ORIGINAL ARTICLES

Clinical disparity of elevated serum alanine aminotransferase (ALT) levels among the working population of Taipei, Taiwan

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ABSTRACT

Purpose: To explore sex variations in the prevalence and factors of high serum alanine aminotransferase (ALT) level among the working population in Taipei, Taiwan.

Methods: This study included 8,351 healthy adults (5,247 men and 3,104 women) who admitted to a teaching hospital voluntarily for a physical examination in 2009. The definitions of occupations include computer and mathematical occupations, architecture and engineering occupations, community and social service occupations, sales and related occupations, office and administrative support occupations, and production occupations. The age distribution of $\leq$ 29 yrs, 30-39 yrs, 40-49 yrs, and $\geq$ 50 yrs were 22.5%, 36.8%, 23.5%, and 17.2%, respectively. Fasting blood samples were drawn using venipuncture and participants were interviewed with a structured questionnaire.

Results: The overall prevalence of high serum ALT level ($\geq$ 40 U/L) was 17.1%. After stratified the data according to age into four age groups ($\leq$ 29 yrs, 30-39 yrs, 40-49 yrs, and $\geq$ 50 yrs) , the men participants revealed a higher prevalence of high serum ALT levels for all age groups than the women participants. Bases on multiple logistic regression models, for the men, the significant factors were associated with high serum ALT level and included age (OR = 0.96, 95% CI: 0.95-097), BMI [no matter whether overweight (OR = 2.45, 95% CI: 1.99-3.02) or obese (OR = 4.02, 95% CI: 3.22-5.03)], hypercholesterolemia (yes vs. no, OR = 1.25, 95% CI: 1.05-1.48), hypertriglyceridemia (OR = 1.25, 95% CI: 1.04-1.50), high FPG levels (OR = 1.48, 95% CI: 1.05-2.09), high AST levels (OR = 26.71, 95% CI: 19.00-37.54), hyperuricemia (OR = 1.48, 95% CI: 1.25-1.76), high ALP levels (OR = 1.20, 95% CI: 1.00-1.45), and high glutamic acid transaminase levels (OR = 4.31, 95% CI: 3.61-5.14). For the women subjects, the statistically significant factors that were associated with high serum ALT level included BMI [no matter whether overweight (OR = 3.53, 95% CI: 1.87-6.67) or obese (OR = 4.32, 95% CI: 2.26-8.23)], high AST levels (yes vs. no, OR = 38.49, 95% CI: 21.45-49.28), high BUN levels (yes vs. no, OR = 1.66, 95% CI: 1.03-2.29), and high glutamic acid transaminase levels (yes vs. no, OR = 9.87, 95% CI: 5.79-16.83).

Conclusion: In conclusion, the clinical problem of elevated serum ALT level is important in the working population. Many subjects are asymptomatic and the diagnosis of high serum ALT level should be considered with sex, age, hyperuricemia, high AST levels, high ALP levels, high glutamic acid transaminase levels, and metabolic risk factors in mind.

Key Words: Serum alanine aminotransferase, Prevalence, Gender difference, Working population

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1. INTRODUCTION

Serum alanine aminotransferase (ALT) is a type of cytosolic enzyme that is detected in various organs and can catalyze the transfer of an α-amino group of alanine to an α-ketoglutaric acid.[1] This liver enzyme is used as an indicator of hepatocellular damage in hepatitis;[2] however, ALT levels are also frequently used as surrogate markers for hepatocyte injury.[3] The current viewpoint is that high serum ALT levels are related to sex, age, waist-to-hip ratio, obesity, glucose concentration, triglyceride, medication, and viral hepatitis infection history.[1] In Taiwan, few evidence-based studies have determined the morbidity and possible etiology of high serum ALT level for the working population, which has high incidences of liver disease.

ALT screening fulfills the Wilson criteria for screening. The criteria for screening are the following: the disease should be an main health burden; the natural history of the disease natural history should be known; a latent or early symptomatic stage must be recognizable; tests should be acceptable, accurate, reliable, sensitive, specific, and easy to perform and interpret; an accepted treatment should be recognized for the disease; early treatment is more effective; a policy on whom should be treated must be established; diagnosis and treatment should be cost-effective; and case-findings should be a continuous process. In preventative medicine, knowledge of morbidity of elevated serum ALT levels in various regions, and exploration of demographic and biological markers that may be associated with to this disorder, is required. Uncertainty as to whether the morbidity and associated factors of elevated serum ALT level show sex-related variations among working populations still exists. This study identifies the potential for sex-related variations in the prevalence and related factors of high serum ALT level, because these variations might highlight clinical implications of the pathogenesis of high serum ALT level among the working population in Taipei, Taiwan.

