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Nomogram for hepatic steatosis: A simple and economical diagnostic tool for massive screening

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ABSTRACT

Aim: To establish a simple economical diagnostic tool for prediction of hepatic steatosis in patients with hepatitis B virus (HBV) infection.
Methods: From January 2006 to January 2015,a total of 1325 consecutive subjects who underwent liver biopsy were enrolled. According to the results of multivariate logistic regression analysis, a new nomogram was conducted. Then discrimination and calibration were conducted to assess the clinical diagnostic value of nomogram.
Results: The nomogram consisted of age, triglyceride (TG), low-density lipoprotein (LDL), uric acid (UA), haemoglobin (HGB). For prediction of hepatic steatosis, the AUROC of nomogram was 0.792 (95%CI: 0.758–0.826). With cut off value of 0.11, 699 (52.8%) of 1325 patients could be free from liver biopsy with a correct rate of 95.3% for diagnosis of hepatic steatosis.
Conclusion: The nomogram for hepatic steatosis has a better clinical diagnostic value for prediction of hepatic steatosis in patients with HBV infection. From the perspective of cost-effectiveness and clinical practice, it is worth considering the use of the nomogram as a mass screening tool before further liver biopsy or imaging examinations.

1. Introduction

The prevalence of nonalcoholic fatty liver disease (NAFLD) was reported to be 20–30% in the general population [1]. The incidence of hepatic steatosis ranged from 14.0% to 70.0% in patients with hepatitis B virus (HBV) infection [2]. Then the coexistence of HBV infection and NAFLD is becoming more frequent. It was reported that NAFLD patients had an increased overall mortality for cardiovascular disease, extra-hepatic malignancies and liver disease [3]. In 2012, Jin et al. reported that hepatic steatosis was significantly correlated with entecavir treatment failure [4]. Therefore,early diagnosis of fatty liver is of importance for management and therapy of patients with HBV infection.

At present, the gold standard for assessing hepatic steatosis is liver biopsy, which is limited by invasiveness and sampling error [5,6]. As an inexpensive noninvasive method, ultrasonography (US) is recommended in detection of hepatic steatosis. However, US is limited by low sensitivity for mild steatosis and inability to differentiate mild fibrosis from steatosis in clinical practice [7]. Magnetic resonance imaging (MRI), computed tomography (CT), and transient elastography (TE) have a better diagnostic value in detecting of hepatic steatosis. However, these methods are limited by several shortages in clinical practice. First, these methods are too expensive for routine health examinations. Second, these methods are not readily available in most hospitals of developing countries. Third, considering cost-effectiveness, MRI, CT, and TE are not suitable for massive outpatient screening in predicting hepatic steatosis. There is an intense need to find an simple, economical, easier practical, and readily available tool for massive health screening as an alternative to imaging examinations or liver biopsy.

To conduct a simple economical method for massive screening for hepatic steatosis as an alternative to imaging examinations or liver biopsy, we performed this retrospective study in patients with HBV infection.

2. Materials and methods

2.1. Patients

Subjects of this study included 1580 consecutive patients who had been diagnosed with HBV infection and had undergone liver biopsy in department of infectious diseases of Shunde First People's

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Hospital between January 2006 and January 2015. The Patients were enrolled based on the following criteria: chronic hepatitis B defined as hepatitis B surface antigen (HBsAg) positivity for more than 6 months; detectable HBV-DNA with a level $>10^3$ copies/ml. The exclusion criteria were as follows: liver cancer or co-infection with hepatitis C virus, hepatitis D virus or human immunodeficiency virus; autoimmune liver diseases such as autoimmune hepatitis, primary biliary cirrhosis, and primary sclerosing cholangitis; alcohol ingestion in excess of 20 g/day. The patients with missing data in terms of age, triglyceride (TG), low-density lipoprotein (LDL), uric acid (UA), and haemoglobin (HGB) were ruled out.

Therefore, there were 255 (16.1% of the total subjects) patients excluded from the study according to above criteria. There were no significant differences in terms of demographic and clinical parameters between patients included and excluded (data not shown). Finally, a total of 1325 patients (944 males and 381 females) were recruited into the study. All patients were informed and written consents were obtained before inclusion. The study protocol was approved by the Ethics Committee of the Shunde First People's Hospital.

2.2. Liver biopsy

Liver biopsies were performed by two experienced physicians using a 16-gauge needle (16G biopsy Menghini's needle, ShangHai). A minimum of 1.5 cm of liver tissue with at least 7 portal tracts was required for diagnosis. The specimens were fixed, paraffin-embedded and stained with haematoxylin and eosin (HE). Histological grading of necro-inflammation (G0–G4) and staging of the liver fibrosis (S0–S4) were carried out according to Scheuer's classification [8] by one experienced pathologist blinded to the clinical data. Hepatic steatosis was graded according to the percent of hepatocytes affected: none (<5%), mild steatosis (5–32%), moderate steatosis (33–65%), and severe steatosis (≥66%) [9]. Steatosis group was defined as steatosis involving more than or equal 5% of hepatocytes and non-steatosis group was defined as steatosis involving less than 5% of hepatocytes (Fig. 1).

2.3. Clinical parameters

All patients systematically underwent complete biochemical workups, US and liver biopsy within 2 days. Blood samples of the subjects were obtained before liver biopsy. Biochemical tests were performed by commercial assays in our hospital laboratory. The serum HBV-DNA level was detected with a Real-Time polymerase chain reaction (PCR) System (ABI7700; Applied Shenzhen city Daeran Biological Engineering Co., Ltd., Shenzhen, Guangdong, CHN).

2.4. Statistical analysis

Continuous data were expressed as mean ± SD or median (quartile range) depending on the normality of the data. Categorical variables were expressed as proportions. Continuous variables were compared with Student's *t*-test, one-way ANOVA analysis of variance or Kruskal–Wallis *H* test, depending on the normality of the data; Nominal or ordinal variables were compared with Chi-square test or Kruskal–Wallis *H* test.

All variables that significantly associated with hepatic steatosis in univariate logistic regression analyses were included in forward stepwise multivariate logistic regression analysis for establishment of nomogram model. According to the results of multivariate logistic regression analysis, a new nomogram was conducted.

The discriminatory ability of the nomogram was measured by means of the area under the receiver operating characteristic curve (AUROC). The optimal cut off value for clinical utility was determined according to positive likelihood ratio (PLR) ≈ 10.0 for confirming diagnosis of steatosis and negative likelihood ratio (NLR) ≈ 0.1 for excluding diagnosis of steatosis [10]. To furtherly evaluate the clinical utility of new model, the sensitivity (Se), specificity (Sp), positive likelihood ratio (PLR), negative likelihood ratio (NLR), positive predictive value (PPV), and negative predictive value (NPV) were calculated using the ROC curve. Calibration was assessed by plotting the model predicted probability against the observed proportion of hepatic

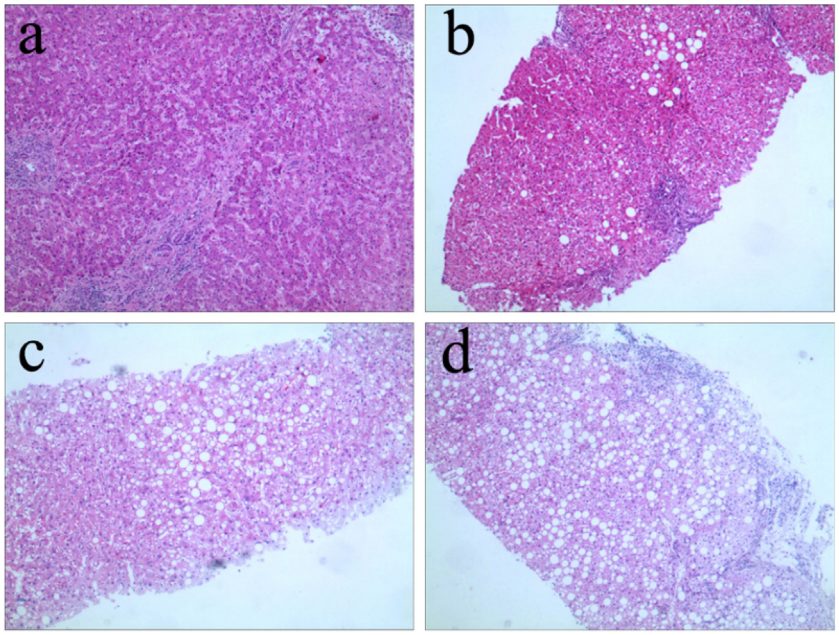

Fig. 1. Pathological characteristics of hepatic steatosis in patients with hepatitis B virus infection (HE staining). (a) None steatosis (200×). (b) Mild steatosis (200×). (c) Moderate steatosis (200×). (d) Severe steatosis (200×).