

# $\gamma$ -Glutamyl Transpeptidase in Men and Alanine Aminotransferase in Women are the Most Suitable Parameters Among Liver Function Tests for the Prediction of Metabolic Syndrome in Nonviral Hepatitis and Nonfatty Liver in the Elderly

Dee Pei\*, Te-Lin Hsia\*, Ting-Ting Chao<sup>1</sup>, Jiunn-Diann Lin<sup>2</sup>, Chun-Hsien Hsu<sup>3</sup>, Chung-Ze Wu<sup>2</sup>, Chang-Hsun Hsieh<sup>4</sup>, Yao-Jen Liang<sup>5</sup>, Yen-Lin Chen<sup>6</sup>

Department of Internal Medicine, Cardinal Tien Hospital, <sup>1</sup>Medical Research Center, Cardinal Tien Hospital, School of Medicine, Fu-Jen Catholic University, <sup>2</sup>Division of Endocrinology and Metabolism, Department of Medicine, Shuang-Ho Hospital, Taipei Medical University, <sup>3</sup>Department of Family Medicine, Cardinal Tien Hospital, School of Medicine, Fu-Jen Catholic University, New Taipei City, Taiwan, <sup>4</sup>Division of Endocrinology and Metabolism, Department of Internal Medicine, Tri-Service General Hospital, National Defense Medical Center, Taipei, Taiwan, ROC, <sup>5</sup>Department of Life-Science, Fu-Jen Catholic University, Taipei, <sup>6</sup>Department of Pathology, Cardinal Tien Hospital, School of Medicine, Fu-Jen Catholic University, New Taipei City, Taiwan

\*These authors contributed equally to this article

## Address for correspondence:

Dr. Yen-Lin Chen,  
Department of Pathology,  
Cardinal Tien Hospital,  
No. 362, Zhongzheng Road,  
Xindian District, New Taipei  
City 231, Taiwan.  
E-mail: anthonypatho@gmail.com

## ABSTRACT

**Background/Aims:** Nonalcoholic fatty liver disease (NAFLD) has been reported as a hepatic manifestation of metabolic syndrome (MetS); it is common and accounts for 80% of the cases with abnormal liver function tests (LFTs). In addition, several studies have proved that there is a correlation between abnormal LFTs and MetS. Therefore, LFTs may represent the abnormal metabolic status of livers in the patients with MetS. To identify the early state of metabolic dysfunction, we investigate the value of LFTs for the future MetS development in the relatively healthy (non-NAFLD) elderly. **Patients and Methods:** A total of 16,912 subjects met the criteria for analysis. In the first stage of this study, subjects were enrolled in the cross-sectional study in order to find out the optimal cutoff value in different LFTs with higher chances to have MetS. In the second stage of the present study, subjects with MetS at baseline were excluded from the same study group, and a median 5.6-year longitudinal study was conducted on the rest of the group. **Results:** Among all LFTs, only aspartate aminotransferase in both genders and the  $\alpha$ -fetal protein in women failed to show the significance in distinguishing subjects with MetS by the receiver operating characteristic curve. In the Kaplan-Meier plot, only  $\gamma$ -glutamyl transpeptidase ( $\gamma$ -GT) in men and the alanine aminotransferase (ALT) in women could be used to successfully separate subjects with higher risk of developing the MetS from those with lower risk. Finally, in the multivariate Cox regression model, similar results were identified. Still, the hazard ratio (HR) to have future MetS,  $\gamma$ -GT in men, and ALT in women showed significance (HR = 1.511 in men and 1.504 in women). **Conclusion:** Among all the different LFTs,  $\gamma$ -GT (>16 U/L) in male and ALT (>21 U/L) in female were the best predictors for the development of MetS in healthy elderly. These two liver markers could be an ancillary test in predicting future MetS development/diagnosis. Elevation of the LFTs without underlying liver diseases should be treated as a warning sign of the possible MetS development in the elderly.

**Key Words:** Alanine aminotransferase, elderly, liver function tests, metabolic syndrome,  $\gamma$ -glutamyl transpeptidase

Received: 23.08.2014, Accepted: 09.12.2014

**How to cite this article:** Pei D, Hsia TL, Chao TT, Lin JD, Hsu CH, Wu CZ, *et al.*  $\gamma$ -glutamyl transpeptidase in men and alanine aminotransferase in women are the most suitable parameters among liver function tests for the prediction of metabolic syndrome in nonviral hepatitis and nonfatty liver in the elderly. Saudi J Gastroenterol 2015;21:158-64.

