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Aspartate aminotransferase to platelet ratio index (APRI) can predict liver fibrosis in chronic hepatitis B

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Abstract

Background. There have been still few valuable markers that can be used as indirect markers of liver fibrosis in chronic hepatitis B.

Aims. This study aimed to evaluate efficacy of several indirect markers of liver fibrosis and to identify the most valuable test in chronic hepatitis B.

Patients and methods. A total of 264 patients with chronic hepatitis B were consecutively enrolled. Fibrosis was staged by a single blinded pathologist according to the METAVIR system. Significant fibrosis was defined as stage ≥2. We investigated diagnostic accuracy of four indirect markers including aspartate aminotransferase to platelet ratio index for predicting significant fibrosis.

Results. Mean age was 28 years. 53% (141/264) had significant hepatic fibrosis. Of indirect markers, aspartate aminotransferase to platelet ratio index yielded the best area under the receiver operating characteristic curve (0.86; 95% confidence interval, 0.82–0.91). Positive predictive value/negative predictive value at 0.5, 1.5 and 2.0 of aspartate aminotransferase to platelet ratio index score for predicting significant fibrosis were 63%/91%, 83%/74% and 86%/65%, respectively. The odds ratio for aspartate aminotransferase to platelet ratio index ≥1.4 relative to less than aspartate aminotransferase to platelet ratio index of 1.4 was 17.971 ($p < 0.0001$; 95% confidence interval, 9.677–33.376).

Conclusions. Of simple markers already developed in chronic hepatitis C, aspartate aminotransferase to platelet ratio index may be the most accurate and simple marker for predicting significant fibrosis in chronic hepatitis B.

Keywords: Aspartate aminotransferase; Hepatitis B; Liver fibrosis; METAVIR

1. Introduction

Chronic liver diseases (CLDs) generally progress to cirrhosis through longstanding repetition of inflammation and healing process regardless of underlying causes. Thus, liver fibrosis should be detected at early stage to prevent cirrhotic complications or even to regress liver fibrosis using the effective anti-fibrotic strategies [1]. Despite that liver biopsy is the golden standard to assess liver fibrosis and to guide therapeutic decisions, it has several limitations of morbidity, mortality [2,3], sampling error resulting from patchy distribution of liver fibrosis [4–7], reluctance of patients to repeat biopsies, and inter-observer variation [1,5]. Furthermore, the result from liver biopsy is static and does not reflect the balance between fibrogenesis and fibrolysis [8]. Therefore, non-invasive and readily applicable methods for the assessment of liver fibrosis should be developed and validated.

Liver fibrosis is a dynamic process composing of extracellular matrix (ECM) deposition and its degradation [8–10]. Markers directly reflecting ECM metabolism are defined as

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direct markers of liver fibrosis, while markers that reflect alterations in liver function are defined as indirect markers. There are several simple tests as indirect markers of liver fibrosis including aspartate aminotransferase (AST)/alanine aminotransferase (ALT) ratio (AAR) [11–16], cirrhosis discriminant score (CDS) [17], age-platelet index (API) [18], Pohl score [19] and AST-to-platelet ratio index (APRI) [20]. On the other hand, the accuracy of direct serum markers of fibrosis (combining age, hyaluronic acid, amino-terminal propeptide of type III collagen, and tissue inhibitor of matrix metalloproteinase 1) was proved to be similar to that of an expert liver pathologist and suggested the usefulness in the assessment of CLDs in a recent international multi-center cohort study [21]. However, the role of direct or indirect serum markers for predicting significant fibrosis in utilizing clinical practice is inconclusive.

Additionally, little has been known about the role of these indirect markers in predicting fibrosis stage of chronic hepatitis B (CHB) [22–25] because most studies were performed in chronic hepatitis C (CHC). To our knowledge, no study that evaluated simple indirect markers in adult with CHB has been reported except two [24,25]. Moreover, South Korea has a high prevalence of hepatoma (approximately 45 and 11.96 cases per 100,000 person-years in men and women, respectively), and chronic HBV infection accounts for over 74% of hepatoma [26]. Therefore, we carried out this study to identify the best practical, and simple indirect marker of liver fibrosis in CHB.

