Serum Alanine Aminotransferase as an Annual Screening Tool for Diseases Among Workers

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Background and purpose: The objective of this study was to assess the performance of serum alanine aminotransferase (ALT) as an annual screening tool for liver diseases in the occupational medical surveillance of asymptomatic workers.

Methods: We collected periodic medical surveillance data in the most recent four years from 700 employees of an oil-refinery. Of these, 326 voluntarily participated in the study and received a complete physical examination including hepatitis B surface antigen (HBsAg), hepatitis C antibody, and abdominal sonogram. The sensitivity and specificity of serum ALT for detecting liver diseases were established, and receiver operating characteristic (ROC) curve analysis was used to clarify the overall value of this test.

Results: Serum ALT had low sensitivity (below 45%) and high specificity (above 80%) in detecting liver diseases. There was no shoulder point or clear cut-off value on the ROC curve. Overall, serum ALT was better at detecting fatty liver and hepatitis virus C infection. However, serum ALT failed to detect both fatty liver disease and hepatic fibrosis in the HBsAg (+) subgroup. Obese workers had a higher risk of liver disease (OR 4.4; 95% CI 2.6-7.2), which was mainly due to fatty liver (OR 6.8; 95% CI 4.0-11.7).

Conclusions: Serum ALT is not a sensitive screening test for liver disease. We recommend an algorithmic approach to the management of workers that is based upon HBsAg, serum ALT value, and obesity. It involves testing for HBsAg prior to serum ALT in workers from high endemic areas. (*Changhua J Med* 2004;**9**:22-27)

Key words: serum alanine aminotransferase, abdominal sonogram, medical surveillance, liver disease, HBV infection

Introduction

In general, detection of liver injury in workplace medical surveillance programs has relied on measurement of conventional liver enzymes. Serum alanine aminotransferase (ALT) is among the most common tests used to detect acute and chronic hepatocyte cytotoxicity. With the continual improvement in occupational hygiene and decreasing exposure to health hazards in most industrialized countries, acute occupational liver damage has become less common [1]. Instead, the growing concern is now for early detection of chronic liver damage, the problem of obesity, and viral hepatic diseases. However, many investigators have questioned the effectiveness of such tests because of their low sensitivity [1-4]. An early study showed that serum ALT had a 90% specificity but only 56% sensitivity in the detection of various hepatobiliary diseases in various populations including hospital staff and patient populations [5]. Another study reported that serum ALT activity (in only 19% patients) underestimated prevalence of mild to moderate hepatic parenchymal changes as determined by sonography (32%) [4]. Therefore, it is important to assess the performance of serum ALT as a screening test for liver diseases especially among asymptomatic workers under current conditions (i.e., obesity and exposure to viral infection).

The objective of this study was to assess the performance of serum ALT as the annual screening tool for liver diseases among asymptomatic oil refinery workers in a hepatitis B virus (HBV) endemic area. On the basis of this study's results, we also suggest some strategies to improve the early detection of liver diseases.

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Materials and Methods

Subjects and data collection

The 326 study subjects (workers in an oil refinery with 700 employees) in this study were recruited between December 1999 and March 2000. All workers received a complete physical examination including ALT, hepatitis B surface antigen (HBsAg), and hepatitis C antibody (anti-HCV). All of them were also invited to fill out a questionnaire and receive an abdominal sonogram.

The questionnaire asked about medical history, occupation (job title, chemical compound usage or exposure, and duration of employment), alcohol consumption (average drinks per week and duration of drinking), and medications taken. All questionnaires were reviewed by a physician to assure data quality and validity. The biochemical tests for HBsAg and anti-HCV were performed in the clinical laboratory of Chia-Yi Christian Hospital, which has a regular intra-laboratory quality assurance/control (QA/QC) program and is a participant in an international QA/QC program (College of American Pathologists, CAP). The ALT examination was performed using a Hitachi 7,150 auto-analyzer (Tokyo, Japan). The reference range of ALT was between 9.0 and 48 IU/L. Enzyme immunoassay was used to measure HBsAg (Murex Diagnostics, Dartford, UK) and anti-HCV (anti-HCV III, Murex Diagnostics, Dartford, UK).

