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**Prevalence of abnormal serum liver enzymes in patients with type 2  
diabetes mellitus: a cross-sectional study from China**

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**Running title:** Prevalence of abnormal liver enzymes in diabetic patients

**Abstract**

**Objective:** This cross-sectional study aimed to determine the prevalence of elevated alanine aminotransferase (ALT) and aspartate aminotransferase (AST) in Chinese type 2 diabetic patients and identify contributing risk factors.

**Methods:** This cross-sectional study was conducted in rural areas of China, and 1,198 type 2 diabetic patients with complete data were recruited. Elevated ALT and AST levels were defined as >40 U/L. Prevalence of abnormal liver enzymes was analyzed and multivariable analysis was used to identify independent risk factors.

**Results:** 10.3% and 6.1% diabetic patients had elevated ALT and elevated AST, respectively. The prevalence of elevated liver enzymes was gender-related; it was 13.8% in men and 7.5% in women for elevated ALT, and 7.4% in men and 3.1% in women for elevated AST. High triglyceride was positively associated with both elevated ALT (OR 1.80, 95% CI 1.08-3.01,  $p=0.024$ ) and elevated AST (OR 2.24, 95%CI 1.08-4.65,  $p=0.031$ ), while taking anti-diabetes medicine was inversely related to both elevated ALT (OR 0.48, 95% CI 0.29-0.80,  $p=0.005$ ) and elevated AST (OR 0.37, 95% CI 0.17-0.82,  $p=0.014$ ). The risk of elevated ALT in diabetic patients increased with the presence of obesity (OR 2.54, 95% CI 1.07-6.01,  $p=0.034$ ), and was lower in women (OR 0.37, 95% CI 0.19-0.72,  $p=0.003$ ). Hypertension (OR 4.33, 95% CI 1.41-13.30,  $p=0.011$ ), current drinking status (OR 2.90, 95% CI 1.21-6.96,

p=0.017) and national minority (OR 3.26, 95%CI 1.31-8.12, p=0.011) were risk factors for elevated AST.

**Conclusions:** A relatively high prevalence of abnormal serum liver enzymes in diabetic patients was demonstrated in China, especially in males. More attention should be paid to preventing liver injuries in diabetic patients.

**Keywords:** Alanine aminotransferase; aspartate aminotransferase; liver enzymes; cross-sectional; type 2 diabetes mellitus.

## 1. Introduction

Serum aminotransferase (ALT) and aspartate aminotransferase (AST) are the common liver enzymes of liver tests and well-known markers of liver damage. During liver inflammation or injury, ALT and AST were released from damaged hepatocytes into the blood, which led to the elevated ALT and AST levels [1 2]. Measurement of serum liver enzymes is common in clinical practice, and even a minor elevation of ALT level correlates with mortality from liver diseases [3].

Diabetes, as a worldwide public health problem, is a metabolic disease characterized by chronic hyperglycemia and it requires urgent attention and control. It is estimated that the global diabetes prevalence will be 7.7% (552 million people) by 2030 [4]. A nationwide epidemiological survey of diabetes in China showed that the prevalence of diabetes was estimated to be 11.6% in the Chinese adult population in 2013 [5]. Non-alcoholic fatty liver disease (NAFLD) is characterized by histological findings from fat accumulation in hepatocytes which forms “simple steatosis” or non-alcoholic steatohepatitis (NASH) [6 7]. NASH has the feature of lobular inflammation and hepatocyte injury (ballooning) with or without fibrosis, and has the

potential to progress to cirrhosis and hepatocellular carcinoma (HCC) [8-12]. Several studies have shown that type 2 diabetes mellitus is positively associated with almost all of the hepatic diseases including abnormal serum liver enzymes, NAFLD, liver cirrhosis and HCC [13 14]. In addition, Type 2 diabetes mellitus has been identified as one of the most prevalent causes of non-alcoholic steatohepatitis (NASH). Moreover, it has been reported that patients with type 2 diabetes mellitus have a higher risk of chronic hepatic diseases [16-19] and death from liver cirrhosis [14 20 21].

Even though the serum liver enzymes are routinely measured in diabetic patients and several population-based studies have reported the prevalence of elevated ALT level in diabetic patients [14 22-28], none of them are conducted on a Chinese population. Type 2 diabetes mellitus has been identified as a risk factor for hepatic diseases, therefore further assessment of serum liver enzymes in patients with type 2 diabetes mellitus may be of value. This is because a different prevalence of abnormal liver enzymes in any population may translate to different cutoff values, which are influenced by age, sex, demography and ethnicity. Thus, the aim of this study was to investigate the prevalence of abnormal liver profiles including of elevated ALT and elevated AST in a representative, general population-based sample of Chinese adults with type 2 diabetes mellitus.

## **2. Methods**

### ***Study population***

This cross-sectional study was conducted from July 2012 to August 2013 in rural areas of Liaoning Province, which is called Northeast China Rural Cardiovascular Health Study (NCRCHS). A representative sample aged  $\geq 35$  years was selected to

describe the prevalence and natural history of cardiovascular risk factors. The study adopted a multi-stage, stratified randomly cluster-sampling scheme. In the first stage, 3 counties (Dawa, Zhangwu and Liaoyang County) were randomly selected which represented east, south and north of Liaoning province. In the second stage, we randomly selected one town from each county (a total of 3 towns). In the third stage, in each township, we randomly selected 8-10 rural villages. Finally, a total of 26 rural villages were included. All eligible permanent residents aged  $\geq 35$  years from each village were selected for participation (a total of 14,016 participants). Among them, 11,956 residents agreed and completed this epidemiological investigation and the response rate was 85.3%. Approval for the NCRCHS was obtained from the Ethics Committee of China Medical University (Shenyang, China). All participants provided written informed consent and all procedures were performed in accordance with the ethical standards. If the participants were illiterate, their proxies wrote the informed consents for them. In this study, we used data of baseline and only participants with type 2 diabetes mellitus and completed data were included, making a final sample size of 1,198.

### ***Data Collection***

Data was collected during a single clinic visit by cardiologists and trained nurses using a standard questionnaire by face-to-face interview. Before the survey was performed, we invited all eligible investigators to attend the organized training. The training contents included the purpose of this study, how to administer the questionnaire, the standard method of measurement, the importance of standardization,

and the study procedures. A strict test was evaluated after this training, only those who scored perfectly on the test could become investigators. During data collection, our inspectors had further instructions and support.

Data on demographic characteristics, lifestyle risk factors, medical history, were obtained by interview with a standardized questionnaire. The questionnaire was designed by statistical experts and clinical specialists. There was a central steering committee with a subcommittee for quality control. The project management office of Liaoning Province randomly checked for 5% questionnaires; the unqualified questionnaires were re-investigated again, and if the investigator made a fake questionnaire, we would cancel the qualification of this investigator and abandon all of his or her questionnaires. Smoking and alcohol consumption status were also surveyed. Smoking and alcohol status were assessed by two types of questions: “Have you ever smoked at least one cigarette per day for over six months/Have you ever taken alcohol at least twice a week for over a year?” and “Do you smoke/take alcohol now?” Respondents were defined as current smokers/drinkers (those who answered YES to both questions), former smokers/drinkers (those who answered YES to the first question and NO to the second one), and never smokers/drinkers (those who answered NO to both questions). The medical treatment for the diabetes control in this survey was oral hypoglycaemic agents or insulin. Physical activity included occupational and leisure-time physical activity. Occupational and leisure-time physical activity were merged and regrouped into the following three categories: 1) low—subjects who reported light levels of both occupational and leisure-time

physical activity, 2) moderate—subjects who reported moderate or high levels of either occupational or leisure-time physical activity and 3) high—subjects who reported a moderate or high level of both occupational and leisure-time physical activity.

### ***Blood Pressure Measurements***

According to American Heart Association protocol, blood pressure was measured three times in a sitting position at 2-min intervals after at least 5 min of rest in a quiet room with the use of an automatic electronic sphygmomanometer (HEM-741C; Omron, Tokyo, Japan). Two doctors checked the calibration of the Omron device using a standard mercury sphygmomanometer every month under the British Hypertension Society protocol [29]. The mean of three BP measurements was taken and used in all analyses.

### ***Anthropometric Measurements***

Waist circumference (WC) was measured at the minimum circumference between iliac crest and the rib cage in standing position at the end of normal expiration using a non-elastic tape, and hip circumference (HC) at the level of the greater trochanters was measured using a flexible tape (to the nearest 0.1 cm). The body mass index (BMI) was calculated using the formula  $\text{weight (kg)}/\text{height}^2 (\text{m}^2)$ . Waist-to-hip ratio (WHR) was calculated by dividing WC by HC.

### ***Biochemical Measurements***

Fasting (12 h overnight) blood samples were collected by venepuncture in EDTA tubes. Plasma was subsequently separated and frozen at  $-20^{\circ}\text{C}$  within 1 h for testing



at a central, certified laboratory after collection. Fasting plasma glucose (FPG), plasma total cholesterol (TC), triglycerides (TG), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), serum ALT, and AST were analyzed enzymatically on an Olympus AU640 auto analyzer (Olympus, Kobe, Japan). All laboratory equipment was calibrated and blinded duplicate samples were used.

### ***Definitions***

According to JNC-7 report [30], hypertension was defined as SBP  $\geq 140$  mm Hg and/or DBP  $\geq 90$  mm Hg and/or use of antihypertensive medications. Diabetes mellitus was diagnosed according to the WHO criteria [31]: FPG  $\geq 7$  mmol/L (126 mg/dL) and/or being on treatment for diabetes. High TC was defined as TC  $\geq 6.21$  mmol/L (240 mg/dL). High TG was defined as TG  $\geq 2.26$  mmol/L (200 mg/dL). High LDL-C was defined as LDL-C  $\geq 4.16$  mmol/L (160 mg/dL). Low HDL-C was defined as HDL-C  $< 1.03$  mmol/L (40 mg/dL) [32]. BMI was categorized into 3 groups as normal (BMI  $< 25$  kg/m<sup>2</sup>), overweight ( $25 \leq$  BMI  $< 30$  kg/m<sup>2</sup>) and obesity (BMI  $\geq 30$  kg/m<sup>2</sup>), according to the World Health Organization (WHO) criteria [33]. Abdominal obesity was defined as WC  $\geq 88$  cm for females and WC  $\geq 102$  cm for males [34]. The Elevated WHR is considered if it exceeded 0.9 in men, and 0.85 in women [35]. Elevated serum ALT or AST level was defined as greater than 40 U/L [36].

### ***Statistical Analysis***

All statistical analyses were performed using SPSS version 19.0 software (SPSS Inc, Chicago, Illinois, USA). Continuous variables were expressed as means  $\pm$  standard deviation (SD) for normally distributed variables, whereas categorical variables were

expressed as frequencies and percentages. To assess the risk factors for elevated liver enzymes, we used multivariable logistic regression analysis including potential confounders. Adjusted odds ratios with a 95% confidence interval (CI) were presented for the final models.  $P < 0.05$  indicated statistical significance.

### 3. Results

A total of 1,198 patients aged  $\geq 35$  years with type 2 diabetes mellitus were included in the study. The subject characteristics were displayed in Table 1. Among the 1,198 diabetic patients enrolled in this present study, 44.2% ( $n=529$ ) were men and 55.8% ( $n=629$ ) were women. Their mean age was  $57.6 \pm 9.7$  years. About race group investigation, we found 94.7% ( $n=1134$ ) were Han nationality and 5.3% ( $n=64$ ) were national minority. Concerning anthropometric indices of the 1,198 diabetic patients, the average BMI was  $26.2 \pm 3.7 \text{ kg/m}^2$ , and the average WC was  $87.1 \pm 9.5 \text{ cm}$ , respectively. In addition, Table 1 also presented the biochemical data of the 1,198 diabetic patients including SBP, DBP, lipid profiles and liver enzymes levels.

Table 2 and Table 3 showed the prevalence and associated risk factors of elevated ALT and AST in diabetic patients. The prevalence of elevated ALT and elevated AST was 10.3% ( $n=123$ ) and 6.1% ( $n=60$ ), respectively. In addition, the prevalence of elevated liver enzymes was significantly higher in males than in females (elevated ALT: 13.8% for men and 7.5% for women; elevated AST: 7.4% for men and 3.1% for women). The prevalence of elevated ALT (Fig. 1A) and AST (Fig. 1B) was higher in men than in women across all of the age categories. The multiple logistic regression analysis showed that male sex was a significant risk factors for the

elevated ALT, but it was not so for elevated AST. The prevalence of elevated ALT seemed to increase with BMI (OR 2.54, 95%CI 1.07-6.01,  $p=0.034$  for obesity). In Table 3, elevated AST was positively associated with hypertension (OR 4.33, 95%CI 1.41-13.30,  $p=0.011$ ), current drinking status (OR 2.90, 95% CI 1.21-6.96,  $p=0.017$ ), and national minority (OR 3.26, 95%CI 1.31-8.12,  $p=0.011$ ). However, multivariate logistic regression had presented that high triglyceride was positively associated with both elevated ALT (OR 1.80, 95%CI 1.08-3.01,  $p=0.024$ ) and elevated AST (OR 2.24, 95%CI 1.08-4.65,  $p=0.031$ ), while taking anti-diabetes medicine was the protective factor for both elevated ALT (OR 0.48, 95%CI 0.29-0.80,  $p=0.005$ ) and elevated AST (OR 0.37, 95%CI 0.17-0.82,  $p=0.014$ ).

#### **4. Discussion**

The prevalence of serum ALT and AST elevation is not well known in type 2 diabetic patients, especially in China. To the best of our knowledge, this is the first cross-sectional survey to assess the prevalence and risk factors of abnormal liver enzymes in Chinese adults with type 2 diabetes mellitus. In the present study, the prevalence of elevated ALT and AST levels (respectively 10.3% and 6.1%) is higher than those reported in our previous studies which reported the prevalence of elevated ALT level was 7.4% [37] and elevated AST level was 3.5% in general Chinese population [38]. In our study, the range of normality of serum liver enzymes had been lowered. This therefore reminded us the routine screening of liver enzymes could help arrest the progress of liver injuries of diabetes. Compared to the results of previous studies which also included patients with type 2 diabetes mellitus, the prevalence of

abnormal liver enzymes in our study was higher than an American survey [39], but substantially lower than those found in other studies [40-43]. In the study from west Algeria [25], the prevalence of ALT and AST elevation was 13.9% and 10%, and this study reported a higher prevalence of elevated liver enzymes in women than in men. Whereas, in the present study and other studies [23 24 44 45], men had higher prevalence of elevated liver enzymes compared to women, which likely mirrored NAFLD [46]. The gender difference could be due to differences in body fat distribution and alcohol intake. The explanation for different prevalence of abnormal liver enzymes in any study may be different cutoff values of serum liver enzymes, which are influenced by age, sex, demography and ethnicity [47].

In clinical practice, the ALT and AST elevations were often attributed to the presence of NAFLD. In patients with type 2 diabetic mellitus, elevations in liver enzymes could be due to NAFLD [23 42]. In the present study, the inverse relationship between elevated liver enzymes and taking anti-diabetes medicine may be explained by rigorous treatment and control of diabetes mellitus. It was notable that a relative small percentage (38.1%) of diabetic patients were using anti-diabetic medications, which showed that the anti-diabetic medications rate of diabetic patients was at a low level in our rural Chinese population. We indicated that the risk of elevated ALT in patients with type 2 diabetes mellitus increased with the presence of obesity (BMI  $>30 \text{ kg/m}^2$  according to WHO [33]), which was consistent with the previous study [23]. It was noteworthy that we used the WHO definition of obesity instead of Chinese definition in which the cutoff of obesity was BMI  $\geq 28 \text{ kg/m}^2$ . In a

few of previous studies, the WHO definition of obesity was considered to be suitable for Chinese population [5 37 38]. This relationship between obesity and elevated ALT was also found in other studies [25 48]. Moreover, high BMI was considered as a risk factor for NAFLD, and even for NASH [48]. In accordance with previous studies [23 49], our results showed that elevated liver enzymes appeared to show positive associations with high TG and current drinking status. Though current smoking status may play a role in abnormal liver tests, no significant association existed between the presence of elevated liver enzymes and smoking in this current study.

Some limitations need to be acknowledged in this present study. First, due to this cross-sectional design, we were unable to determine whether or not there was a causal association. Second, we did not collect information about glycemic control, hepatitis B and C infection, and other chronic liver diseases such as autoimmune liver disease, so confounding effects of these factors should be considered. Third, alcohol ingestion was not quantified, and only one measure of aminotransferases was performed. A better way for screening of NAFLD is by obtaining a liver image by some method; alterations of liver enzymes have a very low predictive value for screening of NAFLD. However, the strengths of this present study were its population-based design, and the first assessment of the prevalence and risk factors of elevated ALT and AST in Chinese patients with type 2 diabetes mellitus.

## **5. Conclusions**

In conclusion, a relatively high prevalence of abnormal serum liver enzymes in patients with type 2 diabetes mellitus was demonstrated in rural areas of China,

especially in male participants. Further work is required to determine the mechanisms of the elevation. Our findings could contribute to a better knowledge about prevalence of elevated ALT and AST in Chinese type 2 diabetic patients, and also help to monitor liver injuries in diabetic patients.

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### ***Declaration of interests***

*The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.*

### **References**

1. Hanley AJ, Williams K, Festa A, et al. Elevations in markers of liver injury and risk of type 2 diabetes: the insulin resistance atherosclerosis study. *Diabetes* 2004;53(10):2623-32
2. Westerbacka J, Corner A, Tiikkainen M, et al. Women and men have similar amounts of liver and intra-abdominal fat, despite more subcutaneous fat in women: implications for sex differences in markers of cardiovascular risk. *Diabetologia* 2004;47(8):1360-9 doi: 10.1007/s00125-004-1460-1[published Online First: Epub Date]].

3. Kim HC, Nam CM, Jee SH, et al. Normal serum aminotransferase concentration and risk of mortality from liver diseases: prospective cohort study. *BMJ (Clinical research ed)* 2004;328(7446):983 doi: 10.1136/bmj.38050.593634.63[published Online First: Epub Date]].
4. Whiting DR, Guariguata L, Weil C, et al. IDF diabetes atlas: global estimates of the prevalence of diabetes for 2011 and 2030. *Diabetes research and clinical practice* 2011;94(3):311-21 doi: 10.1016/j.diabres.2011.10.029[published Online First: Epub Date]].
5. Xu Y, Wang L, He J, et al. Prevalence and control of diabetes in Chinese adults. *Jama* 2013;310(9):948-59 doi: 10.1001/jama.2013.168118[published Online First: Epub Date]].
6. Ballestri S, Nascimbeni F, Romagnoli D, et al. The independent predictors of NASH and its individual histological features. Insulin resistance, serum uric acid, metabolic syndrome, ALT and serum total cholesterol are a clue to pathogenesis and candidate targets for treatment. *Hepatology research : the official journal of the Japan Society of Hepatology* 2016 doi: 10.1111/hepr.12656[published Online First: Epub Date]].
7. Ballestri S, Zona S, Targher G, et al. Nonalcoholic fatty liver disease is associated with an almost twofold increased risk of incident type 2 diabetes and metabolic syndrome. Evidence from a systematic review and meta-analysis. *Journal of gastroenterology and hepatology* 2016;31(5):936-44 doi: 10.1111/jgh.13264[published Online First: Epub Date]].
8. Ballestri S, Nascimbeni F, Romagnoli D, et al. The Role of Nuclear Receptors in the Pathophysiology, Natural Course, and Drug Treatment of NAFLD in Humans. *Advances in therapy* 2016;33(3):291-319 doi: 10.1007/s12325-016-0306-9[published Online First: Epub Date]].
9. Brunt EM, Wong VW, Nobili V, et al. Nonalcoholic fatty liver disease. *Nature reviews Disease primers* 2015;1:15080 doi: 10.1038/nrdp.2015.80[published Online First: Epub Date]].
10. Singh S, Allen AM, Wang Z, et al. Fibrosis progression in nonalcoholic fatty liver vs nonalcoholic steatohepatitis: a systematic review and meta-analysis of paired-biopsy studies. *Clinical gastroenterology and hepatology : the official clinical practice journal of the American Gastroenterological Association* 2015;13(4):643-54.e1-9; quiz e39-40 doi: 10.1016/j.cgh.2014.04.014[published Online First: Epub Date]].
11. Rinella ME. Nonalcoholic fatty liver disease: a systematic review. *Jama* 2015;313(22):2263-73 doi: 10.1001/jama.2015.5370[published Online First: Epub Date]].
12. Nascimbeni F, Pais R, Bellentani S, et al. From NAFLD in clinical practice to answers from guidelines. *Journal of hepatology* 2013;59(4):859-71 doi: 10.1016/j.jhep.2013.05.044[published Online First: Epub Date]].
13. Matteoni CA, Younossi ZM, Gramlich T, et al. Nonalcoholic fatty liver disease: a spectrum of clinical and pathological severity. *Gastroenterology* 1999;116(6):1413-9



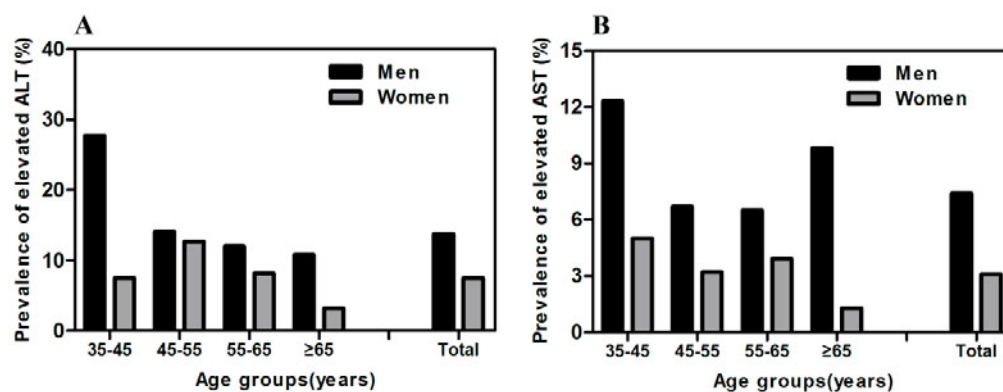
14. Tolman KG, Fonseca V, Dalpiaz A, et al. Spectrum of liver disease in type 2 diabetes and management of patients with diabetes and liver disease. *Diabetes care* 2007;30(3):734-43 doi: 10.2337/dc06-1539[published Online First: Epub Date]].
15. Daniel S, Ben-Menachem T, Vasudevan G, et al. Prospective evaluation of unexplained chronic liver transaminase abnormalities in asymptomatic and symptomatic patients. *Am J Gastroenterol* 1999;94(10):3010-4 doi: 10.1111/j.1572-0241.1999.01451.x[published Online First: Epub Date]].
16. Ioannou GN, Boyko EJ, Lee SP. The prevalence and predictors of elevated serum aminotransferase activity in the United States in 1999-2002. *Am J Gastroenterol* 2006;101(1):76-82 doi: 10.1111/j.1572-0241.2005.00341.x[published Online First: Epub Date]].
17. El-Serag HB, Tran T, Everhart JE. Diabetes increases the risk of chronic liver disease and hepatocellular carcinoma. *Gastroenterology* 2004;126(2):460-8
18. Davila JA, Morgan RO, Shaib Y, et al. Diabetes increases the risk of hepatocellular carcinoma in the United States: a population based case control study. *Gut* 2005;54(4):533-9 doi: 10.1136/gut.2004.052167[published Online First: Epub Date]].
19. Loria P, Lonardo A, Anania F. Liver and diabetes. A vicious circle. *Hepatology research : the official journal of the Japan Society of Hepatology* 2013;43(1):51-64 doi: 10.1111/j.1872-034X.2012.01031.x[published Online First: Epub Date]].
20. de Marco R, Locatelli F, Zoppini G, et al. Cause-specific mortality in type 2 diabetes. The Verona Diabetes Study. *Diabetes care* 1999;22(5):756-61
21. Trombetta M, Spiazzi G, Zoppini G, et al. Review article: type 2 diabetes and chronic liver disease in the Verona diabetes study. *Alimentary pharmacology & therapeutics* 2005;22 Suppl 2:24-7 doi: 10.1111/j.1365-2036.2005.02590.x[published Online First: Epub Date]].
22. Clark JM, Brancati FL, Diehl AM. The prevalence and etiology of elevated aminotransferase levels in the United States. *Am J Gastroenterol* 2003;98(5):960-7 doi: 10.1111/j.1572-0241.2003.07486.x[published Online First: Epub Date]].
23. West J, Brousil J, Gazis A, et al. Elevated serum alanine transaminase in patients with type 1 or type 2 diabetes mellitus. *QJM : monthly journal of the Association of Physicians* 2006;99(12):871-6 doi: 10.1093/qjmed/hcl116[published Online First: Epub Date]].
24. Meybodi MA, Afkhami-Ardekani M, Rashidi M. Prevalence of abnormal serum alanine aminotransferase levels in type 2 diabetic patients in Iran. *Pakistan journal of biological sciences : PJBS* 2008;11(18):2274-7
25. Belkacemi L, Belalia M. Cross-sectional pilot study about the liver enzymes profile in type 2 diabetic patients from an Algerian west region: Wilaya of Mostaganem. *Diabetes & metabolic syndrome* 2015 doi: 10.1016/j.dsx.2015.10.013[published Online First: Epub Date]].
26. Jiamjarasrangsi W, Lertmaharit S, Sangwatanaroj S, et al. Type 2 diabetes,