2. METHODS

2.1 Data resources and data collection

This cross-sectional study was conducted with 8,351 participants (5,247 men and 3,104 women) at a teaching hospital from January 2009 to December 2009 in Taipei, Taiwan. Fasting blood samples were drawn using venipuncture by well-trained clinical nurses. Overnight-fasting serum and plasma (from whole blood preserved with EDTA and NaF) samples were kept frozen (-20°C) until ready for analysis. Face-to-face interviews with a structured questionnaire and blood pressure tests were also conducted during the participants' visits. For the ethics consideration, subjects eligible for participation were first asked whether they would be willing to answer questions and confirmed their willingness to participate by signing a consent form. All the participants' information was anonymous and used for statistical analysis only.

2.2 Criteria for definitions

To determine smoking and alcohol consumption habits, subjects were asked in multiple-choice questions to describe alcoholic drinks. We categorized daily ethanol intake in grams into 4 categories: nondrinkers, < 20 g (mild), 20-70 g (moderate), and > 70 g (heavy). A nondrinker was defined as someone who explicitly recorded zero for current alcohol consumption of any alcoholic beverage and zero or blank for previous alcohol consumption. A heavy drinker was defined as someone who recorded a daily alcohol intake of > 70 g.[4] Participants were classified into 3 groups based on their smoking status: never smoked, ex-cigarette smokers, and current smokers. A current smoker was defined as someone who smoked at least 1 cigarette per day during the previous year.[5]

Another variable in this study was age, which was divided into the following groups: $\leq$29, 30-39, 40-49, and $\geq$ 50 years. Participants who displayed a serum ALT level of $\geq$ 40 U/L were classified as elevated ALT level.[1,6] Criteria for the following diseases or conditions were the following: hyperuricemia $\geq$ 7 mg/dl for men and $\geq$ 6 mg/dl for women,[7] high AST $\geq$ 40 U/L,[6] hypercholesterolemia $\geq$ 200 mg/dl, hypertriglyceridemia $\geq$ 150 mg/dl,[8,9] high fasting plasma glucose level (FPG) $\geq$ 110 mg/dl, high BUN level $\geq$ 20 mg/dl, high creatinine level $\geq$ 1.2 mg/dl, high alkaline phosphatase level (ALP) $\geq$ 95 mg/dl, and high glutamic acid transaminase level $\geq$ 36 U/L. Participants were classified according to weight as follows: normal weight (BMI < 24 kg/m^2), overweight (BMI between 24 kg/m^2 and 27 kg/m^2), and obese (BMI $\geq$ 27 kg/m^2).[8]

According to 2010 Standard Occupational Classification Major Groups from The United States Department of Labor, the definitions of occupations describe as follows: computer and mathematical occupations, architecture and engineering occupations, community and social service occupations, sales and related occupations, office and administrative support occupations, and production occupations.

2.3 Statistical analysis

Statistical analysis was performed using SPSS 18.0 (SPSS, Chicago, IL). The continuous and categorical variables were expressed as the mean $\pm$ standard deviation (SD) and percentage. Crude and adjusted odds ratios and 95% confidence intervals were estimated. Multiple logistic regression was performed to explore the independent factors related to high

ALT levels. A p value less than .05 was considered a statistical significance.

3. Results

In this study, the mean value of serum ALT levels for the screened population was 28.00 $\pm$ 20.16 U/L. The men revealed a higher serum ALT level than the women (33.34 $\pm$ 12.24 U/L vs. 18.96 $\pm$ 8.31 U/L, respectively, $p < .01$). Figure 1 shows the sex- and age-specific prevalence of high serum ALT level ($\geq$ 40 U/L) of the screened population. The prevalence of high serum ALT level for the screened population was 17.1% and revealed a significant increase with an increased participants' ages in female population, using the χ^2 trend test ($p < .001$). The men displayed substantially high serum ALT levels than the women (23.9% vs. 5.7%, $p < .001$). In addition, after stratified the data according to age into four age groups, the men participants revealed a higher prevalence for all age groups than the women participants (see Figure 1).