Abdominal sonogram was performed and interpreted by two skilled hepatology specialists. A real-time ultrasound machine, Panasonic PANAVISTA-LSCI (Panasonic Co. Ltd., Tokyo, Japan), equipped with a linear-type 3.5 MHz transducer was used. We used the following parameters to identify the lesions by sonogram [6]. (1) Fatty liver disease (FLD): The major indicator was the contrast in echogenicity between the liver and the cortex of the right kidney. We also applied additional contrast-enhancing strategies including masking of walls of portal vein branches in the right lobe, masking of the gallbladder wall, and distance-based gain attenuation of the liver. (2) Liver fibrotic change: A nodular surface having coarse or heterogenous echotexture compared to that of the spleen and irregular narrowing of the hepatic vein suggested the diagnosis of fibrosis.

One of the concerns in our study was the use of the abdominal sonogram as the gold standard instead of liver biopsy, which is more accurate but also more invasive and generally not feasible in an asymptomatic worker. Several studies have shown that the accuracy, sensitivity and specificity of sonograms in detecting fatty liver were all above 95%, and correlated well with the grades of fatty change in histology [6,7]. In contrast, sonograms were less sensitive in detecting fibrosis (around 80%), especially mild cases. However, since the specificity of sonogram in diagnosing fibrosis could be above 93% [6-8], we believe that a positive result may at least indicate moderate or advanced fibrosis. In our study, the two hepatologists had the same background and training in sonography and used the same ultrasonic diagnostic criteria proposed by Yang et al. for liver diseases [6]. Therefore, the bias between operators was minimized.

Data analysis

In our study, the liver diseases included FLD, liver fibrotic change, liver tumors, and chronic HBV and hepatitis C (HCV) infection based on sonographic and viral hepatitis markers. A *t*-test was used to compare the demographic and health characteristics between respondents and non-respondents in the refinery. Incremental cut-off values (at every 10 IU/L) were used to calculate the sensitivity and specificity of serum ALT for detecting these liver diseases. The overall accuracy of the test was described as the area under the receiver operating characteristic (ROC) curve [9-10]. The results were stratified by HBsAg and obesity and the performance of serum ALT was further assessed by ROC curves and cross-tabulation. Because there was no specific shoulder point on ROC curves, we decided to use 40 IU/L as our cut-off point in other stratified analyses. Body mass index (BMI) was calculated as weight in kilograms divided by squared height in meters. A value greater than 25 kg/m^2 was defined as obesity [11]. All of the statistical analyses were conducted using a software package SPSS/PC 9.0® on a personal computer [12].

Results

More than three-fourths of all workers were male and the average age was 48 years old. There was no significant difference in the demographic characteristics (except sex ratio) of the respondents and non-respondents. Details are summarized elsewhere [13]. The abnormal findings in 326 workers who received sonograms are shown in Table 1. We also found 39 workers with hepatic cysts, 6 with hepatic hemangioma, 11 with gallbladder stones, and 22 with gallbladder polyps, but these disorders were not included as liver diseases in our study.

Various ALT levels were used as cut-off points to establish the sensitivity and specificity of ALT in detecting FLD, liver fibrotic change, and HBV and HCV infection. When the cut-off level was set at 40 IU/L, the specificity of serum ALT in detecting these diseases was above 80% , but the sensitivity was below 45%. The rate of detection of liver fibrotic change seemed to be the lowest (17%). When the cut-off level was set at 30 IU/L, the sensitivity increased to more than 63% for all diseases except liver fibrotic change, while the specificity declined to 60~70%, which is inadequate for clinical use. Setting the cut-off point at 48 IU/L, as suggested by clinical laboratory specialists of Chia-Yi Christian Hospital, did not improve the test's performance. Using the area under the ROC curve (AUC) as a summary measure of the information provided by the test results, the overall performance of single serum ALT level in detecting the liver diseases is shown in Figure 1. An ALT may be more useful in detecting FLD and HCV infection, but less useful for detecting HBV infection and fibrotic change.

