)
First 3 years of deaths excluded	268,707	4,112	1.00	87,788	2,312	1.11	(1.1, 1.2)	17,719	831	1.89	(1.8, 2.0)	4,963	533	3.47	(3.2, 3.8)	22,682	1,364	2.30	(2.2, 2.5)
HBV(+) or HCV(+) excluded	264,483	5,093	1.00	84,832	2,847	1.11	(1.1, 1.2)	15,860	1,004	1.90	(1.8, 2.0)	5,075	690	3.83	(3.5, 4.2)	20,935	1,694	2.39	(2.3, 2.5)
Drinking frequently excluded	254,272	4,421	1.00	79,117	2,366	1.11	(1.1, 1.2)	15,516	848	1.90	(1.8, 2.0)	4,634	513	3.53	(3.2, 3.9)	20,150	1,361	2.29	(2.2, 2.4)
Injury and suicide excluded	269,231	4,636	1.00	88,148	2,672	1.12	(1.1, 1.2)	17,905	1,017	2.02	(1.9, 2.2)	5,683	720	3.99	(3.7, 4.3)	23,588	1,737	2.53	(2.4, 2.7)
Liver disease history excluded	252,441	4,894	1.00	77,827	2,645	1.10	(1.0, 1.2)	14,728	811	1.71	(1.6, 1.8)	3,972	451	3.15	(2.9, 3.5)	18,700	1,262	2.05	(1.9, 2.2)
FIB-4 >3.25 or APRI >1.5 excluded	269,682	5,135	1.00	88,359	2,917	1.12	(1.1, 1.2)	17,798	999	1.83	(1.7, 2.0)	3,671	301	2.67	(2.4, 3.0)	21,469	1,300	1.98	(1.9, 2.1)
Alpha-fetoprotein ≥ 10 ng/mL excluded	267,651	5,128	1.00	87,561	2,864	1.10	(1.1, 1.2)	17,402	918	1.71	(1.6, 1.8)	4,734	425	2.64	(2.4, 2.9)	22,136	1,343	1.92	(1.8, 2.0)
Results based on second visits	119,439	1,954	1.00	40,416	1,037	1.10	(1.0, 1.2)	7,722	398	2.08	(1.9, 2.3)	2,376	261	4.38	(3.8, 5.0)	10,098	659	2.59	(2.4, 2.8)
Results based on old age (≧60)	27,341	3,223	1.00	15,157	1,892	1.05	(1.0, 1.1)	3,170	626	1.72	(1.6, 1.9)	1,227	413	3.23	(2.9, 3.6)	4,397	1,039	2.12	(2.0, 2.3)
Results based on young age (<60)	242,402	1,925	1.00	73,253	1,042	1.25	(1.2, 1.4)	14,806	462	2.38	(2.1, 2.6)	4,494	345	4.68	(4.2, 5.3)	19,300	807	2.99	(2.7, 3.3)
Liver disease mortality																			
Total cohort	269,743	154	1.00	88,410	353	4.75	(3.9, 5.7)	17,976	414	26.72	(22.1, 32.3)	5,721	430	73.15	(60.5, 88.4)	23,697	844	39.18	(32.9, 46.7)
First 3 years of deaths excluded	268,707	127	1.00	87,788	285	4.72	(3.8, 5.8)	17,719	314	24.75	(20.1, 30.5)	4,963	300	63.97	(51.7, 79.2)	22,682	614	35.24	(29.0, 42.9)
HBV(+) or HCV(+) excluded	264,483	150	1.00	84,832	324	4.54	(3.7, 5.5)	15,860	369	25.66	(21.2, 31.1)	5,075	384	73.98	(60.9, 89.9)	20,935	753	38.05	(31.8, 45.6)
Drinking frequently excluded	254,272	133	1.00	79,117	273	4.47	(3.6, 5.5)	15,516	318	25.79	(21.0, 31.7)	4,634	296	72.09	(58.5, 88.8)	20,150	614	37.11	(30.6, 45.0)
Injury and suicide mortality excluded	269,231	154	1.00	88,148	353	4.75	(3.9, 5.7)	17,905	414	26.78	(22.2, 32.3)	5,683	430	73.29	(60.7, 88.5)	23,588	844	39.27	(32.9, 46.8)
Liver disease history excluded	252,441	127	1.00	77,827	246	4.14	(3.3, 5.1)	14,728	239	20.64	(16.6, 25.7)	3,972	217	59.10	(47.1, 74.1)	18,700	456	29.78	(24.3, 36.5)
FIB-4 >3.25 or APRI >1.5 excluded	269,682	153	1.00	88,359	346	4.66	(3.8, 5.6)	17,798	344	22.68	(18.7, 27.5)	3,671	119	37.43	(29.3, 47.7)	21,469	463	25.41	(21.1, 30.7)
α-fetoprotein ≥ 10 ng/mL excluded	267,651	150	1.00	87,561	306	3.66	(2.7, 5.0)	17,402	271	14.10	(10.2, 19.6)	4,734	170	28.25	(19.7, 40.5)	22,136	441	17.84	(13.2, 24.2)
Results based on second visits	119,439	74	1.00	40,416	121	3.51	(2.6, 4.7)	7,722	153	21.86	(16.5, 29.0)	2,376	161	71.22	(53.7, 94.4)	10,098	314	33.09	(25.5, 42.9)
Results based on old age (≧60)	27,341	94	1.00	15,157	158	2.47	(1.6, 3.7)	3,170	206	12.15	(8.1, 18.2)	1,227	226	30.54	(20.2, 46.1)	4,397	432	17.67	(12.3, 25.4)
Results based on young age (<60)	242,402	60	1.00	73,253	195	6.79	(4.2, 11.1)	14,806	208	26.37	(16.0, 43.5)	4,494	204	8,522	(52.2, 139.1)	19,300	412	42.1	(26.4, 67.2)

