Determination of the upper cut-off values of serum alanine aminotransferase and aspartate aminotransferase in Chinese

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Abstract

AIM: To determine the upper cut-off values of serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST) in a Northern Chinese population.

METHODS: A total of 3769 subjects in Jilin Province Northeast China were stratified to determine the potential factors affecting serum ALT and AST levels. The upper cut-off values of serum ALT and AST in these subjects were determined using receiver operating characteristic analysis and their sensitivity and specificity were evaluated.

RESULTS: Stratification analysis revealed that serum ALT and AST levels were associated with gender, alcohol consumption, serum cholesterol and triglyceride levels, and body mass index. The upper cut-off values of serum ALT and AST were 22.15 U/L and 25.35 U/L for healthy men and 22.40 U/L and 24.25 U/L for healthy women, respectively. The new cut-off values had a higher sensitivity, but a slightly lower specificity than the current standards.

CONCLUSION: Our results indicate that the new upper cut-off values of serum ALT and AST are markedly lower than current standards and may be valuable for the evaluation of liver function.

Key words: Alanine aminotransferase; Aspartate aminotransferase; Upper cut-off value; Northern Chinese population; Serum alanine aminotransferase and aspartate aminotransferase

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alcohol consumption, serum cholesterol and triglyceride levels, and body mass index. The upper cut-off values of serum ALT and AST were 22.15 U/L and 25.35 U/L for healthy men and 22.40 U/L and 24.25 U/L for healthy women, respectively, which are markedly lower than current standards.

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INTRODUCTION

Serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels are two biomarkers frequently used for the assessment of hepatic diseases. ALT is predominantly expressed by hepatocytes, while AST is mainly expressed by both myocardial cells and hepatocytes. An increase in the levels of serum ALT and AST usually reflects various degrees of hepatic injury. As a result, changes in the levels of serum ALT and AST are useful serological markers for the diagnosis of hepatic diseases and for the evaluation of therapeutic efficacy and adverse hepatic effects of drug treatment[11]. Therefore, the application of an optimal upper cut-off value for serum ALT and AST levels is of particular significance due to their high clinical relevance.

The levels of serum ALT and AST can be affected by age, gender, alcohol consumption, body mass index (BMI), fasting blood glucose, strenuous physical exercise, dietary and living habits, nutrition, metabolic status, and drug treatment[12-18]. During the past few decades, social, economic and people's health conditions in China have notably changed. However, since their introduction in the 1950s, the old upper cut-off values for the levels of serum ALT (40 U/L) and AST (50 U/L) have been used in China without substantial modification[11,16-18]. Due to limited knowledge, the upper cut-off values for the levels of serum ALT and AST were established without consideration of various risk factors. Whether the current upper cut-off values can accurately reflect healthy liver function in the Chinese population is questionable. Indeed, these upper cut-off values have recently been challenged in other countries[19,23-26]. Previous studies have found that some patients with chronic hepatitis B (CHB) or chronic hepatitis C (CHC) have persistently normal levels of serum ALT, but many of them display severe liver inflammation and fibrosis, as evidenced by histological examination of biopsied specimens[27,28]. Apparently, the upper cut-off values for the levels of serum ALT and AST may underestimate the prevalence of chronic liver diseases. In addition, hepatitis B virus (HBV) and hepatitis C virus (HCV) infection are highly prevalent in China, which can progress to CHB and CHC, respectively, or even to liver cirrhosis and hepatocellular carcinoma (HCC). Therefore, it is critical to re-evaluate the upper cut-off values for the levels of serum ALT and AST in Chinese for the early and accurate diagnosis of liver diseases.

In the present study, we evaluated the upper cut-off values of the levels of serum ALT and AST in a Northeast Chinese population and identified potential risk factors that affected the values of serum ALT and AST levels in the diagnosis of liver diseases.