Access this article online	
Quick Response Code: 	Website: <a href="http://www.saudijgastro.com">www.saudijgastro.com</a>
	DOI: 10.4103/1319-3767.157564

Cardiovascular disease (CVD) is one of the main threats to human health that affects quality of life. Therefore, early detection of high-risk subjects becomes an important issue. It is clearly stated that people with metabolic syndrome (MetS) have higher risk for future development of CVD. MetS represents a group of metabolic abnormalities, including impaired glucose tolerance, central obesity, elevated blood

pressure, and dyslipidemia. These components are the core of MetS and are called “traditional factors.” However, there are many others called “nontraditional factors” associated with MetS, including the liver status. Not only nonalcoholic fatty liver disease (NAFLD) but also liver function tests (LFTs) have been found to be frequently associated with MetS in many studies.<sup>[1-6]</sup> NAFLD has been reported as a hepatic manifestation of MetS, and it accounts for 80% of the cases with abnormal LFTs.<sup>[7]</sup> Although NAFLD is not included in the definition of MetS, there is evidence showing that abnormal LFTs are related to the worsening of insulin resistance and the development of hypertension, which are all components of MetS. Therefore, it is logical to regard the liver as another main target organ to reflect metabolic dysfunction.

Among different LFTs, the association of alanine aminotransferase (ALT) with the risk of MetS development is determined in studies in Caucasian and Australian populations.<sup>[8,9]</sup> Both of them supported the positive correlation between ALT elevation and MetS. In addition, other studies stated that ALT and  $\gamma$ -glutamyl transpeptidase ( $\gamma$ -GT) were correlated with most MetS components.<sup>[10-12]</sup>  $\gamma$ -GT is an enzyme participating in catalyzing glutathione breakdown, and excessive environmental oxidative stress may elevate  $\gamma$ -GT concentration, which in turn may cause the development of MetS.<sup>[13,14]</sup> Based on these reports, it is assumed that LFTs may be an indicator of the abnormal status of the liver in patients with MetS. The present study discusses whether LFTs could be a good future MetS predictor in subjects without NAFLD so that metabolic dysfunction can be detected early. In addition, aging is one of the biggest issues in the world in terms of the cost in health, such as multiple chronic diseases.

Therefore, the aim of the current study is to investigate the value of LFTs for MetS in the relatively healthy elderly with a median of 5.6 years cohort study.

## PATIENTS AND METHODS

### Patients

Subjects recruited in the study were all aged over 60 years who underwent their annual routine health checkup at one of the MJ Health Screening Centers in Taiwan. The MJ Health Screening Centers are private clinics located throughout Taiwan where routine/general health examinations are conducted for their members. The study protocol was approved by the institutional review board of the MJ Health Screening Centers and informed consents were signed by each participating subject. Originally, 27,679 subjects were randomly selected from the pool of people, with records at the center, between 1999 and 2007. The following exclusion steps were performed in order to fit the present study criteria.

- 1,121 subjects were excluded due to missing data of MetS components, LFTs, hepatitis B core antibody, hepatitis B surface antigen, or hepatitis C virus antibody
- 4,785 subjects were excluded due to chronic hepatitis B or C infection
- 4,852 were excluded due to a history of alcohol consumption more than 20 grams per day in men and 10 grams per day in women
- People diagnosed with liver fibrosis, cirrhosis, acute hepatitis, autoimmune hepatitis, primary biliary cirrhosis, metabolic liver diseases, and/or NAFLD were also excluded from this study. The exclusion was based on both past history and liver sonogram results.

Finally, 16,912 subjects were eligible for the analysis in the first part, the cross-sectional study. They were further divided into two groups, one with 7,639 subjects who had a history, and the other 9,282 subjects who hadn't had a history of diabetes, hypertension, hyperlipidemia, CVD, and taking medications for above diseases or medications known to affect the components of MetS. The purpose of the separation was to identify the newly diagnosed MetS subjects at the time of their first visit in health checkup clinics, and to further study the true relationships between MetS and LFTs. In the second part of the study, 7,958 subjects from the 9,282 subjects without any past history and/or taking medications, were MetS free at baseline, were followed-up for a median of 5.6 years, which was the second part of the study—a longitudinal study. The shortest and longest followup period was a year and 10 years, respectively.

### Data collection

Each participant who underwent the health exam was followed up each year afterwards. However, some subjects missed their annual examination and the laboratory data for that year were lost. The missing data was for less than 1% of the total participants in this study. Participants visited the clinic at 8 am after at least a 10-h fast. Information regarding medical history, lifestyle, alcohol intake, smoking, and physical exercise was obtained through an interview with the senior nursing staff. A complete physical examination was conducted, and the waist circumference (WC) was taken at the midpoint between the inferior margin of the last rib and the crest of the ilium, in a horizontal plane. Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured by the nursing staff using a computerized auto-mercury sphygmomanometer on the right arm of the participants, who had rested for 5 min in a sitting position before the measurement was taken. A venous blood sample was collected for the following biochemistry study. Plasma was separated from the blood within 1 h and was stored at a temperature of  $-30^{\circ}\text{C}$  and analyzed for fasting plasma glucose (FPG) and lipid profiles. The FPG was detected using a glucose oxidase method (YSI 203 glucose analyzer,