AST, aspartate aminotransferase; CI, confidence index; HR, hazard ratio.



b

AST levels

Age	15-24 (1)	25-39 (2)	40-69 (3)	≥ 70 (4)	Diff1 (1)-(4)	≥ 40 (5)	Diff2 (1)-(5)
30	53.52	52.35	46.07	36.82	16.7	43.3	10.22
40	43.78	42.74	36.77	28.04	15.74	34.12	9.66
50	34.21	33.36	28.08	20.75	13.46	25.79	8.42
60	25.14	24.56	20.52	14.6	10.54	18.69	6.45
70	16.89	16.56	13.93	10.42	6.47	12.95	3.94

d

ALT levels

Age	15-24 (1)	25-39 (2)	40-69 (3)	≥ 70 (4)	Diff1 (1)-(4)	≥ 40 (5)	Diff2 (1)-(5)
30	53.53	53.36	50.03	44.8	8.73	48.34	5.19
40	43.8	43.67	40.48	35.36	8.44	38.83	4.97
50	34.26	34.24	31.18	26.48	7.78	29.66	4.6
60	25.29	25.33	22.56	18.63	6.66	21.27	4.02
70	17.14	17.29	14.97	12.66	4.48	14.24	2.9

Figure 3. Life expectancy analysis for AST and ALT in men (for women see Supplemental Figure 4, Supplementary Digital Content 1, http://links.lww.com/AJG/B248). Estimated life loss for male participants among AST (**a**) and ALT (**c**) categories, with 15–24 IU/L as reference. Estimated life expectancy for male participants among AST (**b**) and ALT (**d**) categories. Diff1 = life expectancy gap between those with AST/ALT ≥ 70 and 15–24. Diff2 = life expectancy gap between those with AST/ALT ≥ 40 and 15–24. ALT, alanine aminotransferase; AST, aspartate aminotransferase.

with values ≥40 IU/L, 3 times more subjects for ALT than for AST (Figure 1) and, yet, identifying far less equivalent number of associated deaths for liver cancer and for all-cause mortality by ALT would unravel the mystery. Indeed, in our previous article on liver cancer, relative risks of AST were 3 times larger than ALT (15). Requiring less people to predict similar mortality, AST was more efficient and more valuable.