In analyses stratified by HBsAg status, serum ALT failed to detect FLD in the HBsAg (+) subgroup. The positive predictive value (PPV) of ALT in detecting FLD was much higher in HBsAg (-) workers than in HBsAg (+) workers (73% vs. 33%). Using serum ALT greater than 40 IU/L as the cut-off point, the negative predictive value (NPV) in detecting liver diseases in the HBsAg (-) workers with normal serum ALT was 75.8 %. The specificity was high (94.0%) and sensitivity was even lower (40.2%) (see Table 1). Of those 55 workers with various liver diseases undetected by ALT and HBsAg tests, 44 workers had FLD alone, 6 had liver fibrotic change alone, 3 had HCV infection alone, and 2 had both FLD and HCV infection.

Because obesity may contribute to ALT elevation and FLD, the serum ALT levels and prevalence of liver diseases in obese and non-obese workers were compared (Figure 2). The prevalence of liver diseases except FLD was not affected by obesity. The mean (± S.D) serum ALT was 38.3 (± 13.0) IU/L in obese workers and 23.6 (± 13.0) IU/L in non-obese workers. An obese worker had a high risk of contracting some liver disease (OR 4.4; 95% CI 2.6-7.2), particularly FLD (OR 6.8; 95% CI 4.0-11.7). Interestingly, both obese and non-obese workers with ALT≤40U/L had a similarly high risk (The obese: OR 5.4, 95% CI 1.9-15.4; the non-obese: OR 6.1, 95% CI 2.2-16.8). The result is not altered after stratification according to HBsAg carrier status.

There was a female worker found to have hepatocellular carcinoma (HCC). Although she was an HBV carrier, her ALT value was within the normal range and her sonogram did not show any other abnormality. Another male worker was found to have colon cancer with liver metastases and FLD. His ALT values were all above 58 IU/L in the past four years.

Table 1. Frequencies of various liver diseases, stratified by HBsAg carrier states. The sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of serum ALT with the cut-off of 40 IU/L in detecting these liver diseases were also presented.

	HBsAg (+)		HBsAg (-)		Total
	ALT ≧ 40	ALT < 40	ALT ≧ 40	ALT < 40	
Study subjects	12	39	48	227	326
FLD	4	6	35	46	91
Hepatic fibrosis	2	12	2	7	23
Chronic HBV infection	12	39	0	0	51
Chronic HCV infection	0	0	3	5	8
Hepatocellular carcinoma	0	1	0	0	1
Metastatic liver tumor	0	0	1	0	1
All liver diseases	12	39	37	55	143
Sensitivity		23.5%		40.2%	
Specificity				94.0%	
PPV		100%		77.1%	
NPV		0		75.8%	

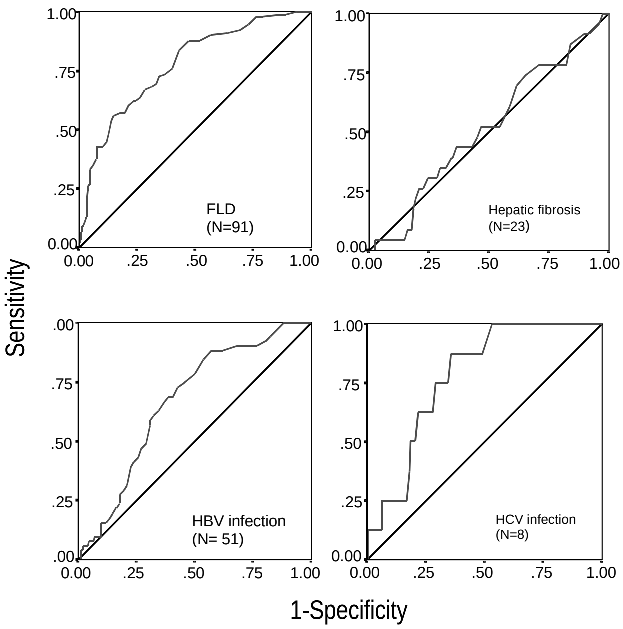

Figure 1. The receiver operating characteristic (ROC) curves for the serum ALT in detecting fatty liver disease (FLD), hepatic fibrosis, and chronic HBV and HCV infection in 326 workers. There was no "shoulder point" appeared on these curves. The performance of serum ALT in detecting hepatic fibrosis was not statistically significant.