MATERIALS AND METHODS

Study population

Data were collected from an epidemiological study of chronic diseases in Jilin, China from September 2007 to October 2007. The questionnaire-based study was supervised and assisted by the National Bureau of Statistics of China. This study questionnaire was approved by the Ethics Committee of the First Hospital of Jilin University. A total of 6043 subjects from local rural and urban areas were included in the study, of whom 3769 (1798 men and 1971 women) received physical examinations (including height, body weight, waist circumference, and blood pressure), B-mode ultrasonography, and blood tests (liver function tests, routine blood tests, and anti-hepatitis C virus antibodies (HBsAg, HBsAb, HBeAg, HBeAb, and HBCAb). The study population had an average age of 45.0 ± 19.0 years and consisted predominantly of Han Chinese (n = 3749, 99.5%). The exclusion criteria included: subjects with hepatic steatosis; liver cirrhosis; liver enlargement; a history of HBV or HCV infection; current administration of medicine and a history of ALT and/or AST levels > 60 U/L; triglyceride (TG) ≥ 1.7 mmol/L; cholesterol ≥ 6.0 mmol/L; low density lipoprotein (LDL) ≥ 4.3 mmol/L; high density lipoprotein (HDL) < 1.04 mmol/L in men or < 1.3 mmol/L in women; BMI ≥ 23; alcohol consumption > 40 g/wo; daily cigarette consumption > 30. According to the assay results, we excluded 1632 individuals with factors affecting serum ALT and AST levels. The upper cut-off values of ALT and AST were evaluated in the remaining 2137 individuals.

Methods

Individuals were fasted overnight and their blood samples were collected, followed by centrifugation to prepare serum samples. The levels of fasting blood glucose, serum ALT and AST levels were measured using specific kits, according to the manufacturers’ instructions (Kehua Bio-Engineering, Shanghai, China). The levels of serum anti-hepatitis C virus antibodies, HBsAg, HBsAb, HBeAg, HBeAb, and HBCAb were determined by ELISA using assay kits from Abbott (Illinois, United States). Blood cell counts were performed using an automatic biochemical analyzer.
Potential factors affecting the levels of serum alanine aminotransferase and aspartate aminotransferase

| Factors          | Normal   | Abnormal | OR (95%CI) | P value | Normal   | Abnormal | OR (95%CI) | P value |
|------------------|----------|----------|------------|---------|----------|----------|------------|---------|
| Gender           |          |          |            |         |          |          |            |         |
| Male             | 1506 (44.8) | 292 (71.6) | 1.0        | 342.1254 | < 0.0001 | 1739 (47.3) | 59 (64.1) | 1.0     | 192.1106 | < 0.0001 |
| Female           | 1855 (55.2) | 116 (28.4) | 0.32 (0.26-0.40) | 0.0017 | 45 ± 19 | 45 ± 16 | 1.00 (0.98-1.02) | 0.03995 | 0.0891 |
| Drinking         |          |          |            |         |          |          |            |         |
| No               | 2220 (66.1) | 198 (48.5) | 1.0        | 0.98 (0.98-0.99) | < 0.0001 | 2371 (64.5) | 47 (51.1) | 1.0     | 120.0163 | < 0.0001 |
| Previous         | 53 (1.6) | 13 (3.2) | 2.75 (1.47-5.13) | 182.001 | < 0.0001 | 65 (1.8) | 1 (1.1) | 0.78 (0.11-5.71) | 197 (48.3) | < 0.0001 |
| Current          | 1088 (32.4) | 197 (48.3) | 2.03 (1.65-2.51) | 1241 (33.8) | 44 (47.8) | 1.79 (1.18-2.71) | 197 (48.3) | < 0.0001 |
| Smoking          |          |          |            |         |          |          |            |         |
| No               | 2120 (63.1) | 238 (58.3) | 1.0        | 29.8714 | 1362 (37.6) | 29 (31.5) | 0.76 (0.49-1.19) | 9.9796 | < 0.0001 |
| Smoker           | 1241 (36.9) | 170 (41.7) | 1.22 (0.99-1.50) | 3234 (92.6) | 55 (49.7) | 0.85 and 0.97 | 3.89 (25.9) | < 0.0001 |
| HCV              |          |          |            |         |          |          |            |         |
| Negative         | 3330 (99.1) | 399 (97.8) | 1.0        | 10.4863 | 3527 (95.9) | 72 (78.3) | 1.0     | 62.2821 | < 0.0001 |
| Positive         | 31 (0.9) | 43 (10.5) | 3.00 (2.09-4.31) | 150 (4.1) | 20 (21.7) | 6.53 (3.88-11.01) | 9.1076 | < 0.0001 |
| BMI              | 22.2 ± 3.91 | 23.6 ± 4.47 | 1.16 (1.13-1.20) | 33 (0.9) | 7 (7.6) | 9.10 (7.91-21.14) | 0.2593 | 0.0008 |
| Cholesterol      | 4.23 ± 1.2 | 4.57 ± 1.22 | 1.42 (1.28-1.56) | 30.0180 | < 0.0001 | 4.5 ± 1.2 | 14.2 (1.19-1.70) | 1.37468 | < 0.0001 |
| LDL              | 2.90 ± 0.90 | 3.20 ± 1.09 | 1.37 (1.23-1.52) | 2.56544 | < 0.0001 | 3.10 ± 1.2 | 0.50 (0.90-0.77) | 1.23 (0.95-1.56) | 1.16700 | < 0.0001 |
| HDL              | 1.30 ± 0.40 | 1.30 ± 0.45 | 1.06 (0.90-1.25) | 0.35468 | 0.5918 | 1.50 ± 0.4 | 1.00 (0.90-1.05) | 1.47788 | 0.0005 |
| Triglyceride     | 1.17 ± 0.97 | 1.76 ± 1.66 | 1.24 (1.17-1.30) | 2.03651 | < 0.0001 | 1.21 ± 0.6 | 1.14 (1.07-1.22) | 0.93770 | < 0.0001 |

