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Aspartate aminotransferase-to-platelet ratio index is associated with liver cirrhosis in patients undergoing surgery for hepatocellular carcinoma

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ABSTRACT

Background: Among various preoperative evaluations of liver function, accurate assessment of liver cirrhosis (LC) is especially important in patients undergoing surgery for hepatocellular carcinoma (HCC).

Objective: To explore the most significant laboratory parameter associated with LC in patients undergoing surgery for HCC.

Methods: From among 588 HCC patients in our collected database who underwent liver surgery, 371 for whom sufficient laboratory data were evaluable, including direct serum fibrosis markers such as hyaluronic acid and type 3 procollagen peptide (P-3-P), were enrolled. Receiver operating characteristic (ROC) curve analysis was used to define the ideal cutoff values of laboratory parameters, and the area under the ROC curve for LC was measured. Univariate and multivariate analyses were performed to clarify the laboratory parameter most significantly associated with LC.

Results: Multivariate analysis of 13 laboratory parameters that had been selected by univariate analysis showed that the aspartate aminotransferase-to-platelet ratio index (APRI) (≤0.8/>0.8) (odds ratio, 2.687; 95% confidence interval 1.215–5.940; $P = 0.015$) was associated with LC, along with the aspartate aminotransferase to alanine aminotransferase ratio, the indocyanine green retention ratio at 15 min (ICG R15), and the level of hyaluronic acid. Among these four parameters associated with LC, ROC curve analysis revealed that APRI (0.757) had the largest area under the ROC (aspartate aminotransferase to alanine aminotransferase 0.505, ICG R15 0.714, and hyaluronic acid 0.743).

Conclusions: APRI is closely associated with LC in patients undergoing surgery for HCC.

1. Introduction

Although liver biopsy is the current gold standard for assessment of liver fibrosis, it is poorly suited to frequent monitoring because of its expense and morbidity, and its accuracy suffers from sampling variation [1,2]. Therefore, noninvasive assessment of hepatic fibrosis, particularly liver cirrhosis (LC), is a critical issue in the fields of hepatology [3] and hepatobiliary

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surgery, and a determinant of whether patients can undergo surgery safely [4].

Among several noninvasive methods for assessment of hepatic fibrosis, such as indirect and direct serum markers and imaging techniques [2], serum fibrosis markers can be determined easily in the perioperative period in patients with hepatocellular carcinoma (HCC) because most such markers are included in routine preoperative laboratory tests. Particularly, direct markers of serum fibrosis such as the levels of hyaluronic acid [5,6] and type 3 procollagen peptide (P-3-P) [7,8] have been used for this purpose.

In comparison with liver biopsy, background fibrosis of the liver can be diagnosed correctly using surgically resected specimens because the large amount of tissue makes sampling variation less likely. Few studies have evaluated the relationship between laboratory parameters including serum fibrosis markers and liver fibrosis in patients undergoing surgery for HCC because most such studies used data from patients with viral hepatitis infection [9] or chronic hepatitis because of nonalcoholic steatohepatitis [10] or nonalcoholic fatty liver disease [11]. Therefore, patients undergoing surgery for HCC are an ideal model for investigating such a relationship because data from large samples of surgically resected liver tissue can be correlated with laboratory data, including serum fibrosis markers, obtained before surgery.

In the present study, we attempted to clarify the laboratory parameter most significantly associated with LC in patients undergoing surgery for HCC.

2. Methods

We retrospectively reviewed a database of 588 patients who had undergone surgery for HCC, performed by the same trained surgical team at the Department of Gastroenterological Surgery, Dokkyo Medical University Hospital, between April 2000 and January 2012. Among these patients, 371 (male:female = 290:81) for whom sufficient data were evaluable were enrolled in the study. There were 75 who had undergone surgery for recurrent HCC. In this study, hepatitis B virus (HBV) infection was defined as positivity for HBV antigens such as HBs antigen (Ag) and HBe Ag or positivity for HBV antibodies such as HBc antibody (Ab), HBe Ab and HBs Ab. Hepatitis C virus (HCV) infection was defined as positivity for HCV antibody.

All patients underwent preoperative routine laboratory tests including those for direct serum markers of fibrosis such as hyaluronic acid (upper physiological value: 50 ng/mL) and type 3 procollagen peptide (P-3-P) (upper physiological value: 0.8 U/mL).

The cutoff values of the laboratory parameters were determined using receiver operating characteristic (ROC) curve analyses, based on the most prominent point on the ROC curve for "sensitivity" and "1-specificity", respectively. Then, the ideal cutoff values were defined using the Youden index (maximum [sensitivity + specificity-1]) [12]. The area under the ROC curve (AUROC) was also calculated.

Univariate analyses were performed to examine the relationship between LC and various laboratory parameters such as aspartate aminotransferase (AST) (≤28/>28) (U/L), alanine aminotransferase (ALT) (≤37/>37) (U/L), AST/ALT (≤1.65/>1.65), aspartate aminotransferase-to-platelet ratio index (APRI) (≤0.8/>0.8), fibrosis 4 score (≤2.6/>2.6), cholinesterase (≤187/>187) (U/L), prothrombin time-international normalized ratio (≤1.1/>1.1), prothrombin time (≤86/>86) (%), albumin (≤3.7/>3.7) (g/dL), indocyanine green retention ratio at 15 min (ICG R15) (≤17/>17) (%), hyaluronic acid (≤133/>133) (ng/mL), P-3-P (≤0.97/>0.97) (U/mL), and platelet count (≤13.3/>13.3) ($\times 10^4/mm^3$).

The APRI is calculated as AST (U/L)/upper limit of the normal × 100/platelet count (10^9/L) [2,13]. The fibrosis 4 score is calculated as age (y) × AST (U/L)/(platelet count (10^9/L) × ALT $(U/L)^{1/2}$) [13]. All these cutoff values were defined using the ROC curve analyses.

Multivariate analysis was performed using the laboratory parameters found to have a significance level of $P < 0.05$ in the univariate analysis to clarify those most closely associated with LC.

Pathologic characteristics such as background liver (normal liver, chronic hepatitis, and LC) and fibrosis grade (fo, f1, f2, f3, and f4) [14] were evaluated by the same pathologists. Among these fibrosis grades, f4 was diagnosed as LC. In addition, we also investigated the relationship between liver fibrosis grade and hepatitis because of viral infection.

2.1. Statistical analysis

Data are presented as mean ± standard deviation. Differences between two groups were analyzed using Mann–Whitney *U* test and differences among five groups were analyzed using Kruskal–Wallis test. Odds ratios with 95% confidence interval (95% CI) were calculated using univariate and multivariate logistic regression analysis.

ROC curve analyses were used to define the ideal cutoff values of laboratory parameters and to calculate the AUROC for LC.

Statistical analyses were performed using the SPSS statistical software package, version 16.0 (SPSS Inc, Chicago, IL) at a significance level of $P < 0.05$.

3. Results

Table 1 shows the background laboratory parameters of the patients who underwent surgery for HCC, and Table 2 shows the results of the ROC curve analyses using those parameters. The ideal cutoff values, sensitivities and specificities for LC, and the AUROC data are shown.

Univariate analyses that were used to evaluate the relationship between the laboratory parameters and LC showed that these parameters were divisible into two groups using the cutoff values. Under such conditions, all the investigated laboratory parameters were shown to be associated with LC (Table 3).

Then, the laboratory characteristics found to have a significant level of $P < 0.05$ in the univariate analysis were subjected to multivariate analysis to clarify those most closely associated with LC. The results demonstrated that APRI (≤0.8/>0.8) (odds ratio, 2.687; 95% CI 1.215–5.940; $P = 0.015$) was associated with LC, along with AST/ALT (≤1.65/>1.65) (odds