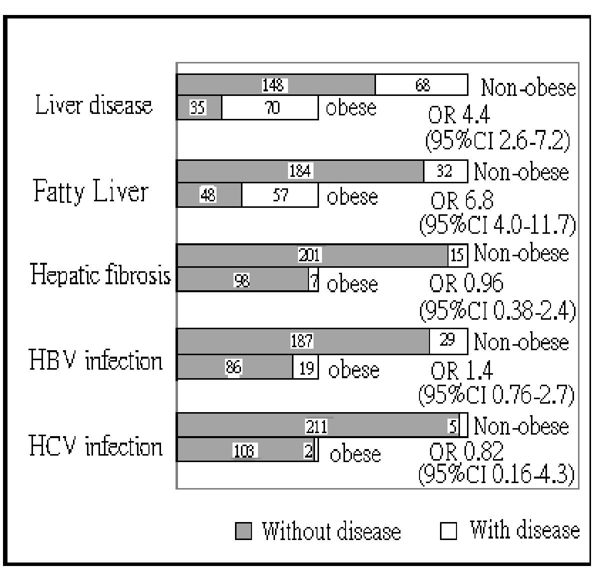

Figure 2. Frequencies and odds ratio (OR) of different types of liver diseases stratified by obesity (body mass index ≧ 25)

Discussion

The results of our study find that using serum ALT increase as a screening criterion is not sensitive in the detection of all liver diseases in a working population. No " shoulder point" appeared on the ROC curve, which means that the serum ALT test has no clear cut-off value to ensure maximal sensitivity and specificity, as shown in Figure 1. Chronic and/or intermittent liver damage may not be caught by an annual screening of transaminase activities, since the sensitivity of ALT testing could be as low as 56% [5], which is consistent with our observations. Using ALT elevation alone to detect FLD and hepatic fibrosis in HBsAg carriers is particularly insensitive, as demonstrated in Figure 3. Thus, we recommend an initial HBsAg screening for any population with a high prevalence rate of chronic hepatitis viral infections.

Although not very sensitive for screening, serum ALT may still be useful because workers with abnormal ALT had a higher risk of liver diseases (OR 8.2; 95% CI 4.0-16.4) in our study. In other words, an abnormal ALT can sound an alarm to alert medical staff to the possibility of some kinds of liver diseases, which require further medical workup.

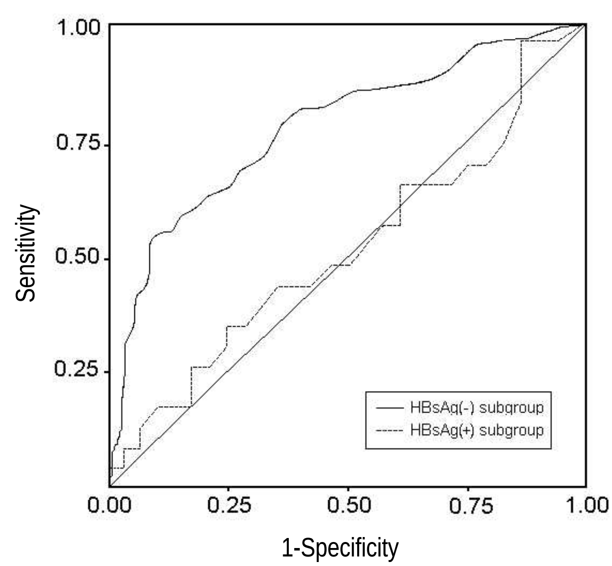

Figure 3. Analysis by the receiver operating characteristic (ROC) curves showed a low sensitivity and specificity on using elevated serum ALT alone to detect diffuse liver parenchymal disease including fatty liver disease (FLD) and hepatic fibrosis among the HBsAg carriers as it is in a working population without HBV infection.