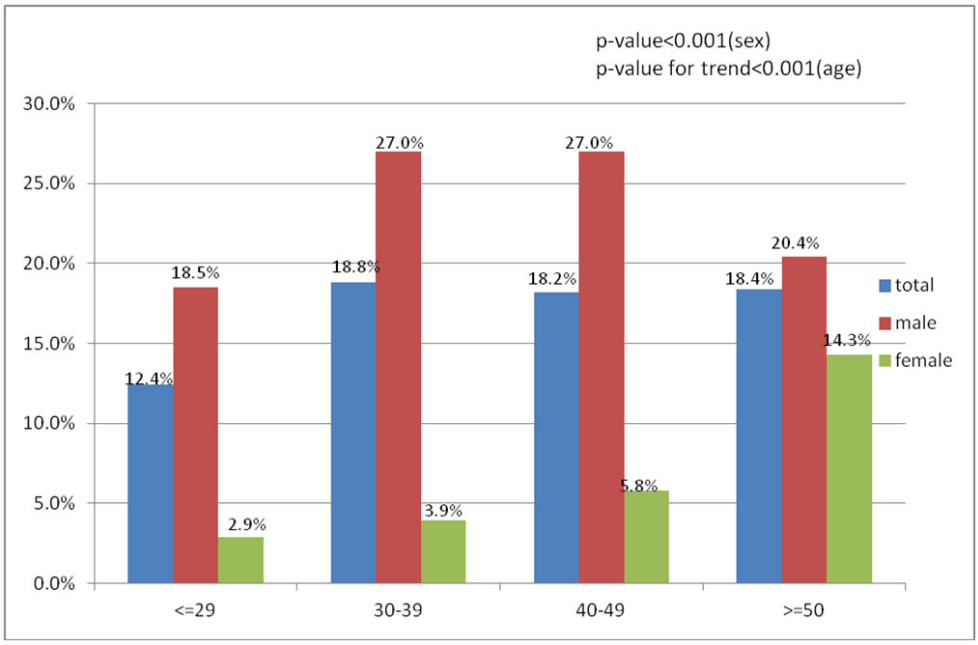

Figure 1. Sex- and age-specific prevalence of elevated ALT level ($\geq$ 40 U/L) among screened population participants (n = 8,351)

Table 1 shows the crude and adjusted odds ratios among various relevant related factors and high serum ALT levels. After adjusting for sex and age, elevated serum ALT levels revealed high alcohol consumption (moderate alcohol consumption [adjusted OR = 0.76, 95% CI: 0.58-0.90] and heavy alcohol consumption [adjusted OR = 1.41, 95% CI: 1.17-1.65]), high BMI (no matter whether overweight [adjusted OR = 3.30, 95% CI: 2.82-3.88] or obese [adjusted OR = 8.26, 95% CI: 7.05-9.68]), hypertension (adjusted OR = 2.34, 95% CI: 2.07-2.65), hypercholesterolemia (adjusted OR = 1.95, 95% CI: 1.73-2.20), hypertriglyceridemia (adjusted OR = 3.42, 95% CI: 3.01-4.88), high FPG levels (adjusted OR = 3.27, 95% CI: 2.62-4.09), high AST levels (adjusted OR = 78.31, 95% CI: 58.80-95.27), high ALP levels (adjusted OR = 1.56, 95% CI: 1.37-1.79), hyperuricemia (adjusted OR = 2.89, 95% CI: 2.55-3.27), and high glutamic acid transaminase levels (adjusted OR = 11.16, 95% CI: 9.73-12.80).

The multiple logistic regression models were used to test the independent effect between associated factors and high serum ALT levels. As presented in Table 2, sex (men vs. women, OR = 3.62, 95% CI: 2.86-4.58), age (OR = 0.97, 95% CI: 0.96-0.98), BMI [no matter whether overweight (OR = 2.53, 95% CI: 2.07-3.08) or obese (OR = 4.03, 95% CI: 3.26-4.96)], hypertension (OR = 1.51, 95% CI: 1.02-1.36), hypercholesterolemia (OR = 1.27, 95% CI: 1.08-1.50), hypertriglyceridemia (OR = 1.21, 95% CI: 1.01-1.44), high FPG levels (OR = 1.43, 95% CI: 1.04-1.97), high AST levels (OR = 30.05, 95% CI: 23.66-38.71), hyperuricemia (OR = 1.52, 95% CI: 1.29-1.79), high ALP levels (OR = 1.23, 95% CI: 1.03-1.46), and high glutamic acid transaminase levels (OR = 4.65, 95% CI: 3.93-5.50) appeared to be statistically significant regarding elevated serum ALT level. Moderate alcohol consumption (20 g to 70 g vs. no drinking/d, OR = 0.82, 95% CI: 0.67-0.97) was independently and negatively correlated with elevated ALT levels, however, heavy alcohol consumption ($\geq$ 70 g/d vs. no drinking/d, OR = 1.35, 95% CI: 1.08-1.76) showed the positive relationship to was not.

Table 1. Crude and adjusted odds ratios of associated factors for elevated serum alanine aminotransferase (ALT) level (≥ 40 U/L) among screened population participants (n = 8,351)

