

Original Article

Study of the cut-off level of ALT and TG to predict the risk of nonalcoholic fatty liver disease in eastern China

Zhen Cang^{1*}, Ningjian Wang^{1*}, Qin Li¹, Bing Han¹, Yi Chen¹, Chunfang Zhu¹, Yingchao Chen¹, Fangzhen Xia¹, Xiaoqi Pu¹, Chaoxia Zhu¹, Meng Lu¹, Chi Chen¹, Dongping Lin¹, Weiping Tu², Bin Li³, Ling Hu⁴, Yingli Lu¹

¹Institute and Department of Endocrinology and Metabolism, Shanghai Ninth People's Hospital Affiliated to Shanghai Jiaotong University School of Medicine, Shanghai, China; ²Department of Endocrinology and Metabolism, Shangyu People's Hospital, Zhejiang, China; ³Department of Endocrinology and Metabolism, Fengcheng Hospital, Shanghai, China; ⁴Department of Endocrinology and Metabolism, The Third Affiliated Hospital of Nanchang University, Jiangxi, China. *Co-first authors.

Received October 16, 2016; Accepted March 20, 2017; Epub May 15, 2017; Published May 30, 2017

Abstract: Objective: This study aimed at researching the cut-off level of liver enzyme and serum lipid to predict the risk of nonalcoholic fatty liver disease (NAFLD) in people who live in the Eastern China, which could provide a new insight for prevention of NAFLD. Methods: This study statistics were obtained from 2014 SPECT-China data base. 4448 subjects were included in this study. According to Ultrasonic diagnosis, they were divided into 2 groups: normal group (NG) and nonalcoholic fatty liver disease group (FDG). We analyzed the difference of liver enzyme, serum lipid, body mass index (BMI), waist-to-hip ratio (WHR) between the two groups and study the correlation between the liver enzyme, lipid profile, BMI, WHR and NAFLD. Results: (1) The ratio of NAFLD in Eastern China was 15%. It was higher in males than in females ($P < 0.01$). (2) Compared with control group, the alanine aminotransferase (ALT), aspartate aminotransferase (AST), serum total triglycerides (TG), serum total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), BMI and WHR values were all higher in the NAFLD group. (3) The multi-factor logistic regression analysis revealed that ALT, TG, BMI and WHR were the independent risk factors for female during the development of NAFLD, and ALT, TG, LDL-C, BMI and WHR were the independent risk factors for male. (4) The ROC curve showed that ALT or TG could be used as predictor of NAFLD, and the area under the curve (AUC) were 0.70, 0.75 for female, and 0.67, 0.71 for male. Additionally, for female the cut-off level of ALT and TG were 17.5 U/L, 1.39 mmol/L, whereas the cut-off level of ALT and TG were 22.5 U/L, 1.35 mmol/L for male. Conclusion: ALT or TG could be used as the predictor of NAFLD.

Keywords: Nonalcoholic fatty liver disease, ALT, TG, cut-off level

Introduction

Nonalcoholic fatty liver disease (NAFLD) has gradually become one of the most common liver diseases in the world [1]. NAFLD encompasses a wide spectrum of conditions, ranging from simple fatty steatosis to nonalcoholic steatohepatitis (NASH), cirrhosis, liver failure and hepatocellular carcinoma (HCC), without excessive alcohol consumption [2]. Previous studies have shown that the early stage of the disease may be reversible, so it is crucial to control the development of NAFLD with early detection, early diagnosis and early treatment [3]. Unfortunately, in the early stage of NAFLD, there is lack of specific clinical manifestations, thus it is not easy to early detection and treatment.

Liver biopsy is the gold standard for NAFLD diagnosis. However, there are many limitations to the use of a liver biopsy including cost, sampling error, and invasion [4]. It is necessary to find a safe, noninvasive, and relatively inexpensive means for detecting NAFLD.