1Data were expressed as median ± interquartile range in years; HBV positive was defined as HBsAg positive. ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; BMI: Body mass index.

RESULTS

Potential factors affecting serum ALT and AST levels

In this study, abnormal rates of serum ALT and AST levels in males were 16% and 3.3%, respectively. The abnormal rates in females were 5.9% and 1.7%, respectively; the rates of ALT and AST abnormalities in drinkers (alcohol consumption > 40 g/mo) were 15.3% and 3.4%, respectively. The abnormal rates in non-drinkers were 8.2% and 1.9%, respectively; the rates of ALT and AST abnormalities in drinkers (alcohol consumption > 40 g/mo) were 15.3% and 3.4%, respectively. The abnormal rates in females were 5.9% and 1.7%, respectively; the rates of ALT and AST abnormalities were 16% and 3.3%, respectively. The abnormal rates of serum ALT and AST levels were 25.3% and 11.8%, respectively; for HBV positive subjects were 25.3% and 11.8%, respectively; for HBV negative subjects were 10.1% and 2.0%, respectively; for HCV positive subjects were 22.5% and 17.5% respectively; for HCV negative subjects were 10.7% and 2.3%, respectively. As shown in Table 1, serum cholesterol, TG, LDL, BMI, alcohol consumption, smoking, gender, and hepatic diseases were associated with the serum levels of ALT and AST in this population. Furthermore, HDL levels were positively correlated with serum AST levels, and serum cholesterol, LDL and TG levels were positively correlated with serum ALT levels in this population. In addition, a higher level of serum HDL was the strongest factor associated with abnormal levels of serum AST, followed by higher levels of serum cholesterol, and LDL. Moreover, regular alcohol consumption was strongly associated with abnormal levels of serum ALT and AST in this population.