Variable		Elevated serum ALT					
		Yes (n = 1,432)	No (n = 6,919)	Crude OR (95%CI)	*p*	Adjusted OR* (95%CI)	*p*
Sex	women	178	2,926	1.00	----	----	----
	men	1,254	3,993	5.16 (4.38-6.08)	<.001	----	----
Age (yr)	≦ 29	233	1,647	1.00	----	----	----
	30-39	578	2,499	1.64 (1.39-1.93)	<.001	----	----
	40-49	357	1,600	1.58 (1.32-1.89)	<.001	----	----
	≧ 50	264	1,173	1.59 (1.31-1.93)	<.001	----	----
Smoking	no	931	5,220	1.00	----	----	----
	yes	186	761	1.37 (1.15-1.63)	<.001	1.12 (0.95-1.41)	.07
	ex-smoker	315	938	1.88 (1.63-2.18)	<.001	1.47 (0.98-1.90)	.06
Alcohol drinking	no	1,234	5,881	1.00	----	----	----
	< 20 g/day	71	298	1.14 (0.87-1.48)	.35	1.07 (0.80-1.69)	.41
	20-70 g/day	58	535	0.52 (0.39-0.68)	<.001	0.76 (0.58-0.90)	.03
	≧ 70 g/day	69	205	1.60 (1.21-2.12)	.001	1.41 (1.17-1.65)	.03
BMI (kg/m^2)	≦ 24	300	4,318	1.00	----	1.00	----
	24-27	480	1,640	4.21 (3.61-4.92)	<.001	3.30(2.82-3.88)	<.001
	≧ 27	652	961	9.77 (8.38-11.39)	<.001	8.26(7.05-9.68)	<.001
Hypertension	no	722	5,213	1.00	----	1.00	----
	yes	710	1,706	3.01 (2.67-3.38)	<.001	2.34 (2.07-2.65)	<.001
Hypercholesterolemia	no	713	4,643	1.00	----	1.00	----
	yes	719	2,285	2.05 (1.82-2.29)	<.001	1.95 (1.73-2.20)	<.001
Hypertriglyceridemia	no	724	5,658	1.00	----	1.00	----
	yes	708	1,261	4.39 (3.89-4.95)	<.001	3.42 (3.01-4.88)	<.001
Higher FPG	no	1,266	6,684	1.00	----	1.00	----
	yes	166	235	3.73 (3.03-4.59)	<.001	3.27 (2.62-4.09)	<.001
Higher AST	no	883	6,849	1.00	----	1.00	----
	yes	549	70	60.83 (46.98-78.77)	<.001	78.31 (58.80-95.27)	<.001
Higher ALP	no	1,003	5,584	1.00	----	1.00	----
	yes	429	1,335	1.79 (1.57-2.03)	<.001	1.56 (1.37-1.79)	<.001
Higher BUN	no	1,332	6,516	1.00	----	1.00	----
	yes	100	403	1.21 (0.97-1.52)	.09	0.90 (0.71-1.14)	.38
Higher Creatinine	no	1,098	5,752	1.00	----	1.00	----
	yes	334	1,167	1.50 (1.31-1.72)	<.001	0.89 (0.77-1.02)	.10
Hyperuricemia	no	500	4,655	1.00	----	1.00	----
	yes	932	2,264	3.83 (3.40-4.32)	<.001	2.89 (2.55-3.27)	<.001
Higher glutamic acid transaminase	no	463	5,968	1.00	----	1.00	----
	yes	969	951	13.13 (11.53-14.96)	<.001	11.16 (9.73-12.80)	<.001

*Adjustment for sex and age

Table 2 also indicates the considerably dissimilar sex differences of multiple logistic regression. For the men, the significant factors were related to high serum ALT level and included age (OR = 0.96, 95% CI: 0.95-097), BMI (no matter whether overweight [OR = 2.45, 95% CI: 1.99-3.02) or obese (OR = 4.02, 95% CI: 3.22-5.03]), hypercholesterolemia (OR = 1.25, 95% CI: 1.05-1.48), hypertriglyceridemia (OR = 1.25, 95% CI: 1.04-1.50), high FPG levels (OR = 1.48, 95% CI: 1.05-2.09), high AST levels (OR = 26.71, 95% CI: 19.00-37.54), hyperuricemia (OR = 1.48, 95% CI: 1.25-1.76), high

ALP levels (OR = 1.20, 95% CI: 1.00-1.45), and high glutamic acid transaminase levels (OR = 4.31, 95% CI: 3.61-5.14). For the women subjects, the statistically significant factors that were associated with high serum ALT level included BMI (no matter whether overweight [OR = 3.53, 95% CI: 1.87-6.67] or obese [OR = 4.32, 95% CI: 2.26-8.23]), high AST levels (OR = 38.49, 95% CI: 21.45-49.28), high BUN levels (OR = 1.66, 95% CI: 1.03-2.29), and high glutamic acid transaminase levels (OR = 9.87, 95% CI: 5.79-16.83).

The disparity of occupational professions of elevated serum ALT level was also examined. Table 3 shows that, sex, hypertension, higher BMI, higher AST, and higher glutamic acid transaminase are the common factors related to high serum ALT level.

Table 2. Multiple logistic regression of associated factors for elevated serum alanine aminotransferase (ALT) level ($\geq$ 40 U/L) among screened population participants (n = 8,351)