2. Methods

2.1. Patients

A total of 337 patients were consecutively enrolled. All the patients were diagnosed as having CHB by percutaneous liver biopsy at Hallym University Medical Center from January 1999 to December 2005. Chronic hepatitis B virus (HBV) infection was defined by positive surface antigen of HBV for at least 6 months. Exclusion criteria were as follows: (1) additional causes of CLDs such as CHC or coinfection with hepatitis D; (2) clinically overt cirrhosis on the basis of ultrasonography and/or esophagogastroduodenoscopy; (3) antiviral treatments before liver biopsy; (4) alcohol consumption in excess of 20 g per day in men and excess of 10 g per day in women; and (5) HIV infection. Of the total patients, 73 patients were excluded because their biopsy specimens had fewer than six portal fields. Data were retrospectively analysed.

2.2. Histological analysis

Liver tissue was obtained by sono-guided percutaneous biopsy using a Tru-Cut needle (ACECUT®, Automatic Biopsy System, 18 gauge, 22 mm type, Tochigi) and stained with hematoylin–eosin–safran and Masson's trichrome. A single blinded pathologist staged fibrosis from F0 to F4 according to the METAVIR system (F0, no fibrosis; F1, portal fibrosis without septa; F2, periportal fibrosis with few septa; F3, septal fibrosis with many septae; F4, cirrhosis) [27]. As the American Association for the Study of Liver Disease practice guidelines recommended, we defined significant liver fibrosis as METAVIR fibrosis score ≥2 (F2–F4) [28].

Table 1
The calculation of indirect fibrosis markers

Indirect fibrosis markers	Way of calculation
APRI	([AST/ULN[a]]/platelet count [$\times 10^9$/L]) × 100
API	Age (years): <30 = 0; 30–39 = 1; 40–49 = 2; 50–59 = 3; 60–69 = 4; ≥70 = 5 Platelet count ($\times 10^9$/L): ≥225 = 0; 200–224 = 1; 175–199 = 2; 150–174 = 3; 125–149 = 4; <125 = 5 API is the sum of the above numbers, which ranged from 0 to 10.
AAR	AST/ALT

APRI, aspartate aminotransferase (AST)-to-platelet ratio index; API, age-platelet index; AAR, AST/alanine aminotransferase (ALT) ratio; ULN, upper limits of normal.
[a] The upper limit of normal AST value was 38 IU/L in this study.

2.3. Calculation of indirect fibrosis markers

For calculating APRI, API and AAR as indirect markers derived from studies with CHC patients, laboratory values such as AST ALT and platelet count was tested on the same day of liver biopsy. Using these laboratory values, APRI, API and AAR were calculated as described in Table 1.

2.4. Statistical analysis

Data was analysed using statistical software SPSS version 13.0 (SPSS, Chicago, IL, USA). Patients were divided randomly into two groups: approximately 65% of all cases in estimation set ($n = 173$) and 35% in validation set ($n = 91$). We compared mean value of age, AST, ALT, platelet count and length of biopsy core between F0–F1 and F2–F4 group by t-test in estimation set. And then, variables with $p < 0.05$ were analysed by multiple logistic regression to assess independent variables for predicting significant liver fibrosis. To validate each variable for predicting significant fibrosis, the independent variables that were derived from the estimation set were then applied to the validation set. We evaluated the predictive power of detecting significant fibrosis based on the area under the receiver operating characteristic curve (AUROC) and regarded its AUROC of 0.85–0.95 as a useful indirect marker of significant fibrosis [1].

Bivariate Spearman's rank correlation coefficient and AUROC were performed to assess correlation between variables, and significant fibrosis in all patients. Additionally, we assessed the accuracy of useful indirect marker using sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV).