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Elevation of liver enzymes within the normal limits and metabolic syndrome

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SUMMARY

1. Metabolic syndrome is frequently associated with elevated liver enzymes. However, the current 'normal' limits for liver enzymes often fail to identify patients with metabolic syndrome and the associated non-alcoholic fatty liver disease (NAFLD).

2. In the present study, 1503 participants, aged between 18 and 95 years, were recruited from the physical examination centre of Shanghai Zhongshan Hospital and Shanghai Changfeng Community Health Centre. The association between liver enzymes within the 'normal' range and metabolic syndrome was investigated and optimal cut-off values for liver enzymes in metabolic syndrome were determined. We further compared the diagnostic performance of the new cut-off values for liver enzymes in metabolic syndrome and NAFLD with the traditional 'normal' range for liver enzymes.

3. Serum liver enzymes within the traditional 'normal' limits, especially alanine aminotransferase (ALT) and γ-glutamyl transpeptidase (GGT), were correlated with most of components of the metabolic syndrome, as determined by Spearman's partial correlation analysis. Logistic regression analysis revealed that within the 'normal' range of liver enzymes, the frequency of metabolic syndrome was significantly increased in the higher quintile for ALT and GGT compared with the lowest quintile. Receiver operating characteristic curve analysis revealed that the optimal cut-off values for ALT, aspartate aminotransferase and GGT to identify metabolic syndrome were 26, 25 and 29 U/L, respectively, in men and 20, 23 and 21 U/L, respectively, in women. These values were much more effective in detecting patients with potential metabolic syndrome and NAFLD than the traditional cut-off values.

4. A slight elevation of liver enzymes within the 'normal' limits, especially ALT and GGT, indicates the presence of metabolic syndrome and NAFLD. Revision of the current normal limits for liver enzymes is advisable so that patients with potential metabolic disorders can be identified.

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INTRODUCTION

Metabolic syndrome (MS) is defined by a cluster of metabolic disorders including glucose intolerance, insulin resistance, abdominal obesity, atherogenic dyslipidaemia and elevated blood pressure. At present, MS affects approximately 39% adults in the US and 14.8–28.8% of the Asian population.[1,2] Although the prevalence of MS varies according to different diagnostic criteria, it is an important public health concern because of its high and quickly increasing prevalence and because MS significantly increases the risks of cardiovascular diseases (CVD).[3] Recent studies indicate that non-alcoholic fatty liver disease (NAFLD) is a hepatic manifestation of MS and should be considered as one of the disorders making up MS.[4,5] Nearly 90% of NAFLD patients have more than one feature of MS and approximately 36% are diagnosed as having MS,[6] a much higher prevalence than in the general population.[7]

Liver enzymes are the most commonly used serum markers to assess liver function and liver disease.[8] Previous studies have shown that serum γ-glutamyl transpeptidase (GGT) and alanine aminotransferase (ALT) are important predictors for the development of MS.[9,10] However, the current 'normal' limits set for liver enzymes often fail to identify patients with potential hepatic fat infiltration or multiple metabolic disorders, thus underestimating the risks of Type 2 diabetes and CVD. The prevalence of NAFLD diagnosed by liver enzymes also seems lower than that diagnosed using other methods.[11] Recent studies report that higher levels of liver enzymes still within the 'normal' limits reflect the presence of MS.[12,13] In fact, the current range of 'normal' values for hepatic enzymes were determined in blood donors long ago and, it was found later, the so-called 'normal' population included many people with NAFLD.[14] So, doubts remain regarding the current 'normal' limits for liver enzymes. Some have recommended that, in Western countries, the cut-off values for ALT in men and women should be revised to 30 and 19 U/L, respectively, to identify NAFLD.[14]

The aim of the present study was to clarify the association between liver enzymes within 'normal' limits and MS and to determine the optimal cut-off values for liver enzymes for the detection of MS. Furthermore, we compared the sensitivity and specificity of the new liver enzyme cut-off values for the diagnosis of MS and NAFLD with those of traditional liver enzyme cut-off values to determine

whether lowering of the current 'normal' range of liver enzymes would contribute to the early detection of metabolic disorders, such as MS and NAFLD.