Variable	Elevated serum ALT (yes vs. no)					
	Men		Women		Total	
	OR	95%CI	OR	95%CI	OR	95%CI
Age (yrs)	0.96	0.95-0.97	1.02	0.99-1.04	0.97	0.96-0.98
Sex (men vs. women)	----	----	----	----	3.62	2.86-4.58
BMI (24-27 vs. < 24 kg/m^2)	2.45	1.99-3.02	3.53	1.87-6.67	2.53	2.07-3.08
($\geqq$ 27 vs. < 24 kg/m^2)	4.02	3.22-5.03	4.32	2.26-8.23	4.03	3.26-4.96
Alcohol drinking (< 20 g/day vs. no)	1.20	0.81-1.57	0.81	0.66-1.23	1.05	0.87-1.32
(20-70 g/day vs. no)	0.79	0.61-0.90	----*	----	0.82	0.67-0.97
($\geqq$ 70 g/day vs. no)	1.44	1.12-1.78	----*	----	1.35	1.08-1.76
Hypertension (yes vs. no)	1.96	1.18-2.87	1.20	1.05-1.76	1.51	1.02-1.36
Hypercholesterolemia (yes vs. no)	1.25	1.05-1.48	1.45	0.86-2.42	1.27	1.08-1.50
Hypertriglyceridemia (yes vs. no)	1.25	1.04-1.50	0.91	0.49-1.70	1.21	1.01-1.44
Higher FPG (yes vs. no)	1.48	1.05-2.09	1.10	0.43-2.80	1.43	1.04-1.97
Higher AST (yes vs. no)	26.71	19.00-37.54	38.49	21.45-49.28	30.05	23.66-38.71
Higher BUN (yes vs. no)	1.03	0.75-1.41	1.66	1.03-2.29	1.24	0.74-1.71
Higher Creatinine (yes vs. no)	1.78	0.65-1.94	1.50	0.76-3.61	1.33	0.65-1.94
Hyperuricemia (yes vs. no)	1.48	1.25-1.76	1.64	0.98-2.75	1.52	1.29-1.79
Higher ALP (yes vs. no)	1.20	1.00-1.45	1.13	0.60-2.10	1.23	1.03-1.46
Higher glutamic acid transaminase (yes vs. no)	4.31	3.61-5.14	9.87	5.79-16.83	4.65	3.93-5.50

*Due to very few women had habits of alcohol drinking. The model did not the estimated the association

4. Discussion

ALT is not only related to liver fat accumulation, but also it is often viewed as a surrogate marker for non-alcoholic fatty liver disease (NAFLD).[10] Liver function tests are frequently ordered in clinical practice because these tests are relatively cheap and convenient. ALT is the most specific screening approach for hepatic necroinflammation. Elevated ALT activity often reflects the prevalent NAFLD after excluded other causes.[11] Nevertheless, the exact pathogenesis of raised ALT levels in NAFLD remains unclear. In this study, the prevalence of high serum ALT levels in the men and women were 23.9% and 5.7%, respectively. Men sex, younger age, high BMI, hypercholesterolemia, hypertriglyceridemia, high FPG levels, high AST levels, hyperuricemia, high ALP levels, and high glutamic acid transaminase levels were independent associated factors of high ALT level. These results often been not noticed when the serum ALT level was slightly abnormal.[12]

The prevalence of high serum ALT level among different screened populations appears to vary based on the findings of various studies conducted in several other areas.[1, 10, 13] The possible reasons of disparity may due to dissimilarities among different population stocks in addition to variations in the diagnostic criteria. In Taiwan, good health and effective training are also essential for a working population. Long or irregular working time may occur adverse health effects. The prevalence of elevated serum ALT levels in this study (17.1%) was relatively higher than previous population-based study that was conducted among the general Chinese population.[1, 13–15] The working population always faces hard

work loading, job stress, and unbalanced working and resting hours. Irregular and unhealthy lifestyles are also main problems. This may explain partially the higher prevalence of elevated serum ALT levels observed in our findings. Another possible reason for the variation between the results of the general population-based studies and this study may simply be associated with the different study populations and diagnostic criteria. In addition, the different factors related to elevated serum ALT level in different occupational professions suggested that multiple strategies for the personal health promotion of occupational professions are important to reduce the risk of elevated serum ALT level.

Table 3. Multiple logistic regression of associated factors for elevated serum alanine aminotransferase (ALT) level ($\geq$ 40 U/L) stratified by occupational professions (n = 8,351)