Results in men

Upper normal limits for the levels of serum ALT and AST in men: The areas under the receiver operating characteristic (ROC) curve of ALT and AST were 0.94 and 0.80, respectively (Figure 1, Table 2), which were statistically different from A = 0.5 (ALT: P < 0.05; AST: P < 0.05). The upper normal limit for the level of serum ALT was 22.15 U/L with a sensitivity of 0.89 and a specificity of 0.86. The upper normal limit for the level of serum AST was 25.35 U/L with a sensitivity of 0.85 and a specificity of 0.81 (Table 3).
DISCUSSION

The levels of serum ALT and AST are the most commonly used serological markers for the evaluation of hepatic diseases. However, a number of recent studies have challenged the currently used cut-off values for the levels of serum ALT and AST due to the presence of normal or near normal levels of serum ALT and AST in patients with chronic liver diseases [3,9,10,12]. The goal of CHB treatment is to reduce viral replication, subsequently decrease liver inflammation, fibrosis, and the risk of developing cirrhosis and HCC. Treatment guidelines for initiating treatment are based on the presence of active liver inflammation or elevated serum levels of liver transaminases [13,14]. According to the current upper normal limits for the levels of serum ALT, although 40% of HBeAg-positive patients had persistently normal serum ALT levels they had significant liver fibrosis on liver biopsy [15]. In another study, 35% of adult (> 35 years) HBeAg-positive patients had normal levels of serum ALT, but they already had advanced liver fibrosis [16]. Therefore, disease activity in patients during the immune tolerance phase may be erroneously judged by assessing HBV DNA and serum ALT levels alone [15,17]. In a retrospective study of 192 CHB patients, it was found that 37% of patients with significant hepatic fibrosis and inflammation had

Comparison of the new cut-off values with the current standards for the levels of serum ALT and AST in men: The new cut-off values for the levels of serum ALT and AST had slightly lower specificity, but much higher sensitivity than that of current standards (Table 2).

Results in women

Upper normal limits for the levels of serum ALT and AST in women: The areas under the ROC curve of the levels of serum ALT and AST in women were 0.90 and 0.84, respectively (Figure 2), which were statistically different from A = 0.5 (ALT: P < 0.05; AST: P < 0.05). The upper normal limit of the level of serum ALT was 22.4 U/L with a sensitivity of 0.90 and a specificity of 0.82. The upper normal limit of the level of serum AST was 24.25 U/L with a sensitivity of 0.85 and a specificity of 0.80 (Table 3).

Comparison of the new cut-off values with the current standards for the levels of serum ALT and AST in women: The new cut-off values for the levels of serum ALT and AST had slightly lower specificity, but much higher sensitivity than that of current standards (Table 4).
persists.
and adverse hepatic effects of drug treatment. Due to limited knowledge, the upper cut-off values for the levels of serum ALT and AST were established without consideration of various risk factors. Whether the current upper cut-off values can accurately reflect healthy liver function in the Chinese population is questionable.

**Research frontiers**

The upper cut-off values for the levels of serum ALT and AST may underestimate the prevalence of chronic liver diseases. In addition, hepatitis B virus (HBV) and hepatitis C virus (HCV) infection are highly prevalent in China, which can progress to chronic hepatitis B and C, respectively, or even to liver cirrhosis and hepatocellular carcinoma. It is critical to re-evaluate the upper cut-off values for the levels of serum ALT and AST in Chinese for the early and accurate diagnosis of liver diseases.

**Innovations and breakthroughs**

The results indicate that the new upper cut-off values of serum ALT and AST are markedly lower than current standards and may be valuable for the evaluation of liver function.

**Applications**

Present data showed that the upper normal limits for the levels of serum ALT and AST were significantly lower than the currently used values. In addition, given the strong gender effect on the levels of serum ALT and AST, we suggest that new upper normal limits of ALT and AST need to be determined for both men and women.

**Terminology**

ALT, a transaminase enzyme, is found in plasma and in various bodily tissues, but is most commonly associated with the liver. AST is a pyridoxal phosphate-dependent transaminase enzyme found in the liver, heart, skeletal muscle, kidneys, brain, and red blood cells. Serum ALT and AST are commonly measured clinically as markers of liver health.

**Peer-review**

This is a good retrospective study in which the authors determined the upper normal limits for the levels of serum ALT and AST in Chinese population and suggest that the upper normal limits for the levels of serum ALT and AST were dramatically lower than the currently used values.

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