METHODS

Subjects

From June 2009 to June 2010, 1774 subjects (800 men and 974 women) who visited the Physical Examination Centre of Shanghai Zhongshan Hospital and Shanghai Changfeng Community Health Service Centre for routine health examinations were asked to participate in the study. Subjects were excluded from the study if they had: (i) a positive test for hepatitis B virus surface antigen (HBsAg) or hepatitis C virus (HCV) antibody or a history of viral hepatitis; (ii) autoimmune chronic hepatitis; (iii) drug-induced liver disease; (iv) another congenital liver disease; (v) excess alcoholic intake (≥ 20 g/day for men and ≥ 10 g/day for women);[15] (vi) been using a hepatic protectant; (vii) cancer; and (viii) been using an insulin secretagogue or sensitizer. Thus, of the original 1774 subjects, 1503 were eligible for inclusion (634 men and 869 women; age range 18–95 years). Of these, 237 agreed to undergo [^{1}H]-magnetic resonance spectroscopy (MRS) hepatic fat quantification.

The present study was approved by the Ethics Committee of Zhongshan Hospital, Shanghai. Written informed consent was obtained from all participants.

Anthropometric measurements

Information regarding medical history, current medication, family history, alcohol intake and smoking status was obtained by interview. The questionnaire regarding alcohol intake included items about the type of alcohol beverage consumed, the frequency of alcohol consumption on a weekly basis and the usual amount of alcohol consumed daily. Weekly alcohol intake was calculated and then converted to daily alcohol consumption. Subjects were classified as non-drinkers or current or excessive drinkers when they consumed no alcohol or averaged < 140 g/week for men (70 g/week for women) or > 140 g/week for men (70 g/week for women), respectively.[15] Smoking status was defined as non-smoker or smoker (former or current). Height and weight were determined in subjects wearing light clothing and no shoes. The body mass index (BMI) was calculated as weight (kg) divided by height squared (m^2). Waist circumference was measured using a soft tape midway between the lowest rib and the iliac crest in standing subjects. Blood pressure was measured on the right arm in seated subjects after a 5 min rest.

Biochemical analysis

Biochemical tests to determined serum levels of ALT, aspartate aminotransferase (AST) and GGT, the serum lipid profile and fasting plasma glucose (FPG) levels were performed using an autoanalyser (Hitachi 7300; Hitachi, Tokyo, Japan). Reference ranges for ALT and AST were 5–40 and 8–40 IU/L, respectively; For GGT, the reference ranges were 11–50 IU/L in men and 7–32 IU/L in women. Tests evaluating the presence of HBsAg and HCV markers were performed by enhanced electrochemiluminescence.

Measurement of hepatic triglyceride content using [^{1}H]-MRS

Hepatic triglyceride was determined in 237 (125 men and 112 women) of 1503 participants using [^{1}H]-MRS and a 1.5 T magnetic resonance scanner (Siemens Avanto, Erlangen, Germany) equipped for proton spectroscopy acquisitions by a radiologist (X-ZY or R-KL). Signal intensities of the water peak at 4.8 p.p.m. (Sw) and the fat peak at 1.4 p.p.m. (Sf) were measured and hepatic fat percentage was calculated using the formula $100 \times Sf/(Sf + Sw)$, as described previously.[16] The normal upper limit for hepatic triglyceride content by [^{1}H]-MRS was determined to be 5.56%.[17,18]

Definition of MS

In the present study, MS was defined according to the 2005 International Diabetes Federation criteria.[19] The criteria for MS were central obesity (waist circumference ≥ 90 cm in men and ≥ 80 cm in women) plus two or more of following: (i) raised triglyceride levels (≥ 1.7 mmol/L) or specific treatment for this lipid abnormality; (ii) reduced high-density lipoprotein–cholesterol (HDL-C; < 1.03 mmol/L (40 mg/dL) in men and < 1.29 mmol/L (50 mg/dL) in women) or specific treatment for this lipid abnormality; (iii) increased blood pressure (systolic blood pressure (SBP) ≥ 130 mmHg; diastolic blood pressure (DBP) ≥ 85 mmHg) or treatment of previously diagnosed hypertension; and (iv) hyperglycaemia (FPG ≥ 5.6 mmol/L) or previously diagnosed Type 2 diabetes.[19]

Statistical analysis

Data are presented as the mean ± SD, except for skewed variables, which are presented as the median (25–75% interquartile range). Comparisons between men and women were performed by independent sample *t*-test or the Chi-squared test (for classified variables). Because significant differences existed for most variables, other statistical analyses were performed separately for men and women. Furthermore, because normal distribution could not be assumed for all the variables included, Spearman's partial correlation analysis was used to clarify the quantitative association between liver enzymes and each component of MS adjusted for age, BMI, alcohol consumption and smoking status. Subjects were divided into different groups based on quintiles of liver enzymes (ALT, AST and GGT) and logistic regression analysis was performed to estimate the adjusted odds ratios (ORs) for MS in each quintile using the lowest quintile as the reference category. Receiver operating characteristic (ROC) curve analyses were used to determine the appropriate cut-off values for liver enzymes to identify individuals with MS. The optimal cut-off values were obtained from the Youden index (maximum (sensitivity + specificity − 1)). Greater accuracy is indicated by a larger Youden index.[20] All statistical analyses were performed using SAS 9.2 (SAS Institute, Cary, NC, USA). All P values reported are two-tailed and $P < 0.05$ was considered significant.

RESULTS

The clinical characteristics of study subjects are given in Table 1. Of 634 men and 869 women, 222 (35.0%) and 215 (24.7%) had MS, respectively. In men, the median levels (in IU/L) of ALT, AST and GGT were 22 (15–37), 22 (18–27) and 30 (21–45), respectively. In women, the median levels (in IU/L) of ALT, AST and GGT were 16 (12–25), 20 (17–25) and 22 (16–32), respectively.

The partial correlation coefficients between liver enzymes and components of MS are given in Table 2. Both ALT and GGT were significantly associated with most components of MS in both men and women after adjustment for age, BMI, smoking status and alcohol intake, except that there was no correlation between ALT levels and HDL-C and blood pressure, or between GGT and SBP, in women. Serum AST levels were correlated with waist circumference, triglyceride levels, FPG and serum cholesterol levels in men and with waist circumference and DBP in women.

Table 3 gives results of logistic regression analyses for the presence of MS in relation to the ALT, AST and GGT quintiles. The ORs for MS increased progressively with increasing liver enzyme levels. For ALT, after adjustment for age, BMI, smoking status and alcohol intake, the ORs for men and women increased up to 2.510 and 2.671, respectively, in the fourth quintile and up to 4.623 and 3.889, respectively, in the fifth quintile. The ORs for GGT were 2.074 in the third quintile for women, 2.579 in the fourth quintile for men and 3.944 and 5.465 in the fifth quintile for men and women, respectively.

Table 1 Demographic and laboratory characteristics of the study participants

	All patients (n = 1503)	Men (n = 634)	Women (n = 869)	P*
Age (years)	60 (52–69)	59 (49–71)	60 (53–68)	0.001
BMI (kg/m^2)	24.8 ± 3.4	25.2 ± 3.3	24.6 ± 3.5	0.002
Waist circumference (cm)	84.5 ± 10.0	88.3 ± 9.7	81.7 ± 9.3	< 0.001
SBP (mmHg)	135.5 ± 20.7	136.2 ± 19.5	135.1 ± 21.5	0.299
DBP (mmHg)	78.5 ± 10.7	80.5 ± 10.7	77.0 ± 10.5	< 0.001
ALT (IU/L)	18 (13–29)	22 (15–37)	16 (12–25)	< 0.001
AST (IU/L)	21 (18–26)	22 (18–27)	20 (17–25)	0.001
GGT (IU/L)	24 (18–37)	30 (21–45)	22 (16–32)	< 0.001
Triglycerides (mmol/L)	1.4 (1.0–2.1)	1.5 (1.0–2.2)	1.4 (1.0–2.0)	0.086
Cholesterol (mmol/L)	5.1 ± 1.0	4.8 ± 0.9	5.3 ± 1.0	< 0.001
HDL-C (mmol/L)	1.3 (1.1–1.6)	1.2 (1.0–1.4)	1.4 (1.2–1.7)	< 0.001
LDL-C (mmol/L)	2.9 ± 0.8	2.8 ± 0.8	3.1 ± 0.9	< 0.001
Fasting glucose (mmol/L)	5.2 (4.8–5.7)	5.2 (4.8–5.7)	5.2 (4.8–5.7)	0.972
Alcohol drinkers	205 (13.6%)	151 (23.8%)	54 (6.2%)	< 0.001
Smokers	329 (21.9%)	291 (45.9%)	38 (4.4%)	< 0.001
Central obesity	607 (40.4%)	294 (46.4%)	313 (36.0%)	< 0.001
Hypertension	1011 (67.3%)	454 (71.6%)	557 (64.1%)	0.002
Hypertriglyceridaemia	625 (41.6%)	280 (44.2%)	345 (39.7%)	0.083
Low HDL-C	530 (35.3%)	215 (33.9%)	315 (36.2%)	0.349
Hyperglycaemia	492 (32.7%)	212 (33.4%)	280 (32.2%)	0.567
Metabolic syndrome	437 (29.1%)	222 (35.0%)	215 (24.7%)	< 0.001

Data are presented as either the mean ± SD, median (interquartile range) for continuous variables or as the number of subjects with percentages given in parentheses, as appropriate.

*P values for the overall comparisons between men and women.

BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; HDL-C, high density lipoprotein–cholesterol; LDL-C, low density lipoprotein–cholesterol; AST, aspartate aminotransferase; ALT, alanine aminotransferase; GGT, γ-glutamyl transpeptidase.

Table 2 Spearman partial correlation coefficients between liver enzymes and components of metabolic syndrome

Components of MS	ALT		AST		GGT	
	Model 1	Model 2	Model 1	Model 2	Model 1	Model 2
Men						
WC	0.396‡	0.179‡	0.228‡	0.115†	0.315‡	0.168‡
SBP	0.238‡	0.136‡	0.109†	0.048	0.181‡	0.101*
DBP	0.210‡	0.119†	0.092*	0.036	0.197‡	0.128†
TG	0.318‡	0.214‡	0.196‡	0.135‡	0.400‡	0.334‡
HDL-C	−0.255‡	−0.136‡	−0.065	0.009	−0.221‡	−0.129*
FPG	0.256‡	0.203‡	0.128†	0.092*	0.165‡	0.118†
Cholesterol	0.067	0.054	0.122†	0.116†	0.224‡	0.220‡
LDL-C	0.033	0.032	0.072	0.072	0.155‡	0.158‡
Women						
WC	0.291‡	0.163‡	0.127‡	0.120‡	0.318‡	0.141‡
SBP	0.054	−0.010	0.021	0.003	0.132‡	0.059
DBP	0.135*	0.061	0.098†	0.081†	0.190‡	0.102†
TG	0.232‡	0.178‡	0.071*	0.058	0.391‡	0.337‡
HDL-C	−0.127‡	−0.053	−0.008	0.011	−0.229‡	−0.147‡
FPG	0.203‡	0.148‡	0.037	0.021	0.258‡	0.194‡
Cholesterol	0.123‡	0.131‡	0.063	0.064	0.176‡	0.190‡
LDL-C	0.063	0.055	0.006	0.003	0.117‡	0.109†

*P < 0.05, $^{\dagger}P$ < 0.01, $^{\ddagger}P$ < 0.001.

Model 1: adjusted for age, smoking and drinking.

Model 2: adjusted for age, body mass index (BMI), smoking and drinking.

MS, metabolic syndrome; WC, waist circumference; SBP, systolic blood pressure; DBP, diastolic blood pressure; TG, triglycerides; HDL-C, high density lipoprotein–cholesterol; LDL-C, low density lipoprotein–cholesterol; FPG, fasting plasma glucose; AST, aspartate aminotransferase; ALT, alanine aminotransferase; GGT, γ-glutamyl transpeptidase.