Scientific Division, Yellow Springs Instruments, Yellow Springs, OH, USA). Total cholesterol and triglycerides (TG) were measured using the dry, multilayer analytical slide method in the Fuji Dri-Chem 3000 analyzer (Fuji Photo Film, Minato-Ku, Tokyo, Japan). Serum high-density lipoprotein cholesterol (HDL-C) concentration was analyzed using an enzymatic cholesterol assay following dextran sulfate precipitation. Aspartate aminotransferase and alanine aminotransferase were analyzed by UV with P5P method (ARCHITECT c System, Abbott, USA). Hepatitis C antibody, hepatitis B surface antigen, and hepatitis B core antibody were analyzed by chemiluminescent microparticle immunoassay (ARCHITECT i System, Abbott, USA). LFTs including  $\gamma$ -GT, direct bilirubin (D-Bil), total bilirubin (T-Bil), ALT, aspartate aminotransferase (AST),  $\alpha$ -fetal protein (AFP), and alkaline phosphatase (ALP) were analyzed using CX7 biochemistry analyzer (Beckman, Fullerton, CA, USA).

### Liver sonogram

An abdominal sonogram was performed and the results were interpreted for every participant by two well-experienced radiologists using a high-resolution B-mode scanner (SSA-240A, Toshiba Corporation, Tokyo, Japan). The radiologists met regularly to discuss all the radiologic results to reduce the reader bias. The normal liver echogenicity was labeled as “0” and the increasing echogenicity was labeled as “1” based on liver–kidney echo discrepancy and loss of echoes from the walls of the portal veins.<sup>[15]</sup> Liver cyst, mass, or cirrhosis was all excluded by the radiologists.

### Definition of metabolic syndrome

The latest harmonized criteria of MetS in 2009<sup>[16]</sup> was used, with some modifications. The WC was  $\geq 90$  and 80 cm for Taiwanese males and females, respectively.<sup>[17]</sup> Other four criteria remained the same: SBP  $\geq 130$  mmHg or DBP  $\geq 85$  mmHg, TG  $\geq 150$  mg/dL, FPG  $\geq 100$  mg/dL, HDL  $\leq 40$  and 50 mg/dL for males and females, respectively, or intake of related medications. Subjects had to meet at least three criteria to be diagnosed with MetS. The subjects at this time included the people who were newly diagnosed with MetS and the ones with past history and/or taking medications as well. Therefore, those with a past history of MetS related disease including diabetes, hypertension, hyperlipidemia, and CVD were separated from the group and formed another group. In the follow-up period, the definition of MetS completely followed the latest harmonized criteria of MetS in 2009.<sup>[16]</sup>

### Statistical analysis

The data were analyzed with SPSS version 18.0 (SPSS, Chicago, IL, USA). The study design of the present study consisted of two parts. The first part was a cross-sectional

study, and the purpose was to find out the optimal cutoff value in different LFTs to predict future MetS. All data were tested for normal distribution with the Kolmogorov–Smirnov test and for homogeneity of variances with the Levene’s test. Continuous variables were expressed as mean  $\pm$  SEM. The *t* test was used to evaluate the differences between the two groups. The ANOVA with Bonferroni *post hoc* analysis were applied in the three groups comparison. The optimal cutoff value was calculated by receiver operating characteristic (ROC) curves of each LFTs. The area under the curve (AUC) and 95% confidence interval were also estimated and compared. In the second part of the study, a longitudinal study, Kaplan–Meier plot and log rank test were adopted to see whether the cutoff value of LFTs from ROC curves could distinguish subjects with higher risk of MetS. Finally, Cox regression was performed to see the hazard ratio (HR) developing MetS during the follow-up period. All statistical tests were two sided and considered statistically significant when  $P < 0.05$ .

## RESULTS

In the first part, the cross-sectional study, a total of 16,912 elderly were recruited. Table 1 shows the demographic data of the study population with and without MetS. In addition, they were further divided into two groups—with and without past history and/or taking medications. Among all LFTs in the subjects without past history and taking medications, AST and AFP failed to show the differences between the subjects with and without MetS in both genders. Additionally, D-Bil in the men showed a nonsignificant result. However, among the subjects with past history and/or taking medications, only AFP in both genders failed to show the significant difference between the subjects with and without MetS. In ROC curve, the ability of each LFT to distinguish MetS is quite different. AST in both sexes and AFP in women who had no past history and/or taking medications failed to show the significance in distinguishing the subjects with MetS from the ones without [Table 2]. Moreover, only AFP in men with past history and/or taking medications failed to show the significance in separating the subjects with MetS from the ones without MetS. In the second part of the study, we excluded the subjects with MetS at baseline and those who had a past history and/or taking medications related to MetS. There were 7,958 subjects without MetS at baseline, and without past history or taking medications. They were then followed for a median of 5.6 years. In the Kaplan–Meier plot, only  $\gamma$ -GT in men and ALT in women successfully helped identify the subjects with higher risk of developing MetS [Figure 1]. Finally, in the multivariate Cox regression model, similar results were identified. Still,  $\gamma$ -GT in men and ALT in women showed significantly higher chances to develop MetS (HR = 1.511 in men and 1.504 in women) [Table 3].