- impaired fasting glucose, and their association with increased hepatic enzyme levels among the employees in a university hospital in Thailand. *Journal of the Medical Association of Thailand = Chotmaihet thangphaet* 2009;92(7):961-8
27. Leeds JS, Forman EM, Morley S, et al. Abnormal liver function tests in patients with Type 1 diabetes mellitus: prevalence, clinical correlations and underlying pathologies. *Diabet Med* 2009;26(12):1235-41 doi: 10.1111/j.1464-5491.2009.02839.x[published Online First: Epub Date]].
  28. Morling JR, Strachan MW, Hayes PC, et al. Prevalence of abnormal plasma liver enzymes in older people with Type 2 diabetes. *Diabet Med* 2012;29(4):488-91 doi: 10.1111/j.1464-5491.2011.03492.x[published Online First: Epub Date]].
  29. O'Brien E, Petrie J, Littler W, et al. An outline of the revised British Hypertension Society protocol for the evaluation of blood pressure measuring devices. *J Hypertens* 1993;11(6):677-9
  30. Chobanian AV, Bakris GL, Black HR, et al. Seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. *Hypertension* 2003;42(6):1206-52 doi: 10.1161/01.HYP.0000107251.49515.c2[published Online First: Epub Date]].
  31. Alberti KG, Zimmet PZ. Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: diagnosis and classification of diabetes mellitus provisional report of a WHO consultation. *Diabet Med* 1998;15(7):539-53 doi: 10.1002/(sici)1096-9136(199807)15:7<539::aid-dia668>3.0.co;2-s[published Online First: Epub Date]].
  32. Executive Summary of The Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, And Treatment of High Blood Cholesterol In Adults (Adult Treatment Panel III). *Jama* 2001;285(19):2486-97
  33. Hypertension control. Report of a WHO Expert Committee. *World Health Organ Tech Rep Ser* 1996;862:1-83
  34. Diet, nutrition and the prevention of chronic diseases. *World Health Organ Tech Rep Ser* 2003;916:i-viii, 1-149, backcover
  35. Browning LM, Hsieh SD, Ashwell M. A systematic review of waist-to-height ratio as a screening tool for the prediction of cardiovascular disease and diabetes: 0.5 could be a suitable global boundary value. *Nutrition research reviews* 2010;23(2):247-69 doi: 10.1017/s0954422410000144[published Online First: Epub Date]].
  36. Chen ZW, Chen LY, Dai HL, et al. Relationship between alanine aminotransferase levels and metabolic syndrome in nonalcoholic fatty liver disease. *J Zhejiang Univ Sci B* 2008;9(8):616-22 doi: 10.1631/jzus.B0720016[published Online First: Epub Date]].
  37. Chen S, Guo X, Zhang X, et al. Association between elevated serum alanine aminotransferase and cardiometabolic risk factors in rural Chinese population: a cross-sectional study. *BMC cardiovascular disorders* 2015;15:65 doi: 10.1186/s12872-015-0060-y[published Online First: Epub Date]].

38. Chen S, Guo X, Yu S, et al. Metabolic Syndrome and Serum Liver Enzymes in the General Chinese Population. *International journal of environmental research and public health* 2016;13(2) doi: 10.3390/ijerph13020223[published Online First: Epub Date]].
39. Erbey JR, Silberman C, Lydick E. Prevalence of abnormal serum alanine aminotransferase levels in obese patients and patients with type 2 diabetes. *The American journal of medicine* 2000;109(7):588-90
40. Lebovitz HE, Kreider M, Freed MI. Evaluation of liver function in type 2 diabetic patients during clinical trials: evidence that rosiglitazone does not cause hepatic dysfunction. *Diabetes care* 2002;25(5):815-21
41. Forlani G, Di Bonito P, Mannucci E, et al. Prevalence of elevated liver enzymes in Type 2 diabetes mellitus and its association with the metabolic syndrome. *Journal of endocrinological investigation* 2008;31(2):146-52 doi: 10.1007/bf03345581[published Online First: Epub Date]].
42. Hickman IJ, Russell AJ, Prins JB, et al. Should patients with type 2 diabetes and raised liver enzymes be referred for further evaluation of liver disease? *Diabetes research and clinical practice* 2008;80(1):e10-2 doi: 10.1016/j.diabres.2007.11.016[published Online First: Epub Date]].
43. Hermos JA, Cohen SA, Hall R, et al. Association of elevated alanine aminotransferase with BMI and diabetes in older veteran outpatients. *Diabetes research and clinical practice* 2008;80(1):153-8 doi: 10.1016/j.diabres.2007.11.008[published Online First: Epub Date]].
44. Judi L, Toukan A, Khader Y, et al. Prevalence of elevated hepatic transaminases among Jordanian patients with type 2 diabetes mellitus. *Annals of Saudi medicine* 2010;30(1):25-32 doi: 10.4103/0256-4947.59369[published Online First: Epub Date]].
45. Dufour DR, Lott JA, Nolte FS, et al. Diagnosis and monitoring of hepatic injury. I. Performance characteristics of laboratory tests. *Clinical chemistry* 2000;46(12):2027-49
46. Lonardo A, Bellentani S, Argo CK, et al. Epidemiological modifiers of non-alcoholic fatty liver disease: Focus on high-risk groups. *Digestive and liver disease : official journal of the Italian Society of Gastroenterology and the Italian Association for the Study of the Liver* 2015;47(12):997-1006 doi: 10.1016/j.dld.2015.08.004[published Online First: Epub Date]].
47. Siest G, Schiele F, Galteau MM, et al. Aspartate aminotransferase and alanine aminotransferase activities in plasma: statistical distributions, individual variations, and reference values. *Clinical chemistry* 1975;21(8):1077-87
48. Angulo P, Keach JC, Batts KP, et al. Independent predictors of liver fibrosis in patients with nonalcoholic steatohepatitis. *Hepatology (Baltimore, Md)* 1999;30(6):1356-62 doi: 10.1002/hep.510300604[published Online First: Epub Date]].
49. Sherman KE. Alanine aminotransferase in clinical practice. A review. *Archives of internal medicine* 1991;151(2):260-5

**Fig. 1.** Age and sex-specific prevalence of elevated ALT (A) and AST (B) in Chinese type 2 diabetic patients. Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase.



**Table 1 Baseline characteristics of the 1,198 participants with type 2 diabetes mellitus.**

Variables	n (%) / mean $\pm$ SD
Age, yr	57.6 $\pm$ 9.7
Sex, %	
Male	529(44.2)
Female	669(55.8)
Race, %	
Han	1134(94.7)
Others	64(5.3)
BMI (kg/m <sup>2</sup> )	26.2 $\pm$ 3.7
WC, cm	87.1 $\pm$ 9.5
WHR	0.9 $\pm$ 0.1
SBP, mm Hg	153.2 $\pm$ 24.1
DBP, mm Hg	85.5 $\pm$ 12.5
TC, mmol/L	5.6 $\pm$ 1.2
TG, mmol/L	2.5 $\pm$ 2.5
HDL-C, mmol/L	1.3 $\pm$ 0.3
LDL-C, mmol/L	3.2 $\pm$ 0.9
ALT, U/L	25.4 $\pm$ 17.8
AST, U/L	22.4 $\pm$ 14.0
Current smoking status, %	369(30.8)
Current drinking status, %	257(21.5)
Family history of diabetes, %	344(28.7)
Anti-diabetes medicine, %	456(38.1)
Physical activity, %	
Low	476(39.7)
Moderate	648(54.1)
High	74(6.2)

Data are expressed as the mean  $\pm$  SD or as n (%).

Abbreviations: BMI, body mass index; WC, waist circumference; WHR, waist-to-hip ratio; SBP, systolic blood pressure; DBP, diastolic blood pressure; TC, total cholesterol; TG, triacylglycerol; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; ALT, alanine aminotransferase; AST, aspartate aminotransferase.

**Table 2 Multivariate analysis of risk factors associated with elevated ALT in patients with type 2 diabetes mellitus.**

Variables	Normal ALT n (%)	Elevated ALT n (%)	OR	95% CI	P value
Age, yr					
35-45	104(9.7)	24(19.5)	1		
45-55	297(27.6)	41(33.3)	0.82	0.40-1.67	0.579
55-65	430(40.0)	43(35.0)	0.46	0.22-0.97	0.041*
≥65	244(22.7)	15(12.2)	0.27	0.11-0.70	0.006*
Sex,%					
Male	456(42.4)	73(59.3)	1		
Female	619(57.6)	50(40.7)	0.37	0.19-0.72	0.003*
Race, %					
Han	1022(95.1)	112(91.1)	1		
Others	53(4.9)	11(8.9)	1.09	0.47-2.52	0.836
BMI (kg/m <sup>2</sup> )					
Normal	430(40.0)	26(21.1)	1		
Overweight	515(47.9)	61(49.6)	1.57	0.80-3.06	0.186
Obesity	130(12.1)	36(29.3)	2.54	1.07-6.01	0.034*
abdominal obesity					
No	796(74.0)	80(65.0)	1		
Yes	279(26.0)	43(35.0)	1.56	0.79-3.08	0.198
WHR					
Normal	406(37.8)	31(25.2)	1		
Elevated	669(62.2)	92(74.8)	1.42	0.76-2.69	0.275
Hypertension					
No	269(25.0)	28(22.8)	1		
Yes	806(75.0)	95(77.2)	1.04	0.58-1.89	0.890
TC					
Normal	788(73.3)	85(69.1)	1		
high	287(26.7)	38(30.9)	0.94	0.46-1.91	0.858
TG					
Normal	691(64.3)	57(46.3)	1		
high	384(35.7)	66(53.7)	1.80	1.08-3.01	0.024*
HDL-C					
Normal	886(82.4)	92(74.8)	1		
low	189(17.6)	31(25.2)	1.33	0.73-2.42	0.347
LDL-C					
Normal	936(87.1)	101(82.1)	1		
high	139(12.9)	22(17.9)	1.96	0.83-4.64	0.124
Current smoking status					
No	746(69.4)	83(67.5)	1		