Table 3 Odds ratios and 95% confidence intervals for metabolic syndrome according to levels of different liver enzymes

Liver enzyme	Men			Women		
	Concentration (IU/L)	Model 1	Model 2	Concentration (IU/L)	Model 1	Model 2
ALT						
Q1	0–13.4	1.0 (Reference)	1.0 (Reference)	0–11	1.0 (Reference)	1.0 (Reference)
Q2	13.4–19	1.948 (1.072–3.540)	1.683 (0.836–3.388)	11–15	1.352 (0.767–2.382)	1.135 (0.595–2.167)
Q3	19–25	1.988 (1.050–3.764)	1.781 (0.852–3.722)	15–19	1.677 (0.933–3.014)	1.630 (0.832–3.193)
Q4	25–42	3.607 (1.955–6.656)	2.510 (1.225–5.144)	19–29	3.274 (1.869–5.734)	2.671 (1.398–5.101)
Q5	> 42	9.731 (5.000–18.938)	4.623 (2.110–10.128)	> 29	5.259 (3.048–9.076)	3.889 (2.075–7.288)
P for trend		< 0.001	< 0.001		< 0.001	< 0.001
AST						
Q1	0–17.6	1.0 (Reference)	1.0 (Reference)	0–17	1.0 (Reference)	1.0 (Reference)
Q2	17.6–21	0.740 (0.432–1.266)	0.508 (0.267–0.967)	17–19	0.622 (0.357–1.084)	0.730 (0.386–1.381)
Q3	21–24	0.905 (0.513–1.597)	0.732 (0.374–1.431)	19–22	0.833 (0.513–1.353)	1.464 (0.826–2.593)
Q4	24–29.4	1.224 (0.700–2.141)	0.924 (0.473–1.804)	22–26	0.989 (0.593–1.650)	1.101 (0.610–1.986)
Q5	> 29.4	2.551 (1.473–4.418)	1.411 (0.731–2.723)	> 26	2.275 (1.467–3.528)	2.344 (1.392–3.946)
P for trend		< 0.001	0.059		< 0.001	0.001
GGT						
Q1	0–20	1.0 (Reference)	1.0 (Reference)	0–15	1.0 (Reference)	1.0 (Reference)
Q2	20–26	2.722 (1.481–5.004)	1.631 (0.783–3.397)	15–19	1.219 (0.628–2.365)	0.874 (0.396–1.931)
Q3	26–34	2.687 (1.482–4.870)	1.942 (0.961–3.928)	19–24	2.792 (1.538–5.069)	2.074 (1.015–4.240)
Q4	34–51	3.384 (1.854–6.178)	2.579 (1.265–5.262)	24–35	3.078 (1.713–5.533)	1.677 (0.817–3.443)
Q5	> 51	5.729 (3.083–10.646)	3.944 (1.901–8.184)	> 35	8.813 (4.998–15.540)	5.465 (2.758–10.828)
P for trend		< 0.001	< 0.001		< 0.001	< 0.001

Model 1: adjusted for age, smoking status and alcohol drinking.
Model 2: adjusted for age, body mass index, smoking status and alcohol drinking.
AST, aspartate aminotransferase; ALT, alanine aminotransferase; GGT, γ-glutamyl transpeptidase; Q1–Q5, first to fifth quintiles.

Female participants with AST levels in the top quintile had the highest prevalence of MS (OR 2.344; 95% confidence interval 1.392–3.946), but increased AST levels did not increase the risk of MS in men.

Cut-off values were then calculated for ALT, AST and GGT in association with increases in the prevalence of MS using ROC curve analysis (Fig. 1). For men, the cut-off values for a diagnosis of MS were 26, 25 and 29 IU/L for ALT, AST and GGT, respectively; in women, these values were 20, 23 and 21 IU/L, respectively (Table 4).

The sensitivity and specificity of the new liver enzyme cut-off values for the diagnosis of MS and NAFLD was evaluated (Table 5). Compared with the traditional 'normal' limits for liver enzymes, the new liver enzyme cut-off values identified approximately 30% more patients with MS. In addition, the sensitivity of the new liver enzyme cut-off values for the diagnosis of NAFLD was significantly greater than that of the traditional 'normal' liver enzyme limits (64.8 *vs* 34.2%, respectively, for ALT; 68.4 *vs* 36.2%, respectively, for GGT; 43.9 *vs* 14.3%, respectively, for AST), with acceptably high specificity (78.0–90.2%) and positive predictive value (93.7–96.9%).

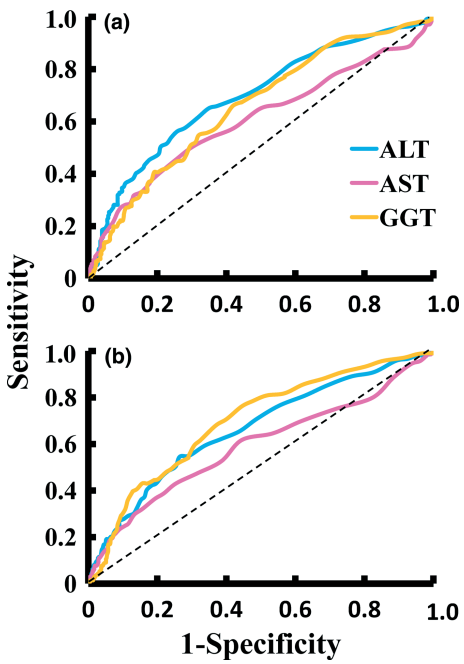

Fig. 1 Receiver operating characteristic (ROC) curves for liver enzymes associated with an increased prevalence of metabolic syndrome in (a) men and (b) women. ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, γ-glutamyl transpeptidase.

DISCUSSION

In the present study, we conducted a cross-sectional study to detect associations between liver enzymes and the components of MS. We found that slight increases of liver enzymes within the 'normal' limits was strongly associated with an increase in the prevalence of MS and that optimal liver enzyme cut-off values for the diagnosis of MS were much lower than the current 'normal' limits. For men, the optimal cut-off values for ALT, AST and GGT to detect MS were found to be 26, 25 and 29 IU/L, respectively; in women, the optimal values were 20, 23 and 21 IU/L, respectively. Compared with the traditional liver enzyme cut-off values, the new lower cut-off values identified

Table 4 Optimal cut-off values for liver enzymes to determine metabolic syndrome based on International Diabetes Federation criteria[19]

	AUC	Cut-off value (IU/L)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	*J*-value
Men							
ALT	0.694*	26	56.4 (52.5–60.3)	72.9 (69.4–76.4)	53.0 (49.1–56.9)	75.5 (72.2–78.8)	0.2927
AST	0.605*	25	45.9 (42.0–49.8)	74.1 (70.7–77.5)	49.3 (45.4–53.2)	71.5 (68.0–75.0)	0.2004
GGT	0.657*	29	65.9 (62.2–69.6)	58.1 (54.3–61.9)	46.1 (42.2–50.0)	75.8 (72.5–79.1)	0.2404
Women							
ALT	0.666*	20	55.4 (52.1–58.7)	72.9 (69.9–75.9)	40.0 (36.7–43.3)	83.3 (80.8–85.8)	0.2825
AST	0.591*	23	43.3 (40.0–46.6)	74.5 (71.6–77.4)	35.5 (32.3–38.7)	80.2 (77.6–82.8)	0.1783
GGT	0.698*	21	76.1 (73.3–78.9)	55.7 (52.4–59.0)	35.7 (32.5–38.9)	87.8 (85.6–90.0)	0.3174

*$P < 0.001$.

Sensitivity, specificity, positive predictive values (PPV) and negative predictive values (NPV) are expressed as percentages with 95% confidence intervals in parentheses.

The optimal cut-off values for alanine aminotransferase (ALT) were obtained when the Youden index was maximal.