Variable	Office and Administrative Support (n = 2,827)	Architecture and Engineering (n = 859)	Community and Social Service (n = 642)	Sales and Related (n = 944)	Computer and Mathematical (n = 1,331)	Production (n = 1,748)
	OR(95% CI)	OR(95% CI)	OR(95% CI)	OR(95% CI)	OR(95% CI)	OR(95% CI)
Sex (men vs. women)	4.96 (4.08-5.49)	2.87 (2.33-3.21)	2.90 (2.58-3.27)	3.12 (2.78-3.65)	4.60 (3.68-5.44)	3.69 (3.00-4.32)
Age (yrs)	0.96 (0.93-0.98)	0.98 (0.96-1.02)	1.04 (0.96-1.11)	0.95 (0.90-0.99)	0.96 (0.94-0.98)	1.01 (0.96-1.06)
Hypertension (yes vs. no)	2.02 (1.45-2.58)	1.42 (1.07-1.89)	1.44 (1.11-1.59)	1.92 (1.58-2.39)	1.37 (1.16-1.53)	1.66 (1.21-1.94)
BMI (24-27 vs. < 24 kg/m^2)	2.31 (1.74-2.93)	2.97 (2.21-4.01)	2.12 (1.50-3.08)	3.08 (2.46-4.10)	2.40 (1.92-3.14)	2.17 (1.78-3.23)
($\geqq$27 vs. < 24 kg/m^2)	4.15 (3.59-5.27)	3.31 (2.84-4.38)	3.48 (2.83-4.31)	3.94 (3.14-5..04)	4.03 (2.87-5.77)	3.67 (3.08-4.80)
Hyperuricemia (yes vs. no)	1.38 (0.95-1.87)	1.77 (1.08-2.29)	1.89 (1.03-2.55)	1.16 (0.88-1.50)	1.86 (1.12-2.03)	1.56 (1.21-2.14)
Higher AST (yes vs. no)	37.12 (29.66-43.27)	31.18 (28.03-39.24)	27.23 (24.76-33.14)	23.95 (20.33-28.67)	30.10 (26.34-35.63)	29.11 (26.55-32.50)
Higher ALP (yes vs. no)	1.09 (0.97-1.90)	1.46 (1.13-1.84)	1.13 (1.62-9.84)	1.05 (0.89-1.30)	1.27 (1.03-1.82)	1.07 (0.85-1.58)
Hypercholestero-lemia (yes vs. no)	1.34 (1.09-1.67)	1.07 (0.91-1.40)	1.28 (1.04-1.95)	1.16 (0.92-1.38)	1.10 (0.94-1.39)	1.15 (1.03-1.39)
Hypertriglyceri-demia (yes vs. no)	1.19 (1.03-1.36)	1.27 (1.06-1.71)	1.09 (0.88-1.42)	1.04 (0.77-1.30)	1.29 (1.12-1.48)	1.02 (0.81-1.45)
Higher FPG (yes vs. no)	1.47 (1.22-1.62)	1.36 (1.15-1.73)	1.36 (1.07-1.86)	1.35 (0.76-1.98)	1.28 (1.13-1.59)	1.23 (0.69-2.07)
Higher glutamic acid transaminase (yes vs. no)	4.36 (3.71-5.00)	4.99 (2.90-6.81)	3.21 (2.03-4.52)	3.44 (2.57-.4.72)	4.78 (3.81-6.34)	4.81 (3.92-5.96)

The normal cut-off value of ALT level was $\geq$ 40 U/L in this study. This value was historically according to previous population-based studies conducted before the availability of blood tests for hepatitis C and NAFLD.[16] The gender variation in the prevalence of an high serum ALT level was significant in this study. The male participants displayed a 3.62-fold (95% CI: 2.86-4.58) risk of a serum ALT level $\geq$ 40 U/L compared with the female participants, after adjusting for confounding factors. Similar sex variations have also been showed in other epidemiological studies.[1,16,17] The men were prone to accumulating visceral fat, regardless of total body fat, and deep subcutaneous adipose tissue was related to insulin resistance in the men but not in the women population.[16,18] In addition, we observed that an elevated serum ALT level decreased with age in the men but not in the women, which corresponds to the findings of other studies.[19,20] The clinical mechanism for this is still unclear; however, both a cohort effect and/or premature mortality in subjects with elevated ALT levels in young age must be considered.[16] ALT may be a novel biomarker for elderly because levels decreased with increasing age, and low levels are related to frailty and increased mortality.[3,21]

High serum ALT levels are related to obesity and metabolic syndrome, which includes features such as abdominal obesity, dyslipidemia, hypertension, and hyperglycemia.[10] Obesity has been suggested as a risk factor for liver function impairment, and high BMI is an adequate predictor of elevated ALT levels.[22,23] To identify a threshold value for this study, BMI was classified into 3 categories: < 24 kg/m^2, 24 kg/m^2 to 27 kg/m^2, and $\geq$ 27 kg/m^2.[8] By logistic regression model, the odds ratios for the BMI in the 3 categories were estimated as 2.53 (95% CI: 2.07-3.08) in the $\geq$ 24 kg/m^2 to 27 kg/m^2 group and 4.03 (95% CI: 3.26-4.96) in the $\geq$ 27 kg/m^2 group, compared with the < 24 kg/m^2 group. This finding not only suggests that ALT may be observed from 24 kg/m^2 but also that clinicians should consider weight control for the prevention of elevated serum ALT levels. In addition, some follow-up epidemiological studies have also indicated that a high activity of ALT, independent of age, obesity, and alcohol intake, is associated with the occurrence of metabolic syndrome and type 2 diabetes.[10,24] Serum ALT concentrations were associated with hepatic insulin resistance, and an elevated ALT level reflected fatty changes in the liver.[25] The elevated ALT may be caused by higher fat deposition in the liver, as a result of various metabolic conditions, and reflect ongoing inflammation that impairs insulin signaling both in the liver and throughout the entire body.[10]

Serum uric-acid levels have also been suggested to be increased not only among participants suffering from chronic liver lesions but also among non-infected participants. Although the previous studies showed the significant relationship between hyperuricemia and high serum ALT level, the extent of such elevation tends to depend on the degree of the hepatic lesions.[1,26] In addition, the magnitude of risk for alcohol consumption of different studies was difficult to compare due to different types of alcohol consumption and behavior. The actual duration of smoking and drinking behavior, as well as the daily alcohol intake and quantity of cigarettes smoking, was also difficult to identify accurately. Our results revealed that only alcohol consumption, and not smoking, was associated with high serum ALT level. This result appears consistent with the findings of other population-based studies.[13] Although cigarette smoking might constitute an important risk factor regarding abnormal liver function, personal smoking habits did not significantly associated with high serum ALT level after adjustment for confounding factors.[27] The relationship between high serum ALT level and alcohol consumption is presented as U or J-shaped in this study. Previous studies indicated that mild to moderate alcoholic beverages were found to have lower total mortality rates, which is mainly a result of a decrease in cardiovascular death, than those of both nondrinkers and heavy drinkers.[5] AST is an important enzyme in amino acid metabolism and measured as a marker for liver function. ALP is also an enzyme in the cells that line the biliary ducts of the liver and is used in one of the most common liver health tests conducted in clinical practice. ALP levels in plasma will increase with large bile duct obstruction, intrahepatic cholestasis, and liver infiltrative diseases. The positive correlation among AST, ALP, glutamic acid transaminase, and high ALT levels is not unexpected after adjusting for confounding factors. However, from the cross-sectional study design, it is difficult to determine the degree at which the increase in serum transaminase level could occur or to what extent the level had arisen before liver disease developed.

4.1 Methodological considerations

The major limitations for this study was due to hospital-based study design, a potential self-selection bias resulted in a screened subjects that was not representative of the general population in Taiwan. However, our results are still useful of elevated serum ALT level according to relative larger sample sizes. Secondly, because no international standard cut-off value for high ALT level has been internationally accepted to diagnose abnormality, each study may elect to set slightly varying cut-off levels for abnormal serum ALT levels such that our estimation could have been affected by a level of non-differential misclassification bias identification.[13]

Thirdly, although this study is to explore whether clinical variables are associated with the outcome, knowing some can be due to false positives is inevitable. Fourthly, no category for people who used to drink, but not currently for the study participates. We also have no information if people decided to quit drinking due to some health conditions related to the outcomes of interest, that is, the presented study results may be biased. Fifthly, it could simply reflect lack of statistical power in females, given that the number of females is significantly lower than males and the elevated ALT is less common in females. Finally, only a single time point, that is, the results may not reflect causal relationship between demographic or biochemical factors and high serum ALT level.

4.2 Conclusion

In conclusion, the clinical problem of elevated serum ALT level is important in the working population. Many subjects are asymptomatic and the diagnosis of high serum ALT level should be considered with sex, age, hyperuricemia, high AST levels, high ALP levels, high glutamic acid transaminase levels, and metabolic risk factors in mind.

CONFLICTS OF INTEREST DISCLOSURE

The authors declare that they have no competing interests.

REFERENCES

[1] Liu CM, Tung TH, Liu JH, et al. A community-based epidemiological study of elevated serum alanine aminotransferase levels in Kinmen, Taiwan. World J Gastroenterol. 2005; 11: 1616-1622. https://doi.org/10.3748/wjg.v11.i11.1616

[2] Chen CH, Huang MH, Yang JC, et al. Prevalence and etiology of elevated serum alanine aminotransferase level in an adult population in Taiwan. J Gastroenterol Hepatol. 2007; 22: 1482-1489. PMid:17716352. https://doi.org/10.1111/j.1440-1746.2006.04615.x

[3] Dong MH, Bettencourt R, Barrett-Connor E, et al. Alanine Aminotransferase Decreases with Age: The Rancho Bernardo Study. PLoS ONE. 2010; 5: e14254.

[4] Shaper AG, Wannamethee G, Walker M. Alcohol and mortality in British men: explaining the U-shaped curve. Lancet. 1988; 2: 1267-1273. https://doi.org/10.1016/S0140-6736(88)92890-5

[5] Wang JJ, Tung TH, Yin WH, et al. Effects of moderate alcohol consumption on inflammatory biomarkers. Acta Cardiol. 2008; 63: 65-72. PMid:18372583. https://doi.org/10.2143/AC.63.1.2025334

[6] Fracanzani AL, Valenti L, Bugianesi E, et al. Risk of severe liver disease in nonalcoholic fatty liver disease with normal aminotransferase levels: A role for insulin resistance and diabetes. Hepatology. 2008; 44: 792-8. PMid:18752331. https://doi.org/10.1002/hep.22429

[7] Tsai CH, Lee YC, Ro YC, et al. Non-alcoholic fatty liver disease and obesity-associated factors: A study in a regional hospital in Mid-Taiwan. Taiwan J Fam Med. 2006; 16: 215-25.

[8] Hwang LC, Bai CH, Chen CJ. Prevalence of obesity and metabolic syndrome in Taiwan. J Formos Med Assoc. 2006; 105: 626-635. https://doi.org/10.1016/S0929-6646(09)60161-3

[9] Caballería L, Auladell MA, Torán P, et al. Risk factors associated with non-alcoholic fatty liver disease in subjects from primary care units. A case-control study. BMC Gastroenterology. 2008; 8: 44-50.

[10] Chen ZW, Chen LY, Dai HL, et al. Relationship between alanine aminotransferase levels and metabolic syndrome in nonalcoholic fatty liver disease. J Zhejiang Univ Sci B. 2008; 9: 616-622. PMid:18763311. https://doi.org/10.1631/jzus.B0720016

[11] Poustchi H, George J, Esmaili S, et al. Gender differences in healthy ranges for serum alanine aminotransferase levels in adolescence. PLoS ONE. 2011; 6: e21178. https://doi.org/10.1371/journal.pone.0021178

[12] Clark JM, Brancati FL, Diehl AM. The prevalence and etiology of elevated aminotransferase levels in the United States. Am J Gastroenterology. 2003; 98: 960-967. PMid:12809815. https://doi.org/10.1111/j.1572-0241.2003.07486.x

[13] Zhang H, Ding Y, Li Q, et al. Relationship between serum aminotransferase levels and metabolic disorders in Northern China. Iran J Public Health. 2012; 41: 15-26.

[14] Oh SY, Cho YK, Kang MS, et al. The association between increased alanine aminotransferase activity and metabolic factors in nonalcoholic fatty liver disease. Metabolism. 2006; 55: 1604-1609. PMid:17142131. https://doi.org/10.1016/j.metabol.2006.07.021

[15] Wang CS, Wang ST, Chou P. Using the prevalence of an elevated serum alanine aminotransferase level for identifying communities with a high prevalence of hepatitis C virus infection. Arch Intern Med. 2001; 161: 392-394. https://doi.org/10.1001/archinte.161.3.392

[16] Pan JJ, Qu HQ, Rentfro A, et al. Prevalence of metabolic syndrome and risks of abnormal serum alanine aminotransferase in Hispanics: A population-based study. PLoS ONE. 2011; 6: e21515.

[17] Kallwitz ER, Kumar M, Aggarwal R, et al. Ethnicity and nonalcoholic fatty liver disease in an obesity clinic: the impact of triglycerides. Dig Dis Sci. 2008; 53: 1358-1363. PMid:18347982. https://doi.org/10.1007/s10620-008-0234-x

[18] Omagari K, Kadokawa Y, Masuda J, et al. Fatty liver in nonalcoholic non-overweight Japanese adults: incidence and clinical characteristics. J Gastroenterol Hepatol. 2002; 17: 1098-1105. https://doi.org/10.1046/j.1440-1746.2002.02846.x

[19] Kariv R, Leshno M, Beth-Or A, et al. Re-evaluation of serum alanine aminotransferase upper limit and its modulation factors in a large-scale population study. Liver International. 2006; 26: 445-450. PMid:16629648. https://doi.org/10.1111/j.1478-3231.2006.01197.x

[20] Elinav E, Ben-Dov IZ, Ackerman E, et al. Correlation between serum alanine aminotransferase activity and age: an inverted U curve pattern. Am J Gastroenterol. 2005; 100: 2201-2204. PMid:16181369. https://doi.org/10.1111/j.1572-0241.2005.41822.x

[21] Le Couteur DG, Blyth FM, Creasey HM, et al. The association of alanine transaminase with aging, frailty, and mortality. J Gerontol A Biol Sci Med Sci. 2010; 65: 712-717. PMid:20498223. https://doi.org/10.1093/gerona/glq082

[22] Fu CC, Chen MC, Li YM, et al. The risk factors for ultrasound-diagnosed non-alcoholic fatty liver disease among adolescents. Ann Acad Med Singapore. 2009; 38: 15-17.

[23] Chen SCC, Yeh JJ, Chang MH, et al. Gender difference of alanine aminotransferase elevation may be associated with higher hemoglobin levels among Male Adolescents. PLoS ONE. 2010; 5: e13269.

[24] Fan JG, Peng YD. Metabolic syndrome and non-alcoholic fatty liver disease: A sia definitions and Asian studies. Hepatobiliary Pancreat Dis Int. 2007; 6: 572-578. PMid:18086620.

[25] Vozarova B, Stefan N, Lindsay RS, et al. High alanine aminotransferase is associated with decrease hepatic insulin sensitivity and predicts the development of type 2 diabetes. Diabetes. 2002; 51: 1889-1895. https://doi.org/10.2337/diabetes.51.6.1889

[26] Bruckert E, Giral P, Ratziu V, et al. A constellation of cardiovascular risk factors is associated with hepatic enzyme elevation in hyperlipidemic patients. Metabolism. 2002; 51: 1071-1076. https://doi.org/10.1053/meta.2002.34046

[27] Ruhl CE, Everhart JE. Coffee and caffeine consumption reduce the risk of elevated serum alanine aminotransferase activity in the United States. Gastroenterology. 2005; 128: 24-32. https://doi.org/10.1053/j.gastro.2004.09.075