Recent studies have shown that NAFLD has many relevant factors, such as liver enzymes, lipid profile, BMI, WHR, blood pressure, fasting plasma glucose and so on [5-7]. In some studies, ALT has been used as a surrogate marker for NAFLD, because it is specific for both liver injury and fat accumulation [8, 9]. However, so far there has no epidemiological survey reported the cut-off level of relevant factor to predict the risk of NAFLD in China. In this paper, we

The predictor of NAFLD

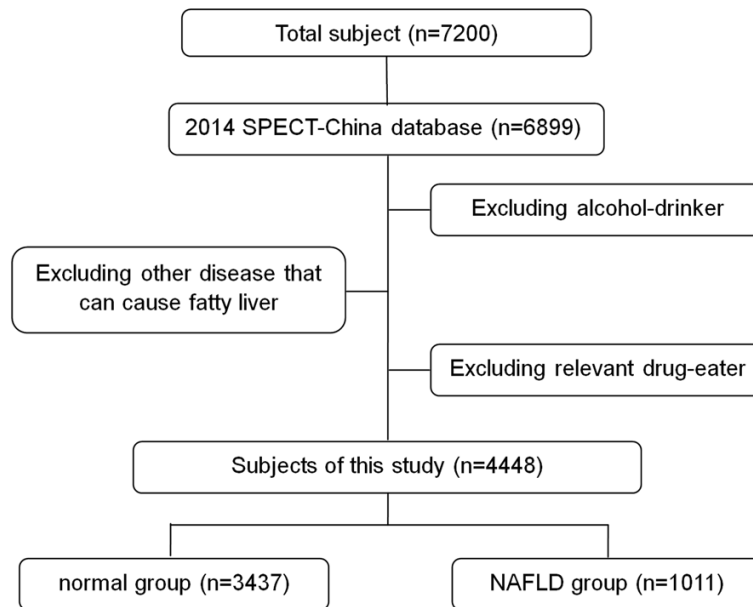


Figure 1. Research object selection flow chart.

study the relationships of liver enzyme, lipids profile and NAFLD, and find out the cut-off level of liver enzyme (alanine aminotransferase (ALT), aspartate aminotransferase (AST)) and serum lipid (serum total triglycerides (TG), serum total cholesterol (TC), high-density lipoprotein cholesterol (HDL-D) and low-density lipoprotein cholesterol (LDL-C)) to predict the risk of NAFLD in Eastern China, through analyzing their liver enzyme and lipid profile.

Methods

Subjects

2014 SPECT-China study: Eastern China is composed of Shanghai and seven provinces, with 395 million people, accounting for 29.2 percentage of the general population. SPECT-China, with registration number of ChiCTR-ECS-14005052 (www.chictr.org), is a population-based cross-sectional survey on prevalence of metabolic diseases and risk factors in Eastern China. Stratified cluster sampling method was used in this research. The first level of sampling was stratified by rural and urban area and the second level was by area economic development. From February to June 2014 this study was performed in urban area in Shanghai and Jiangxi Province, rural area in Shanghai, Zhejiang and Jiangxi Province. Adults aged 18 years old and above who were Chinese citizens

and lived in current residence for 6 months or longer were selected and invited into our study. Excluding those having communication problems, acute disease, or unwilling to attend, 7200 people in total attended this study. In final, we have enrolled 6899 subjects, excluding 183 attendees who had missing lab results ($n=183$), questionnaire data ($n=112$) and were younger than 18 years old ($n=6$). The study protocol was approved by the Ethics Committee of Shanghai Ninth People's Hospital affiliated to Shanghai Jiaotong University School of Medicine. All attendees have been informed consent before data collection.

This study statistics were from 2014 SPECT-China database. There are 4448 subjects included this study, excluding the people who had a history of drinking alcohol (>140 g/week for men, >70 g/week for women), or had other diseases that can cause fatty liver such as virus hepatitis, drug-induced liver disease, autoimmune liver disease and so on, or who were treated with drugs that can influence liver enzyme and serum lipid for nearly three months. The subjects selection flow chart is shown in **Figure 1**.

Methods

Diagnosis standards for NAFLD

The Diagnostic Criteria for NAFLD was stipulated by the Fatty Liver and Alcoholic Liver Disease Study Group of the Chinese Society of Hepatology and the Chinese Medical Association [10, 11]. The details were as follows: (1) no history of drinking or drinking alcohol equal to <140 g/week for men or <70 g/week for women; (2) excluding other diseases that can cause fatty liver such as virus hepatitis, drug-induced liver disease, autoimmune liver disease, Hepatic Lenticular Disease and so on; (3) imageology showed: ① the liver in the near field presented fine spots and the echo was significantly diffuse enhanced, ② the structure of intrahepatic bile duct was obscurity, ③ the liver

The predictor of NAFLD

Table 1. Univariate analysis between NAFLD group and normal groups

	Female			Male		
	NG	FDG	P	NG	FDG	P
Age (year)	50.54±13.88	56.85±10.39	P<0.01	53.44±15.03	52±14.13	P=0.081
AST (mmol/L)	22.99±9.03	26.06±10.19	P<0.01	22.26±8.96	27.48±12.65	P<0.01
ALT (mmol/L)	17.94±12.08	24.67±15.41	P<0.01	22.98±14.99	32.57±22.30	P<0.01
LDL (mmol/L)	2.85±0.74	3.15±0.68	P<0.01	2.81±0.67	3.01±0.66	P<0.01
HDL (mmol/L)	1.55±0.31	1.39±0.28	P<0.01	1.36±0.30	1.22±0.25	P<0.01
TG (U/L)	1.32±1.01	2.14±1.82	P<0.01	1.45±1.26	2.24±2.21	P<0.01
TC (U/L)	5.00±1.01	5.38±0.97	P<0.01	4.86±0.93	5.10±0.94	P<0.01
BMI (Kg/m ²)	23.07±3.14	27.41±3.45	P<0.01	23.35±3.34	26.52±3.20	P<0.01
WHR	0.82±0.07	0.88±0.07	P<0.01	0.87±0.08	0.91±0.07	P<0.01

Data were expressed as mean ± SD. ALT, alanine aminotransferase; AST, aspartate aminotransferase; TG, triglycerides; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; BMI, body mass index; WHR waist-hip ratio; NG, normal group, FDG, nonalcoholic fatty liver disease group.

Table 2. Spearman correlation between risk factor and NAFLD

	Female		Male	
	r	P	r	P
Age	0.2	P<0.01	-0.05	0.08
AST	0.17	P<0.01	0.1	P<0.01
ALT	0.27	P<0.01	0.28	P<0.01
LDL	0.18	P<0.01	0.21	P<0.01
HDL	-0.19	P<0.01	-0.23	P<0.01
TG	0.34	P<0.01	0.34	P<0.01
TC	0.16	P<0.01	0.13	P<0.01
BMI	0.45	P<0.01	0.44	P<0.01
WHR	0.34	P<0.01	0.26	P<0.01

ALT, alanine aminotransferase; AST, aspartate aminotransferase; TG, triglycerides; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; BMI, body mass index; WHR waist-hip ratio; NG, normal group; FDG, nonalcoholic fatty liver disease group; r, coefficient of association.

was large and in full shape and the lower edge of hepatic lobes were obtuse, ④ the envelope of right hepatic lobe and diaphragm were unclear or the echo was obscurity, (satisfying condition ① and any of the rest condition).

General conditions

In every study site, all the data collection was performed by the same staff group from Department of Endocrinology in Shanghai Ninth People's Hospital affiliated to Shanghai Jiao-tong University School of Medicine. They were trained according to a standard protocol that made them familiar with the specific tools and

methods used. Trained staff used a questionnaire to collect information about drinking history and drinking amount, past medical history including hepatitis, other chronic liver diseases and recent medical history.