When another major cause of liver disease, such as chronic HBV infection, is highly prevalent in the working population, the total accuracy (demonstrated by AUC) is even lower. Therefore, we propose an algorithmic approach based upon HBsAg and serum ALT values to the management of liver disease detection in workers, as shown in Figure 4. The approach involves measurement of HBsAg prior to ALT testing in all working populations with a high prevalence rate of chronic HBV infection, such as exists in Taiwan (where the prevalence is 14~20%) [14]. However, annual HBsAg test is not necessary and should be avoided. It is more appropriate to perform an HBsAg test once during the pre-placement health examination. A regular medical follow-up including liver sonogram and α-fetoprotein should be conducted for anyone with chronic HBV infection. If there is any elevation of ALT in the HBsAg (-) subgroup, then a further diagnostic test such as a sonogram must also be performed because of its high specificity for the other liver diseases. Besides, occupational exposures should be assessed and controlled if any unusual change in the prevalence of abnormal ALT occurs in these HBsAg (-) workers.

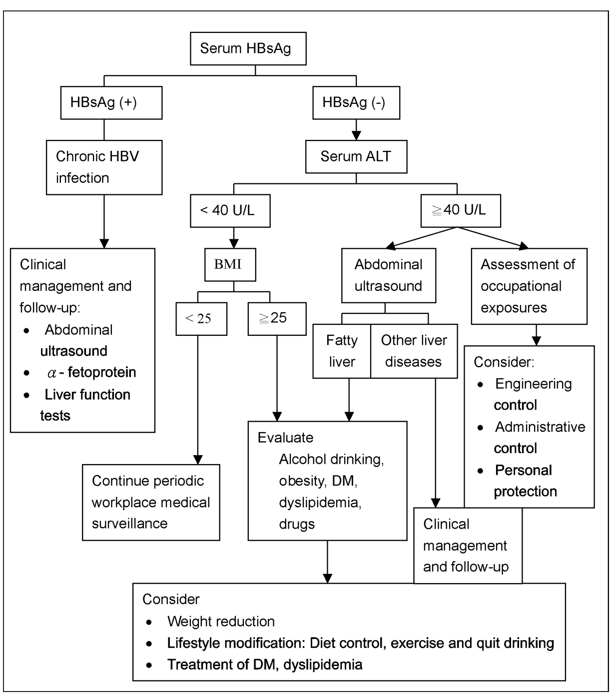

Figure 4. An algorithmic approach to the management of workers based upon HBsAg and serum ALT value. The approach implies that measurement of HBsAg should be prior to the ALT test on an HBV endemic area.

Those workers in our study with HBsAg (-) and ALT < 40 IU/L are not guaranteed to be completely healthy since fatty change on sonograms was noted in one-fifth of them. There is a growing concern that FLD may contribute to the development of hepatic fibrosis and that a minority of subjects may progress to liver failure [15]. In recent studies, FLD seems to play some role in the metabolic syndrome, which includes type 2 diabetes, dyslipidemia, obesity and hypertension [16,17]. However, about half of subjects with fatty liver were not detected by the criterion of elevated ALT. We recommend that all obese workers and those with fatty liver, regardless of ALT value, be enrolled in health promotion programs that include weight reduction, exercise, and lifestyle modification to reduce their cardiovascular risk.

Setting the cut-off point at 40 IU/L, five of eight subjects with chronic HCV infection were not detected by serum ALT using our algorithmic approach (Table 1 and Figure 4). Therefore, the anti-HCV test as a screening tool might also be considered if the prevalence of chronic HCV infection is high enough. Because less than 3% of our study subjects drank more than 140 grams of alcohol per week, we did not further differentiate alcoholic liver disease from the others. Since in Taiwan, the prevalence of chronic HBV infection has become significantly lower in residents born after 1984 (the inception of the HBV vaccination program), the age of a worker should be taken into account when this approach is applied in the future [18]. Because our study is cross-sectional, liver disease may have gone undetected in some healthy workers and thus the prevalence of liver diseases may be underestimated. Therefore, the predicted effectiveness of our strategies of workplace medical surveillance of liver diseases could be even higher.

In conclusion, we provide a practical approach to the medical surveillance of liver diseases in a population of workers. We recommend that a population with a high prevalence rate of HBV infection be screened for HbsAg marker before ALT screening. But such testing should take place only once before choosing strategies for taking care of positive and negative cases.

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