The literature on comparing the mortality effect between elevated AST and ALT was limited. Some studies, with large data set, classified AST or ALT in quartiles (25) and not examining the differences between the elevated and the normal. A comparison of relative risks or HRs between the 2 would have been difficult, because 2 relative risks are ratios based on different reference groups. By cross tabulate the 2 risks with identical reference group, a comparison is possible and clearly showed the superiority of AST over ALT (see Supplemental Table 4, Supplementary Digital Content 1, http://links.lww.com/AJG/B248). Furthermore, we used loss of life expectancy, which is comparable and intuitively understandable, and had made the implication from its comparison more compelling to the public.

A reference group of 15–24 IU/L, instead of the <25 IU/L used in our previous report on liver cancer prediction model (24), was selected because increased mortality for all-cause, but not liver cancer, below 15 IU/L was found for both AST and ALT, forming a J-shaped curve. That low aminotransferase was associated with increased all-cause mortality, but not liver mortality, is intriguing but has been reported, and the phenomenon was generally attributable to the aging or frailty effect (26,27). The magnitude of increased all-cause mortality risk for low values, higher for AST (HR = 1.39) than ALT (HR = 1.19), was supportive of the larger role of AST in its systemic involvement.

Because AST values for men were generally higher than women up to age 65, and there were twice as many elevated AST in men (7.6%) as in women (3.8%), the question arose as to whether there should be gender-specific cut point. However, we found mortality outcome was grossly similar, with significant increases for both men and women, whether the cut-point was >40, >70 or >25 IU/L (see Supplemental Table 2, see Supplementary Digital Content 1, http://links.lww.com/AJG/B248). In addition, cut point for low AST at <15 IU/L also yielded similarly significant increases. As a result, gender-specific consideration may not be warranted for AST.

Based on this study, a normal reference range of 15–24 IU/L would be favored over the conventional <40 IU/L as upper limit of normal. In fact, AST at 25–39 IU/L, a level commonly dismissed as high normal, constituted more than 1/5 (21.2%) of the cohort but had significant increases in liver cancer by 5 folds (5.26), and in all-cause by 12% (HR = 1.12; 95% confidence interval: 1.07–1.17).

A series of sensitivity analyses by excluding high risk individuals were conducted (Table 3). We excluded those with liver related conditions, such as history of liver diseases (n = 15,541),

those carriers of chronic hepatitis (positive for HBV and HCV), those who frequently drank alcohol, or those with abnormal α-fetoprotein or advanced FIB-4 or APRI scores, an index indicative of liver cirrhosis. These exclusions lowered the risk for liver mortality, but not by much, whereas the all-cause mortality remained essentially unaltered. The second group excluded was those deaths occurring within the first 3 years from entry into the cohort, and the third group, those deaths from injury or suicide that were unrelated to medical diseases. We found the results to be largely similar, indicating the minimal effect from preexisting conditions or unrelated causes of deaths.

As AST or ALT is known to vary from test to test, in addition to the above exclusions, we compared those who repeated their screening visits within 2 years with their first visit and found them grossly similar. Prevalence of elevated AST remained the same, 5.3% in first visit and 5.5% in second visits among those with 2 visits. The limited variability of AST or ALT did not alter the outcome results.

Among causes under all-cause mortality, elevated AST, but not ALT, was associated with stroke mortality in this study, contributing to part of the increase for cardiovascular diseases. This finding is in line with some studies that reported elevated AST associated with 2–4 fold of increased risks for hemorrhagic stroke, when stroke was subclassified. Mechanism for this type of stroke is unknown but can only be speculative, such as elevated AST indicating inflammation or poor synthesis of clotting factors by the liver or it may be associated with low cholesterol, a known factor for intracranial hemorrhage (11). Indeed, elevated AST, but not ALT, could be a risk factor for establishing the prediction model for hemorrhagic stroke.

The epidemiological association we observed on AST should not be interpreted as causal. We did, however, notice that this association has met many of the Hill's criteria in approaching causal relationship (28). The high HRs, the dose response relationship, the exclusion of early deaths, the internal consistency in finding this association regardless of gender, age, smoking, hypertension, diabetes, hepatitis carrier status, and many of the confounding risk factors lend support for causality. As a result, every elevated AST should be viewed at least as a marker for increased mortality risk and should be carefully assessed.

Physical activity was found to have a paradoxical effect on AST values. Vigorous exercise increased AST because of muscular involvement, but the effect was transient, lasting only for a week or 2 (29). Sustained or regular exercise for an extended period of time, on the other hand, reduced the levels of elevated AST and improved health (30). Indeed, we found a gain of 3.5 years of life for those active individuals with elevated AST (see Supplemental Figure 5, Supplementary Digital Content 1, http://links.lww.com/AJG/B248). Counseling for regular exercise for individuals with elevated AST should be routinely offered, as, among other benefits of exercise, a gain of a few years could be achieved for this overlooked but extremely large risk. American College of Sports Medicine launched a campaign on "exercise is medicine", highlighting our clinical approach to elevated AST (31).

There are important limitations in this study. First, data were based on a health surveillance program, and participants seeking self-paying screening could have come from higher socioeconomic status (SES). However, screening program was oriented toward targeting extended family, with parents or relatives of low SES included, but paid for by the breadwinner or the high SES individuals. In addition, the relative risks or HRs used in the internal comparison in this study had minimized the SES effect. Second, the data were obtained from an Asian population in Taiwan, and it may not be applicable to non-Asian groups. In the literature, however, we found increased all-cause mortality among elevated AST or ALT levels in American and European populations supporting our conclusions (5,7,9). Third, we used death certificates, instead of liver biopsy, to determine deaths from liver-related diseases. Death certificates are notorious for inaccuracy in causes of death. A previous study, nevertheless, found that the accuracy of underlying cause of death in Taiwan are reasonably reliable, especially for cancer deaths (32). Furthermore, our life expectancy calculations were based on all-cause mortality, and reporting of deaths was nearly 100% in Taiwan. Fourth, although the HRs were multivariable-adjusted, life expectancy, by definition, was presented without considering potential confounding factors. Some critics may view our presentation of life expectancy as cohort-specific. However, such a weakness was mitigated in this study not only by a large sample size mimicking a general population, but also by the use of the differences of life expectancy between 2 AST groups, minimizing the effect of cohort specific and making the results more generalizable.

In conclusion, we are the first to report that elevated AST was associated with a larger loss of life, up to 10.2 years among those with AST ≥40 IU/L, and that AST is superior to predict mortality for both liver-related and non–liver-related than ALT. This large negative systemic effect, if clinically adopted, is a paradigm shift in the interpretation of AST. Finally, "exercise is medicine" and routinely counselling for regular physical activity should be encouraged as a gain of 3.5 years of life were found among those active individuals with elevated AST.

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CONFLICTS OF INTEREST

Guarantors of the article: Xifeng Wu, MD, PhD, and Chi-Pang Wen, MD, DrPH.

Specific author contributions: Kunlin Xie and Chien Hua Chen, co-first authors. Study concept and design: C.-P.W. and X.W. Analysis and interpretation of data: K.X., Y.Y., M.H., P.J.L., J.H.L., M.K.T., C.-P.W., and X.W. Drafting of the manuscript: K.X., S.P.T., H.T., C.H.C., C.W., C.-P.W., and X.W. Critical revision of the manuscript for important intellectual content: K.X., S.P.T., H.T., P.J.L., H.W., Y.Z., Y.Y., C.W., M.K.T., and Y.Z. Statistical analysis: Y.Y., M.H., and J.H.L. Study supervision: C.-P.W. and X.W.

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Potential competing interests: None.

Study Highlights

WHAT IS KNOWN

- ✓ ALT and AST are indicators of liver dysfunction. We previously showed that transaminases were the strongest predictors in the integrative risk prediction model for hepatocellular carcinoma development. The associated all-cause mortality and life-shortening effects of transaminases from liver and non-liver causes have not been well studied.

WHAT IS NEW HERE

- ✓ There is a J-shape relationship between aminotransferase and all-cause mortality.
- ✓ Participants with AST ≥ 40 IU/L showed a loss of life expectancy of 10.2 years, with <15–24 IU/L as reference. There is a linear relationship with reversed longevity, with a 2-month shortening for every unit above 25 IU/L. For AST, the causes of excess mortality included liver diseases, cancers, and stroke. In comparison, elevated ALT was contributed mainly from liver, with loss of life expectancy less than half of that from elevated AST.
- ✓ Physical activity attenuated the loss of life years due to elevated serum transaminases.

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