Biochemical index examination

Venous blood samples were drawn after an overnight fast of at least 8 h. The blood samples for biochemical index test were collected into vacuum tubes with anticoagulant sodium fluoride and centrifuged on the spot in 1 hour after collection. The collected blood samples were stored at -20°C and shipped in dry ice within 2-4 hours by air to one central laboratory, which was certified by the College of American Pathologists. A BECKMAN COULTER AU 680 (Germany) automatic biochemical analyzer was used for biochemical index tests, including TC (total cholesterol), TG (triglycerides), HDL-C (high-density lipoprotein cholesterol), LDL-C (low-density lipoprotein cholesterol); ALT (alanine aminotransferase); AST (aspartate aminotransferase).

Imageological examination

The image examination used in this study was B ultrasound. A mindray MX-35004882 color B ultrasound system (General Electric, USA; convex array probe; probe frequency 3.5 MHz) was used. The operator was a experienced ultrasound doctor. According to their Ultrasonic diagnosis, the 4448 subjects were divided into 2 groups: normal group (NG) and nonalcoholic fatty liver disease group (FDG).

The predictor of NAFLD

Table 3. Logistic regression analysis with NAFLD

	Female			Male		
	OR	95% CI	P	OR	95% CI	P
Age	1.01	1.00-1.02	0.01	1.00	0.99-1.01	0.53
AST	0.99	0.97-1.01	0.25	0.98	0.96-1.00	0.07
ALT	1.03	1.01-1.04	0.00	1.03	1.01-1.04	0.00
LDL-C	1.21	0.83-1.77	0.32	5.60	3.27-9.57	<0.00
HDL-C	0.30	0.18-0.49	<0.00	0.87	0.43-1.75	0.69
TG	1.21	1.09-1.35	0.00	1.45	1.27-1.66	<0.00
TC	1.10	0.81-1.51	0.54	0.33	0.21-0.51	<0.00
BMI	1.36	1.31-1.41	<0.00	1.24	1.18-1.31	<0.00
WHR	28.78	5.63-147.14	<0.00	11.29	1.23-103.66	0.03

The variables entered the Logistic regression model include age AST ALT LDL-C HDL-C TG TC BMI WHR. OR, odds ratio; 95% CI, 95% confidence interval; ALT, alanine aminotransferase; AST, aspartate aminotransferase; TG, triglycerides; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; BMI, body mass index; WHR waist-hip ratio.

Statistical analysis

All statistical analyses were performed using SPSS software version 19. Data were expressed as mean \pm SD. The χ^2 test was used to evaluate frequency variations. Kruskal-Wallis Test was used for intergroup comparisons. The Spearman correlation was used to analyze the correlation between the relevant factors and NAFLD. Logistic regression analysis was carried out for multivariate analyses. Odds ratio (OR) and their confidence intervals (CI) were used to assess the relevant factors of NAFLD. The area under the curve (AUC) was used as a measure of diagnostic efficacy. The optimal cut-off level was determined using the Youden index [12]. *P* value <0.05 was taken to indicate a significant difference.

Results

NAFLD ratio

Among the 6899 subjects, the ratio of NAFLD was 15%, including 430 males (40%) and 632 females (60%). The ratio had significant difference between male and female, the incidence of NAFLD in female was significantly higher than that in male. ($\chi^2=96.3$, $P<0.01$).

Univariate analysis between NAFLD group and normal groups

For female, the age, AST, ALT LDL-C, TG, TC, BMI and WHR were all higher in the NAFLD group

than those in normal groups ($P<0.01$) and the HDL-C in the NAFLD group was significantly less than it in normal groups ($P<0.01$). For male, the age had no significant difference between two groups; the AST, ALT, LDL-C, TG, TC, BMI and WHR were all higher in the NAFLD group than those in normal groups ($P<0.01$); the HDL-C in the NAFLD group was significantly less than it in normal groups ($P<0.01$). The data are shown in **Table 1**.

Spearman correlation between age, liver enzyme, lipid profile, BMI, WHR and NAFLD

For female, the age, AST, ALT, LDL-C, TG, TC, BMI and WHR had a positive relationship with NAFLD ($P<0.01$) and the HDL-C had a negative relationship with NAFLD ($P<0.01$). For male, no significant correlation was observed between the age and NAFLD; the AST, ALT, LDL-C, TG, TC, BMI and WHR had a positive relationship with NAFLD ($P<0.01$) and the HDL-C had a negative relationship with NAFLD ($P<0.01$). The data are shown in **Table 2**.

Logistic regression analysis with NAFLD

For female, when used NAFLD as a dependent variable, we found that age, ALT, TG, BMI and WHR were the independent risk factors for NAFLD by using the logistic regression analysis. For male, we found ALT, LDL-C, TG, BMI and WHR were the independent risk factors to NAFLD. The data are shown in **Table 3**.

ROC analysis of the variables for the prediction of NAFLD

Logistic regression analyses revealed that, for female, ALT, TG, BMI and WHR might be used as predictor of NAFLD; for male, ALT, TG, LDL-C, BMI and WHR might be used as a predictor of NAFLD. Additionally, we measured the diagnostic efficacy of using ALT, TG, BMI and WHR as predictors of NAFLD through ROC curve and AUC. For male, the AUC for ALT, TG, BMI and WHR were 0.70 (CI 0.68-0.73), 0.75 (CI 0.73-0.77), 0.83 (0.83-0.85), 0.75 (0.73-0.77). For female, we measured the diagnostic efficacy of using ALT, TG, LDL-C, BMI and WHR as predic-

The predictor of NAFLD

Table 4. AUC, cut-off level, sensitivity and specificity of all risk factors of NAFLD

	Female				Male			
	AUC (95% CI)	Cut-off	SEN	SPE	AUC (95% CI)	Cut-off	SEN	SPE
AST	0.62 (0.60-0.65)	23.50	0.53	0.66	0.56 (0.53-0.60)	20.50	0.81	0.29
ALT	0.70 (0.68-0.73)	17.50	0.67	0.63	0.67 (0.64-0.71)	22.50	0.62	0.66
LDL	0.63 (0.61-0.66)	2.33	0.90	0.24	0.63 (0.60-0.67)	2.55	0.80	0.38
HDL	0.64 (0.62-0.67)	1.43	0.58	0.38	0.64 (0.61-0.68)	1.35	0.76	0.53
TG	0.75 (0.73-0.77)	1.39	0.71	0.68	0.71 (0.68-0.74)	1.35	0.75	0.62
TC	0.62 (0.59-0.64)	3.90	0.95	0.12	0.58 (0.54-0.61)	4.17	0.85	0.23
BMI	0.83 (0.82-0.85)	18.50	1.00	0.06	0.77 (0.74-0.80)	19.96	0.98	0.02
WHR	0.75 (0.72-0.77)	0.73	1.00	0.10	0.66 (0.63-0.69)	0.81	0.94	0.21

ALT, alanine aminotransferase; AST, aspartate aminotransferase; TG, triglycerides; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; BMI, body mass index; WHR waist-hip ratio; AUC, area under the curve; SEN, sensitivity; SPE, specificity.

tors of NAFLD through ROC curve and AUC. The AUC for ALT, TG, LDL-C, BMI and WHR were 0.67 (CI 0.64-0.71), 0.71 (CI 0.68-0.74), 0.63 (CI 0.60-0.67), 0.77 (0.74-0.80), 0.66 (0.63-0.69).

It is generally recognized that if AUC is less than 0.7, the diagnostic efficacy has little value. Thus, for female, ALT, TG, BMI and WHR could be considered as predictors of NAFLD; for male, TG and BMI could be as predictors of NAFLD. The data are shown in **Table 4**.

For female, the cut-off level of ALT, TG, BMI and WHR were 17.5 U/L, 1.39 mmol/L, 18.5 and 0.73, and for male, the cut-off level of TG and BMI were 1.35 mmol/L and 19.96, which were figured out by Youden index (= sensitivity + specificity - 1). The data are shown in **Table 4**.

Discussion

As the life style and diet structure change, the prevalence of NAFLD increases every year throughout the world. Epidemiological data revealed that the prevalence rate of NAFLD in general population was 10%-24% [13, 14]. Our study also showed that the ratio of NAFLD of Chinese in Eastern China was 15%, with men accounting for 40 percent and women accounting for 60 percent of NAFLD. The ratio had significant difference between male and female, which were consistent with previously reported [15, 16]. The possible reason might be that females are more concerned about their dietary allowance and shape than males, resulting in lower rate of obesity and others metabolic disorders.

Due to the lack of understanding of the pathogenesis of the disease, the diagnose and prevention of NAFLD remains a difficult problem. Additionally, many patients were undiagnosed because of lacking of awareness of the disorder and absence of reliable noninvasive diagnostic tools. For these reasons, there is a pressing need for a safe, noninvasive, and relatively inexpensive diagnostic method. Several studies had revealed that there were many risk factors for NAFLD, such as gender, age, BMI, waist circumference, WHR, insulin resistance, blood pressure, blood lipid, liver enzyme and so on [17-19]. Our study focused on investigating the association between liver enzymes, lipid profile, BMI, WHR and NAFLD. For female, the age, AST, ALT, LDL-C, HDL-C, TG, TC, BMI and WHR had significant correlations with NAFLD, so did those factors for male except age. For male, no significant correlation was observed between the age and NAFLD. The possible reason for it may be bias in our study, such as selection bias-excluding those having communication problems, acute disease, or unwilling to attend, information bias-medical record according to the subjects' recall.

Hepatocyte steatosis, caused by the accumulation of excess triglycerides (TG) in the liver, is one of the major features of NAFLD [20]. ALT is very close to hepatocyte steatosis among liver enzymes (such as AST, ALT, γ -GGT) [21]. Epidemiological studies indicated that TG and ALT were the independent risk factors for the development of NAFLD after adjustment for other relevant factors [22-24]. Therefore, compared with other relevant factors, TG or ALT is more suitable to predict NAFLD.

As we all known, the diagnostic efficacy has little value if AUC is less than 0.7. Thus, for female, ALT, TG, BMI and WHR could be as predictors of NAFLD; for male, TG and BMI could be as predictors of NAFLD. As a diagnostic test, it should have not only high sensitivity but also high specificity. Although the AUC of BMI and WHR was more than 0.7, they were still inappropriate to be as the predictor for their low specificity. In fact, the predictors of NAFLD screened though ROC curve and AUC in our study were TG and ALT. The diagnostic efficacy of the two predictors were medium.

The cut-off level of ALT or TG for NAFLD prediction had low sensitivity. However, combination thresholds of ALT levels and TG levels could increase the sensitivity. Combine ALT and TG cut-off level could improve the NAFLD predictive ability. Therefore, this may be a useful predictive method of NAFLD.

Our study still had some limitations. NAFLD was not diagnosed by liver biopsy. Although B ultrasound is a useful method with a reasonable sensitivity and specificity, it may underestimate the actual rate of NAFLD [25, 26]. There were many bias in our study, such as selection bias, information bias and so on.

Conclusion

NAFLD is a risk factor for diabetes mellitus, cardiovascular disease, other chronic metabolic disorders and hepatic disease, so early detection, early diagnosis and early intervention of NAFLD are very important. TG and ALT are good predictors for screening of NAFLD. The cut-off level of ALT and TG predicting the risk of NAFLD among Chinese in Eastern China were 17.5 U/L and 1.39 mmol/L for female, while they were 22.5 U/L and 1.35 mmol/L for male.

Acknowledgements

The SPECT-China study was supported by ① the National Natural Science Foundation of China (81270885, 81070677), ② fund for Clinical Potential Subject Construction of Shanghai Jiaotong University School of Medicine [2014], ③ “973” fund by Ministry of Science and Technology in China (2012CB524906), ④ major project of Science and Technology Commission of Shanghai Municipality from Yangtze River Delta epidemiological and inter-

vention studies of environmental pollution and type 2 diabetes (14495810700). The authors thank all team members and participants from Shanghai, Zhejiang and Jiangxi Province in the SPECT-China study.

Disclosure of conflict of interest

None.

Authors' contribution

Y.L. designed, performed and supervised this investigation, contributed to the discussion, interpretation of the data and critical revision of the manuscript for important intellectual content, and had full access to all of the data and took responsibility for the integrity of the data and the accuracy of the data analysis. J.M.D. reviewed this investigation proposal and manuscript, edited English language, provided critical revision of the manuscript for important intellectual content, interpretation of the data. B.W. analyzed the data, contributed to the discussion, interpretation of the data and revision of the manuscript for important intellectual content, and took responsibility for the integrity of the data and the accuracy of the data analysis. N.W., X.W., B.H. and Q.L. did perform this investigation, analyzed the data, contributed to the discussion, interpretation of the data, and the manuscript writing. Y.C., C.Z., Y.C., F.X., X.P., Z.C., C.Z., M.L., Y.M., H.G., C.C. and D.L. performed this investigation and contributed to the discussion. W.T., B.L. and L.H. supervised this investigation, provided technical or material support, and contributed to the discussion.

Address correspondence to: Yingli Lu, Institute and Department of Endocrinology and Metabolism, Shanghai Ninth People's Hospital Affiliated to Shanghai Jiaotong University School of Medicine, Shanghai, China. E-mail: luyingli2008@126.com

References

- [1] Leon A. Adams, Paul Angulo, and Keith D. Lindor. Nonalcoholic fatty liver disease. *CMAJ* 2005; 172: 899-905.
- [2] Kareem Hassan, Varun Bhalla, Mohammed Ezz El Regal, H Hesham A-Kader. Nonalcoholic fatty liver disease: a comprehensive review of a growing epidemic. *World J Gastroenterol* 2014; 20: 12082-12101.
- [3] Rahimi RS, Landaverde C. Nonalcoholic fatty liver disease and the metabolic syndrome:

The predictor of NAFLD

- clinical implications and treatment. *Nutr Clin Pract* 2013; 28: 40-51.
- [4] Rockey DC, Caldwell SH, Goodman ZD, Nelson RC, Smith AD; American Association for the Study of Liver Diseases. Liver biopsy. *Hepatology* 2009; 49: 1017-1144.
- [5] Alkassabany YM, Farghaly AG, El-Ghitany EM. Prevalence, risk factors, and predictors of non-alcoholic fatty liver disease among schoolchildren: a hospital-based study in Alexandria, Egypt. *Arab J Gastroenterol* 2014; 15: 76-81.
- [6] Tomizawa M, Kawanabe Y, Shinozaki F, Sato S, Motoyoshi Y, Sugiyama T, Yamamoto S, Sueishi M. Elevated levels of alanine transaminase and triglycerides within normal limits are associated with fatty liver. *Exp Ther Med* 2014; 8: 759-762.
- [7] Chen Z, Han CK, Pan LL, Zhang HJ, Ma ZM, Huang ZF, Chen S, Zhuang XJ, Li ZB, Li XY, Li XJ, Yang SY. Serum alanine aminotransferase independently correlates with intrahepatic triglyceride contents in obese subjects. *Dig Dis Sci* 2014; 59: 2470-2476.
- [8] Scheig R. Evaluation of tests used to screen patients with liver disorders. *Prim Care* 1996; 23: 551-560.
- [9] Yamada J, Tomiyama H, Yambe M, Koji Y, Motobe K, Shiina K, Yamamoto Y, Yamashina A. Elevated serum levels of alanine aminotransferase and gamma glutamyltransferase are markers of inflammation and oxidative stress independent of the metabolic syndrome. *Atherosclerosis* 2006; 189: 198-205.
- [10] Branch Hepatic Adipose Infiltration and Alcoholic Fatty Liver Disease Method Group. Non-alcoholic fatty liver disease diagnosis and therapy manual (2006 revised edition). *Chin J Hepatol* 2006; 12: 266-268.
- [11] Branch Hepatic Adipose Infiltration and Alcoholic Fatty Liver Disease Method Group. Non-alcoholic fatty liver disease diagnosis and therapy manual (2010 revised edition). *Chin J Hepatol* 2006; 18: 163-166.
- [12] Perkins NJ, Schisterman EF. The inconsistency of 'optimal' cutpoints obtained using two criteria based on the receiver operating characteristic curve. *Am J Epidemiol* 2006; 163: 670-675.
- [13] Angulo P. GI epidemiology: nonalcoholic fatty liver disease. *Aliment Pharmacol Ther* 2007; 25: 883-889.
- [14] Clark JM. The epidemiology of nonalcoholic fatty liver disease in adults. *J Clin Gastroenterol* 2006; 40: S5-10.
- [15] Ruhl CE, Everhart JE. Determinants of the association of overweight with elevated serum alanine aminotransferase activity in the United States. *Gastroenterology* 2003; 124: 71-79.
- [16] Clark JM, Brancati FL, Diehl AM. The prevalence and etiology of elevated aminotransferase levels in the United States. *Am J Gastroenterol* 2003; 98: 960-967.
- [17] Wang L, Guo J, Lu J. Risk factor compositions of nonalcoholic fatty liver disease change with body mass index in males and females. *Oncotarget* 2016; 7: 35632-35642.
- [18] Bi WR, Yang CQ, Shi Q, Xu Y, Cao CP, Ling J, Wang XY. Large-scale analysis of factors influencing nonalcoholic fatty liver disease and its relationship with liver enzymes. *Genet Mol Res* 2014; 13: 5880-5891.
- [19] Rodríguez-Hernández H, Gonzalez JL, Márquez-Ramirez MD, Flores-Hernandez M, Rodríguez-Morán M, Guerrero-Romero F. Risk factors associated with nonalcoholic fatty liver disease and its relationship with the hepatic histological changes. *Eur J Gastroenterol Hepatol* 2008; 20: 399-403.
- [20] Hoyumpa AM Jr, Green HL, Dunn GD, Schenker S. Fatty liver: biochemical and clinical considerations. *Am J Dig Dis* 1975; 20: 1142-1170.
- [21] Tiikkainen M, Bergholm R, Vehkavaara S, Rissanen A, Häkkinen AM, Tamminen M, Teramo K, Yki-Järvinen H. Effects of identical weight loss on body composition and features of insulin resistance in obese women with high and low liver fat content. *Diabetes* 2003; 52: 701-707.
- [22] Rinella ME. Nonalcoholic fatty liver disease: a systematic review. *JAMA* 2015; 313: 2263-2273.
- [23] Chang Y, Ryu S, Sung E, Jang Y. Higher concentrations of alanine aminotransferase within the reference interval predict nonalcoholic fatty liver disease. *Clin Chem* 2007; 53: 686-692.
- [24] Chen ZW, Chen LY, Dai HL, Chen JH, Fang LZ. Relationship between alanine aminotransferase levels and metabolic syndrome in nonalcoholic fatty liver disease. *J Zhejiang Univ Sci B* 2008; 9: 616-622.
- [25] Siegelman ES, Rosen MA. Imaging of hepatic steatosis. *Semin Liver Dis* 2001; 21: 71-80.
- [26] Joseph AE, Saverymuttu SH, al-Sam S, Cook MG, Maxwell JD. Comparison of liver histology with ultrasonography in assessing diffuse parenchymal liver disease. *Clin Radiol* 1991; 43: 26-31.