**Table 1: Demographic data of study subjects with and without metabolic syndrome**

	Without past history and/or medication			P	With past history and/or medication		
	MetS (-)		MetS (+)		MetS (-)	MetS (+)	P
	MetS no. =0	MetS no. =1 and 2	MetS no. ≥3		MetS no. <3	MetS no. ≥3	
<b>Male</b>							
<i>n</i>	1064	2688	504		1365	2310	
Age (years)	65.5±5.4	66.3±5.9*	66.6±6.1*	<0.001	68.2±6.1	68.0±6.0	0.216
Body mass index (kg/m <sup>2</sup> )	21.3±2.4	22.3±2.4*	24.1±2.5**	<0.001	22.7±78.9	26.4±2.9	<0.001
Waist circumference (cm)	76.9±6.9	79.9±7.1*	86.7±7.4**	<0.001	84.7±7.2	92.7±7.7	<0.001
Systolic blood pressure (mmHg)	113.5±10.2	130.2±18.4*	138.8±17.6**	<0.001	138.5±20.2	141.2±19.0	<0.001
Diastolic blood pressure (mmHg)	67.8±7.4	75.5±10.8*	80.0±10.8**	<0.001	78.8±12.3	79.8±11.7	<0.001
Fasting plasma glucose (mg/dl)	92.2±5.2	101.9±16.1*	107.9±20.7**	<0.001	114.4±36.1	124.9±38.7	<0.001
High density lipoprotein (mg/dl)	58.5±12.9	53.5±14.2*	41.2±10.9**	<0.001	52.5±12.2	40.7±13.0	<0.001
Triglyceride (mg/dl)	82.5±27.2	101.7±46.2*	164.2±66.3**	<0.001	110.4±49.1	193.0±109.9	<0.001
γ-Glutamyl transpeptidase (U/L)	19.5±14.6	22.8±23.0*	28.5±32.7**	<0.001	27.7±22.6	35.3±28.7	<0.001
Direct bilirubin (mg/dl)	0.2±0.1	0.2±0.3	0.2±0.1**	0.149	0.2±0.1	0.2±0.1	<0.001
Total bilirubin (mg/dl)	0.9±0.3	0.9±0.5	0.8±0.4**	0.007	0.9±0.3	0.9±0.3	<0.001
Alanine aminotransferase (U/L)	21.9±19.4	22.9±17.2	25.4±23.1**	0.002	25.6±14.5	31.5±19.5	<0.001
Aspartate aminotransferase (U/L)	24.9±11.1	24.7±13.0	24.9±13.5	0.934	24.7±9.2	26.9±12.1	<0.001
α-fetal protein (ng/ml)	3.4±1.5	3.9±21.3	3.6±1.7	0.675	3.5±3.5	3.5±3.3	0.533
Alkaline phosphatase (U/L)	133.2±58.2	132.3±60.2	140.6±65.4†	0.018	106.4±53.6	112.7±55.1	<0.001
<b>Female</b>							
<i>n</i>	1106	3100	820		1112	2852	
Age (years)	63.1±3.8	64.8±5.1*	66.8±6.2**	<0.001	66.6±5.4	67.4±5.6	<0.001
Body mass index (kg/m <sup>2</sup> )	21.5±2.3	22.3±2.7*	23.9±2.8**	<0.001	24.2±3.0	26.2±36.4	<0.001
Waist circumference (cm)	70.7±4.8	73.5±6.4*	79.8±7.4**	<0.001	77.4±7.2	85.1±8.5	<0.001
Systolic blood pressure (mmHg)	113.8±10.1	131.8±18.5*	141.9±18.2**	<0.001	141.6±20.6	145.4±19.4	<0.001
Diastolic blood pressure (mmHg)	65.9±7.5	73.8±10.8*	78.2±10.4**	<0.001	77.7±11.6	79.1±11.6	<0.001
Fasting plasma glucose (mg/dl)	92.1±5.1	99.5±13.3*	105.0±18.4**	<0.001	110.6±35.7	127.7±43.1	<0.001
High density lipoprotein (mg/dl)	70.4±14.5	64.4±15.6*	49.5±12.4**	<0.001	62.9±12.5	48.8±15.0	<0.001
Triglyceride (mg/dl)	82.9±26.4	102.5±44.3*	158.1±66.6**	<0.001	111.4±42.7	188.2±102.4	<0.001
γ-Glutamyl transpeptidase (U/L)	17.9±23.3	18.0±15.8	21.2±27.1**	<0.001	22.8±18.5	29.8±25.0	<0.001
Direct bilirubin (mg/dl)	0.2±0.1	0.2±0.1	0.2±0.1**	0.001	0.2±0.1	0.2±0.1	<0.001
Total bilirubin (mg/dl)	0.8±0.3	0.8±0.3	0.7±0.3**	<0.001	0.8±0.3	0.7±0.3	<0.001
Alanine aminotransferase (U/L)	20.0±14.0	20.2±13.0	21.2±16.8	0.005	24.9±16.3	29.1±19.5	<0.001
Aspartate aminotransferase (U/L)	24.0±9.0	24.0±9.9	24.0±11.3	0.999	25.2±11.4	27.1±14.3	<0.001
α-fetal protein (ng/ml)	3.3±1.9	3.3±3.5	3.2±1.7	0.815	3.4±4.5	3.5±2.2	0.511
Alkaline phosphatase (U/L)	121.6±62.7	135.2±62.1*	153.7±70.5**	<0.001	114.1±58.3	125.0±61.2	<0.001

Data are shown as mean±SEM. ANOVA was applied in the “Without past history and/or medication” group. *t*-test was applied in the “With past history and/or medication” group. \**P* value<0.05 when compared with the “MetS No.=0” group. †*P* < 0.05 when compared with the “MetS No.=1 and 2” group

## DISCUSSION

In the current study, the results showed that γ-GT and ALT were the best predictors for future MetS among different LFTs in relatively healthy elderly men and women. Although the AUC of these liver markers were not good enough, it should be pointed out that the participants in the study were healthier than the usual study population. Therefore, we lost the extreme end of the data value to provide higher AUC in the prediction of MetS. In other words, the power to the markers might be more promising in the general population. Due to the endemic area of viral hepatitis, especially hepatitis B, in Taiwan, LFTs usually were included in the annual health checkup program. This was another advantage for the

primary care physicians to have the ancillary test information to predict future MetS development.

There were several studies that looked into the relationship between MetS and γ-GT.<sup>[18-24]</sup> An Asian study’s results showed that a high level of γ-GT was found to be positively associated with clustered components of MetS in both adult men and women after adjusting for age, body mass index, history of alcoholic fatty liver, and the presence of taking antihypertensive, antidiabetic, and antidiabetic drugs.<sup>[25]</sup> They also reported that the optimal cutoff value of γ-GT for men and women was 31.50 U/L and 19.50 U/L, respectively. The results in this study showed similar findings— the optimal cutoff value of γ-GT was lower in

**Table 2: Optimal cut-off value in each liver function test in predicting metabolic syndrome**

	Without past history and/or medication					With past history and/or medication				
	Area under curve	Cut-off value	Sen	Spe	P	Area under curve	Cut-off value	Sen	Spe	P value
<b>Male</b>										
r-GT (U/L)	0.597±0.014	>16	64.9	48.8	<0.001	0.646±0.013	>22	62.5	58.7	<0.001
Dbil (mg/dl)	0.567±0.013	<0.22	62.5	48.2	<0.001	0.548±0.012	<0.17	40.5	66.9	<0.001
Tbil (mg/dl)	0.561±0.013	<0.90	65.5	44.3	<0.001	0.540±0.013	<0.77	46.3	59.8	<0.001
ALT (U/L)	0.554±0.014	>22	41.7	67	<0.001	0.628±0.013	>26	48.8	70.6	<0.001
AST (U/L)	0.524±0.014	<21	37.7	68.7	0.077	0.549±0.014	>26	36.9	72.0	<0.001
AFP (ng/ml)	0.532±0.014	>2.5	73.6	32.3	0.020	0.518±0.012	>2.6	68.0	36.1	0.001
ALP (U/L)	0.534±0.014	>91	77	30.8	0.014	0.506±0.014	<108	51.9	50.1	0.227
<b>Female</b>										
r-GT (U/L)	0.561±0.011	>15	46.6	61.8	<0.001	0.657±0.011	>18	63.3	60.1	<0.001
Dbil (mg/dl)	0.551±0.011	<0.13	33.5	76	<0.001	0.544±0.011	<0.14	46.2	60.6	<0.001
Tbil (mg/dl)	0.567±0.011	<0.76	60.2	50.2	<0.001	0.556±0.012	<0.6	35.4	72.6	<0.001
ALT (U/L)	0.509±0.011	>21	29.1	73.8	0.044	0.612±0.011	>21	55.7	61.1	<0.001
AST (U/L)	0.522±0.011	<23	57.7	47.6	0.439	0.533±0.011	>29	24.2	84.3	<0.001
AFP (ng/ml)	0.502±0.011	>1.7	90	11.3	0.854	0.537±0.012	>2.3	76.7	30.3	<0.001
ALP (U/L)	0.601±0.011	>145	56.2	60.1	<0.001	0.528±0.011	>190	18.0	86.6	<0.001

Sen: Sensitivity, Spe: Specificity, rGT:  $\gamma$ -glutamyl transpeptidase, Dbil: Direct bilirubin, Tbil: Total bilirubin, ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, AFP:  $\alpha$ -fetal protein, ALP: Alkaline phosphatase

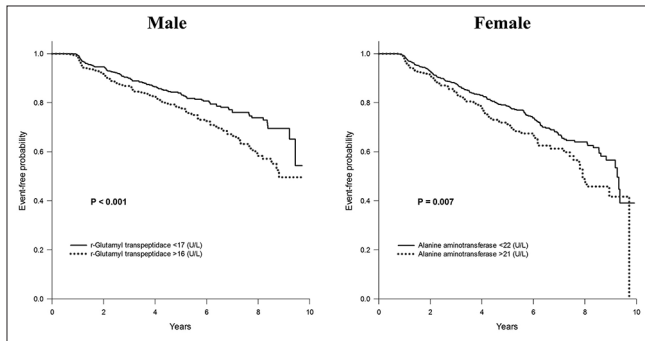
**Table 3: Hazard ratio and area under curve of each liver function test developing metabolic syndrome in follow-up period**

	Hazard ratio	P	AUC	Sensitivity	Specificity
<b>Male</b>					
$\gamma$ -Glutamyl transpeptidase >16 (U/L)	1.511 (1.160-1.968)	0.002	0.555	54.8	53.3
Direct bilirubin <0.22 (mg/dl)	1.182 (0.852-1.641)	0.317	0.517	61.1	43.2
Total bilirubin <0.90 (mg/dl)	1.047 (0.751-1.459)	0.787	0.522	62.3	42.3
Alanine aminotransferase >22 (U/L)	1.149 (0.862-1.531)	0.345	0.554	38.5	65.9
Aspartate aminotransferase <21 (U/L)	1.271 (0.954-1.693)	0.102	0.530	44.1	60.4
$\alpha$ -fetal protein >2.5 (ng/ml)	0.822 (0.632-1.070)	0.145	0.520	35.7	67.4
Alkaline phosphatase >91 (U/L)	0.919 (0.623-1.356)	0.671	0.577	87.3	24.4
<b>Female</b>					
$\gamma$ -Glutamyl transpeptidase >15 (U/L)	0.994 (0.781-1.265)	0.962	0.497	65.5	37.8
Direct bilirubin <0.13 (mg/dl)	1.042 (0.785-1.384)	0.775	0.512	31.5	70.0
Total bilirubin <0.76 (mg/dl)	0.927 (0.727-1.181)	0.54	0.513	58.6	44.7
Alanine aminotransferase >21 (U/L)	1.504 (1.129-2.003)	0.005	0.535	31.2	75.2
Aspartate aminotransferase <23 (U/L)	1.204 (0.932-1.556)	0.154	0.515	59.8	39.4
$\alpha$ -fetal protein >1.7 (ng/ml)	1.023 (0.737-1.421)	0.893	0.523	12.3	87.2
Alkaline phosphatase >145 (U/L)	1.085 (0.870-1.353)	0.471	0.586	57.4	56.1

AUC: Area under curve

women. The results in this study were congruent with that in the study done by Lee *et al.*<sup>[26]</sup> Their results indicated that the  $\gamma$ -GT value in determining MetS was higher in males than that in female adolescents. Although the exact underlining mechanisms were not determined definitely, Haring *et al.*<sup>[27]</sup> found that the testosterone (total and free form), human sex hormone-binding globulin, and dehydroepiandrosterone concentrations were inversely associated with the change in  $\gamma$ -GT after multivariable adjustment. This might partially explain the reason why the optimal cutoff value of  $\gamma$ -GT was higher in male than that in women. Moreover, it was

interesting that the optimal cutoff value of  $\gamma$ -GT reported by Tao *et al.*<sup>[25]</sup> was higher than what was found in this study. Still, the exact underlining mechanisms were not well known but there were two possible explanations. First, the inclusion criteria in the present study were stricter. The subjects on medication would affect the components on MetS, alcoholic hepatitis, viral hepatitis, and NAFLD and therefore were all excluded in the present study. This might reduce the prediction power in the present studies and make the optimal cutoff value lower. Second, the study population was different. Only elderly were recruited in the current study,



**Figure 1:** Kaplan–Meier plot of developing metabolic syndrome in the follow-up periods by each liver function tests' cutoff points. The *P* values of  $\gamma$ -glutamyl transpeptidase, direct bilirubin, total bilirubin, alanine aminotransferase, aspartate aminotransferase,  $\alpha$ -fetoprotein, and alkaline phosphatase are <math><0.001</math>, 0.080, 0.193, 0.168, 0.296, 0.489, and 0.380 in male, and 0.467, 0.090, 0.514, 0.007, 0.905, 0.765, and 0.338 in female, accordingly

while all adults were studied by Tao *et al.*<sup>[25]</sup> Different age groups could affect the results and it was supported by the study conducted by Bradley *et al.*,<sup>[28]</sup> which indicated that age was an important factor correlated with  $\gamma$ -GT. They reported that the associations between  $\gamma$ -GT and MetS weakened with age.

ALT was the first enzyme among different LFTs with MetS. As early as 2004, Hanley *et al.*<sup>[3]</sup> had completed a study focusing on the relationship between ALT and MetS. The results were similar to what has been found in the present study. In addition, ALT was associated with MetS independently of insulin resistance.<sup>[29]</sup> Results of a recent meta-analysis study have proved that there was a linear dose–response relationship between ALT and MetS.<sup>[30]</sup> Of the 489 studies reviewed, relevant data were available on 29,815 nonoverlapping participants, comprising 2,125 incident MetS events from five prospective cohort studies. The risk of MetS increased by 14% for every 5 U/L increment in circulating ALT level (95% CI: 12%–17%). Another meta-analysis study has drawn a similar conclusion from seven prospective cohort studies, with 31,545 participants and 2,873 cases of incident MetS.<sup>[31]</sup> Our results showed that ALT could be a MetS predictor only in women but not in men. Although the underlying mechanisms were not clearly known, one possible factor would be that people with NAFLD were excluded in the current study. Results of previous studies done by Hsu, *et al.* showed that both ALT and abnormal liver echogenicity were related to a higher prevalence of MetS among older Taiwanese men. Of these two abnormalities, abnormal liver echogenicity seemed to be more closely related to MetS.<sup>[2]</sup> Xia *et al.*<sup>[10]</sup> showed the ROC curve analysis revealed the optimal cutoff value for AST to identify that MetS was 25 U/L in men, and 23 U/L in women. These values were much more effective in detecting patients with potential MetS and NAFLD than the traditional cutoff

values. Therefore, ALT is still a good predictor of MetS in women as long as NAFLD does not occur.

The major strength of this study is that this is the first longitudinal study to explore the correlation between LFTs and MetS in the elderly. In addition, this is a relatively large cohort study in the elderly. However, there are several limitations in the current study. First, the subjects were recruited from one private health screening center. Thus, they had better economic status with more medical support, and might not represent the conditions of the general population in Taiwan. Second, the central feature of MetS was insulin resistance, which was not measured in this study. Third, there was no biopsy data collected to support the liver status of the subjects in the study. However, all participants received the liver sonogram to have the indirect evidence of their healthy liver status. In addition, ALT measurement might underestimate the presence of NAFLD. Nevertheless, the aim of this study was to explore the relationship between LFTs and MetS. The underestimation of NAFLD would have very limited impact on the relationship discussed. Fourth, the sensitivity and specificity of the most related LFTs were not good enough in predicting future MetS, and the clinical utility would be low. However, the main purpose of the current study was to shed light on the relationship between LFTs and MetS. Therefore, the cutoff values of these LFTs possessed potential in a certain degree to be indicators for possible MetS development. Finally, there was no available data for cardiovascular events or all-cause mortality, which might have influenced the interpretation of the results.

In conclusion, among all different LFTs,  $\gamma$ -GT (>16 U/L) in male and ALT (>21 U/L) in female was the best predictor for MetS in healthy elderly. These two liver markers could be an ancillary test to help clinicians know how likely the subjects are, to develop MetS. In other words, elevation of LFTs without underlying liver diseases in the elderly should be treated as an indicator of possible MetS development and the situation should be monitored with caution.

## REFERENCES

1. Zheng JQ, Wang K, Pei D, Chen YL, Chang YL, Hsu CH, *et al.* Improvement of abnormal liver enzymes after rosiglitazone treatment in Chinese type 2 diabetes. *Indian J Pharmacol* 2012;44:372-6.
2. Hsu CH, Wang JY, Chen YL, Liu CC, Chang YL, Chen HS, *et al.* Relationships between alanine aminotransferase levels, abnormal liver echogenicity, and metabolic syndrome. *J Am Board Fam Med* 2011;24:407-14.
3. Hanley AJ, Williams K, Festa A, Wagenknecht LE, D'Agostino RB Jr, *et al.* Liver markers and development of the metabolic syndrome: The insulin resistance atherosclerosis study. *Diabetes* 2005;54:3140-7.
4. Dimitrijevic-Sreckovic V, Soldatovic I, Culafic D, Sreckovic B, Popovic S, Djordjevic P, *et al.* Liver function test changes in centrally obese youth with metabolic syndrome in a Serbian population. *Metab Syndr Relat Disord* 2013;11:427-33.

5. Lee K. Metabolic syndrome predicts the incidence of hepatic steatosis in Koreans. *Obes Res Clin Pract* 2010;4:e163-246.
6. Miyatake N, Matsumoto S, Makino H, Numata T. Comparison of hepatic enzymes between Japanese men with and without metabolic syndrome. *Acta Med Okayama* 2007;61:31-4.
7. Athyros VG, Giouleme O, Ganotakis ES, Elisaf M, Tziomalos K, Vassiliadis T, *et al.* Safety and impact on cardiovascular events of long-term multifactorial treatment in patients with metabolic syndrome and abnormal liver function tests: A post hoc analysis of the randomised ATTEMPT study. *Arch Med Sci* 2011;7:796-805.
8. Olynyk JK, Knuiman MW, Divitini ML, Davis TM, Beilby J, Hung J. Serum alanine aminotransferase, metabolic syndrome, and cardiovascular disease in an Australian population. *Am J Gastroenterol* 2009;104:1715-22.
9. Schindhelm RK, Dekker JM, Nijpels G, Stehouwer CD, Bouter LM, Heine RJ, *et al.* Alanine aminotransferase and the 6-year risk of the metabolic syndrome in Caucasian men and women: The Hoorn Study. *Diabet Med* 2007;24:430-5.
10. Xia MF, Yan HM, Lin HD, Bian H, Pan BS, Yao XZ, *et al.* Elevation of liver enzymes within the normal limits and metabolic syndrome. *Clin Exp Pharmacol Physiol* 2011;38:373-9.
11. Rantala AO, Lilja M, Kauma H, Savolainen MJ, Reunanen A, Kesaniemi YA. Gamma-glutamyl transpeptidase and the metabolic syndrome. *J Intern Med* 2000;248:230-8.
12. Sakugawa H, Nakayoshi T, Kobashigawa K, Nakasone H, Kawakami Y, Yamashiro T, *et al.* Metabolic syndrome is directly associated with gamma glutamyl transpeptidase elevation in Japanese women. *World J Gastroenterol* 2004;10:1052-5.
13. Yokoyama H. Gamma glutamyl transpeptidase (gammaGTP) in the era of metabolic syndrome. *Nihon Arukoru Yakubutsu Igakkai Zasshi* 2007;42:110-24.
14. Lee JH, Um MH, Park YK. The Association of Metabolic Syndrome and Serum gamma-Glutamyl Transpeptidase: A 4-Year Cohort Study of 3,698 Korean Male Workers. *Clin Nutr Res* 2013;2:67-75.
15. Saverymuttu SH, Joseph AE, Maxwell JD. Ultrasound scanning in the detection of hepatic fibrosis and steatosis. *Br Med J (Clin Res Ed)* 1986;292:13-5.
16. Alberti KG, Eckel RH, Grundy SM, Zimmet PZ, Cleeman JI, Donato KA, *et al.* Harmonizing the metabolic syndrome: A joint interim statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity. *Circulation* 2009;120:1640-5.
17. Walsh PC. Variation in course of cavernous nerve with special reference to details of topographic relationships near prostatic apex: Histologic study using male cadavers. *J Urol* 2005;174:567.
18. Liu CF, Zhou WN, Fang NY. Gamma-glutamyltransferase levels and risk of metabolic syndrome: A meta-analysis of prospective cohort studies. *Int J Clin Pract* 2012;66:692-8.
19. Demir B, Temizhan A, Keskin G, Baser K, Turak O, Cay S. Comparison of serum gamma-glutamyltransferase levels between patients with cardiac syndrome X and healthy asymptomatic individuals. *Kardiol Pol* 2012;70:31-7.
20. Bian AL, Wang XF. Relationship between serum gamma-glutamyltransferase and the risk of metabolic syndrome. *Zhonghua Liu Xing Bing Xue Za Zhi* 2011;32:625-8.
21. Kawamoto R, Tabara Y, Kohara K, Miki T, Kusunoki T, Takayama S, *et al.* High-sensitivity C-reactive protein and gamma-glutamyl transferase levels are synergistically associated with metabolic syndrome in community-dwelling persons. *Cardiovasc Diabetol* 2010;9:87.
22. Kang YH, Min HK, Son SM, Kim IJ, Kim YK. The association of serum gamma glutamyltransferase with components of the metabolic syndrome in the Korean adults. *Diabetes Res Clin Pract* 2007;77:306-13.
23. Pandeya SN, Kumar A, Singh BN, Mishra DN. Synthesis and biological activity of isodithiobiurets, dithiobiurets, and dithiazoles. *Pharm Res* 1987;4:321-6.
24. Tariq M, Parmar NS, Ageel AM. Gastric and duodenal antiulcer and cytoprotective effects of proglumide in rats. *J Pharmacol Exp Ther* 1987;241:602-7.
25. Tao L, Li X, Zhu H, Gao Y, Luo Y, Wang W, *et al.* Association between gamma-glutamyl transferase and metabolic syndrome: A cross-sectional study of an adult population in Beijing. *Int J Environ Res Public Health* 2013;10:5523-40.
26. Lee K, Yang JH. Which liver enzymes are better indicators of metabolic syndrome in adolescents: The Fifth Korea National Health and Nutrition Examination Survey, 2010. *Metab Syndr Relat Disord* 2013;11:229-35.
27. Haring R, Baumeister SE, Volzke H, Dorr M, Kocher T, Nauck M, *et al.* Prospective inverse associations of sex hormone concentrations in men with biomarkers of inflammation and oxidative stress. *J Androl* 2012;33:944-50.
28. Bradley R, Fitzpatrick AL, Jenny NS, Lee DH, Jacobs DR Jr. Associations between total serum GGT activity and metabolic risk: MESA. *Biomark Med* 2013;7:709-21.
29. Katsiki N, Mikhailidis DP, Athyros VG, Karagiannis A. Alanine aminotransferase is associated with metabolic syndrome independently of insulin resistance. *Circulation J* 2011;75:2027.
30. Kunutsor SK, Seddoh D. Alanine aminotransferase and risk of the metabolic syndrome: A linear dose-response relationship. *PLoS One* 2014;9:e96068.
31. Liu Z, Que S, Ning H, Wang L, Peng T. Elevated alanine aminotransferase is strongly associated with incident metabolic syndrome: A meta-analysis of prospective studies. *PLoS One* 2013;8:e80596.

**Source of Support:** This study was funded by the grant from Cardinal Tien Hospital No.CTH-102-1-2A23 and CTH-103-1-2A10.,  
**Conflict of Interest:** None declared.