Yes	329(30.6)	40(32.5)	0.62	0.35-1.09	0.097
Current drinking status					
No	856(79.6)	85(69.1)	1		
Yes	219(20.4)	38(30.9)	1.49	0.78-2.83	0.222
Family history of diabetes					
No	764(71.1)	90(73.0)	1		
Yes	311(28.9)	33(27.0)	0.95	0.55-1.63	0.846
Anti-diabetes medicine					
No	648(60.3)	93(75.6)	1		
Yes	427(39.7)	30(24.4)	0.48	0.29-0.80	0.005*
High physical acitivity					
Low	427(39.7)	49(39.8)	1		
Moderate	583(54.3)	65(52.9)	0.78	0.46-1.32	0.363
High	65(6.0)	9(7.3)	0.87	0.32-2.39	0.783

Data are expressed as n (%).

Abbreviations: BMI, body mass index; WHR, waist-to-hip ratio; TC, total cholesterol; TG, triacylglycerol; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; ALT, alanine aminotransferase; AST, aspartate aminotransferase.

\*  $p < 0.05$ .

**Table 3 Multivariate analysis of risk factors associated with elevated AST in patients with type 2 diabetes mellitus.**

Variables	Normal AST n (%)	Elevated AST n (%)	OR	95% CI	P value
Age, yr					
35-45	117(10.3)	11(18.3)	1		
			0.78		
45-55	322(28.3)	16(26.7)	0	0.27-2.29	0.652
			0.66		
55-65	451(39.6)	22(36.7)	9	0.23-1.95	0.462
			0.48		
≥65	248(21.8)	11(18.3)	8	0.14-1.75	0.272
Sex,%					
Male	490(43.1)	39(65.0)	1		
Female	648(56.9)	21(35.0)	0.47	0.17-1.27	0.135
Race, %					
Han	1085(95.3)	49(81.7)	1		
Others	53(4.7)	11(18.3)	3.26	1.31-8.12	0.011*
BMI (kg/m <sup>2</sup> )					
Normal	434(38.1)	22(36.7)	1		
Overweight	554(48.7)	22(36.7)	0.57	0.25-1.32	0.189
Obesity	150(13.2)	16(26.6)	0.82	0.26-2.59	0.730
abdominal obesity					
No	834(73.3)	42(70.0)	1		
Yes	304(26.7)	18(30.0)	1.64	0.59-4.57	0.346
WHR					
Normal	418(36.7)	19(31.7)	1		
Elevated	720(63.3)	41(68.3)	1.13	0.51-2.46	0.768
Hypertension					
No	291(25.6)	6(10.0)	1		
				1.41-13.3	
Yes	847(74.4)	54(90.0)	4.33	0	0.011*
TC					
Normal	826(72.6)	47(78.3)	1		
high	312(27.4)	13(21.7)	0.41	0.14-1.24	0.114
TG					
Normal	716(62.9)	32(53.3)	1		
high	422(37.1)	28(46.7)	2.24	1.08-4.65	0.031*
HDL-C					
Normal	931(81.8)	47(78.3)	1		

low	207(18.2)	13(21.7)	1.03	0.44-2.42	0.948
LDL-C					
Normal	985(86.6)	52(86.6)	1		
high	153(13.4)	8(13.4)	2.01	0.53-7.57	0.302
Current smoking status					
No	796(69.9)	33(55.0)	1		
Yes	342(30.1)	27(45.0)	1.11	0.53-2.36	0.776
Current drinking status					
No	908(79.8)	33(55.0)	1		
Yes	230(20.2)	27(45.0)	2.90	1.21-6.96	0.017*
Family history of diabetes					
No	808	46(76.1)	1		
Yes	330	14(23.9)	1.10	0.51-2.37	0.817
Anti-diabetes medicine					
No	692(60.8)	49(81.4)	1		
Yes	446(39.2)	11(18.6)	0.37	0.17-0.82	0.014*
High physical activity					
Low	455(40.0)	21(35.0)	1		
Moderate	609(53.5)	39(65.0)	0.93	0.44-1.99	0.855
High	74(6.5)	0	0.78	0.26-2.15	0.997

Data are expressed as n (%).

Abbreviations: BMI, body mass index; WHR, waist-to-hip ratio; TC, total cholesterol; TG, triacylglycerol; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; ALT, alanine aminotransferase; AST, aspartate aminotransferase.

\*  $p < 0.05$ .