MS, metabolic syndrome; *J*-value, Youden index (sensitivity + specificity − 1); AUC, area under the curve; AST, aspartate aminotransferase; GGT, γ-glutamyl transpeptidase.

approximately 30% more patients with MS or NAFLD, who may have been missed if traditional 'normal' liver enzyme limits were used.

Liver enzyme markers are the most commonly used parameters to reflect hepatic impairment and are easily measurable in a clinical setting. The association between liver enzymes and metabolic disease has been investigated. Unexplained increases in liver enzymes are associated with insulin resistance and metabolic syndrome[21,22] and prospective studies have demonstrated that elevated serum levels of ALT or GGT are independent risk factors for Type 2 diabetes[23] and CVD.[24,25] In the present study, we found that ALT and GGT were strongly correlated with most components of MS, including central obesity, hypertension, hyperlipidaemia and impaired glucose regulation. Although serum AST levels were significantly increased in subjects with MS, as also reported in previous studies,[26] partial correlation analysis indicated that AST was only weakly associated with a few components of MS in the present study. Thus, particular attention should be paid to ALT and GGT when investigating the association between liver enzymes and MS.

It should be noted that, on the basis of results from the present study, elevated liver enzymes even within current 'normal' limits could reflect the presence of MS. Recently, a Korean study of 5020 individuals concluded that the optimal cut-off values for ALT for the diagnosis of MS were 27 IU/L in men and 18 IU/L in women.[27] A Japanese study found that optimal cut-off values for ALT and GGT to identify MS were 25 and 42 IU/L, respectively, in men and 20 and 21 IU/L, respectively, in women.[28] The optimal liver enzyme cut-off values for MS in the present study are similar with these two previous studies. We found the new liver enzyme cut-off values were much more sensitive and effective in detecting MS than traditional liver enzyme cut-off values. Thus, we suggest that the meaning of increased liver enzymes within 'normal' limits should be re-evaluated from the metabolic aspect and that lowering the definition of 'normal' liver enzyme limits would be advantageous for the early detection of potential MS.

Elevated liver enzymes in MS patients may be caused by the hepatic steatosis that accompanies MS. It has been reported that liver enzyme levels are significantly elevated in NAFLD patients[29] and that NAFLD is significantly correlated with abnormalities in multiple metabolic components, such as obesity, insulin resistance and Type 2 diabetes.[30,31] Approximately 60–95% of patients with NAFLD are obese, 28–55% have Type 2 diabetes and 27–92% have dyslipidaemia.[32] As shown recently by our group, even modestly elevated hepatic fat content is associated with an unfavourable glucose profile in subjects without diabetes.[18] Thus, the presence of NAFLD is probably an early sign of MS and could explain, in part, the increase in liver enzyme levels. Although it remains unclear whether hepatic steatosis is a consequence or cause of derangements in metabolic status, our results indicate that hepatic steatosis and MS coexist at a very early stage of the disease; the proposed lowered liver enzyme cut-off values for the detection of MS could also detect approximately 30% more patients with NAFLD with a high specificity. Indeed, when a lower normal limit of ALT was applied in a recent study, there was a significant increase in the prevalence of NAFLD detected in obese women.[33] Furthermore, the Screening ALT for Elevation in Today's Youth (SAFETY) study found that ALT cut-off values were set too high for the detection of paediatric NAFLD.[34]

To a certain degree, hepatic fat accumulation can be visualized using ultrasonography, but the sensitivity of ultrasound in diagnosing mild hepatic steatosis (liver fat content < 20%) is only 55%[35] and it would be not cost-effective to screen entire populations for fatty liver. Therefore, a lowering of current liver enzyme upper limits may be more beneficial in identifying patients with potential hepatic steatosis.

There are several limitations to the present study. First, the present study was cross-sectional study, so it did not permit the identification of causal relationships between clinical markers and MS, which needs to be evaluated in longitudinal studies. Second, the study participants were patients visiting a physical examination centres for routine health checks, with most being middle-aged and aged; thus, the prevalence of MS and NAFLD in the present study is higher than that reported in the general population of China and some of the characteristics of the study population may be differ substantially from those of other populations that do not have access to or make use of medical services. Third, liver enzymes are affected by many factors (e.g. liver disease, gall-bladder disease, food and drugs) and the association between elevated liver enzymes within 'normal' limits and metabolic disorders in the present study existed only when we ruled out various factors known to affect liver enzyme levels. Therefore, the clinical interpretation of elevated liver enzymes as indicators of

Table 5 Sensitivity and specificity of new liver enzyme cut-off values for the diagnosis of metabolic syndrome and non-alcoholic fatty liver disease compared with traditional liver enzyme upper limits of normal

	Metabolic syndrome based on IDF criteria						Hepatic fat content determined by [^{1}H]-MRS					
	MS (+)	MS (−)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	> 5.56% (+)	≤ 5.56% (−)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
ALT (IU/L)												
> 26 (men); > 20 (women)	244/437	777/1066	55.8 (53.3–58.3)	72.9 (70.7–74.9)	45.7 (43.2–48.2)	80.1 (78.1–82.1)	127/196	37/41	64.8 (58.7–70.9)	90.2 (86.4–94.0)	96.9 (94.7–99.1)	34.9 (28.8–41.0)
> 40 (both genders)	126/437	963/1066	28.8 (26.5–31.1)	90.2 (88.7–91.7)	54.8 (52.3–57.3)	75.6 (73.4–77.8)	67/196	40/41	34.2 (28.2–40.2)	97.6 (95.7–99.5)	98.5 (97.0–100.0)	23.7 (18.3–29.1)
AST (IU/L)												
> 25 (men); > 23 (women)	195/437	793/1066	44.6 (42.1–47.1)	74.4 (72.2–76.6)	41.6 (39.1–44.1)	76.6 (74.5–78.7)	86/196	36/41	43.9 (37.6–50.2)	87.8 (83.6–92.0)	94.5 (91.6–97.4)	24.7 (19.2–30.2)
> 40 (both genders)	61/437	1025/1066	14.0 (12.2–15.8)	96.2 (95.2–97.2)	60.0 (57.5–62.5)	73.2 (71.0–75.4)	28/196	39/41	14.3 (9.8–18.8)	95.1 (92.4–97.8)	93.3 (90.1–96.5)	18.8 (13.8–23.8)
GGT (IU/L)												
> 29 (men); > 21 (women)	310/437	603/1066	70.9 (68.6–73.2)	56.6 (54.1–59.1)	40.0 (37.5–42.5)	82.7 (80.8–84.6)	134/196	32/41	68.4 (62.5–74.3)	78.0 (72.7–83.3)	93.7 (90.6–96.8)	34.0 (28.0–40.0)
> 50 (men); > 32 (women)	161/437	893/1066	36.8 (34.4–39.2)	83.8 (81.9–85.7)	48.2 (45.7–50.7)	76.5 (74.4–78.6)	71/196	39/41	36.2 (30.1–42.3)	95.1 (92.4–97.8)	97.3 (95.1–99.4)	23.8 (18.4–29.2)

Sensitivity, specificity, positive predictive values (PPV) and negative predictive values (NPV) are expressed as percentages with 95% confidence intervals in parentheses.
MS, metabolic syndrome; IDF, International Diabetes Federation; AST, aspartate aminotransferase; ALT, alanine aminotransferase; GGT, γ-glutamyl transpeptidase; MRS, magnetic resonance spectroscopy.

the presence of MS and NAFLD should be made with care, because other primary liver disease and many other factors may be impacting on liver enzyme levels.

In conclusion, we detected a relatively high prevalence of MS in apparently healthy individuals who exhibited slight increases in liver enzymes within current normal limits. These findings suggest that slight changes in liver enzymes, even within the so-called 'normal' range, could reflect liver fat deposition and a dysmetabolic state in the absence of known liver diseases. The current 'normal' liver enzyme limits are not appropriate for the identification of patients with metabolic disorders or potential hepatic steatosis. A lowering of normal liver enzyme limits is advisable for the early detection of MS and NAFLD in 'healthy' patients who currently have elevated ALT or GGT levels within 'normal' limits.

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