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Noninvasive indices for monitoring disease course in Chinese patients with autoimmune hepatitis

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ABSTRACT

Objective: Noninvasive and simple tests to forecast cirrhosis is in great need clinically. This study aimed to assess the clinical significance of several noninvasive indices in predicting cirrhosis in Chinese patients with autoimmune hepatitis (AIH). Materials and Methods: Liver function test and blood cell analysis were conducted in 76 AIH patients and 75 paired healthy subjects to calculate aspartate aminotransferase to alanine aminotransferase ratio(AAR), aspartate aminotransferase to platelet ratio index (APRI), fibrosis index based on the four factors (FIB-4), gamma-glutamyl transferase to platelet ratio (GPR), red blood cell distribution width (RDW), neutrophil to lymphocyte ratio (NLR), lymphocyte to monocyte ratio (LMR), and platelet to lymphocyte ratio (PLR). Binary logistic regression was performed to analysis the risk factors of liver cirrhosis and receiver operating characteristic (ROC) curve was conducted to evaluate the diagnostic value of each index and compare their diagnostic performance with serum biomarkers commonly used in the clinical setting for liver fibrosis assessing including hyaluronic acid (HA), laminin(LN), procollagen III N terminal peptide (PIIINP) and type IV collagen (ColIV). Results: AAR, APRI, FIB-4, GPR, NLR and RDW were elevated remarkably in AIH patients with cirrhosis; AAR, FIB-4 and RDW were identified to be independent risk factors of cirrhosis with OR (95%CI) of 3.517 (1.300–9.514), 1.247(1.032–1.506) and 1.414 (1.086–1.842) respectively; ROC analysis showed that the area under the ROC curve (AUC) of AAR, FIB-4 and RDW were 0.801,0.82 and 0.739, with moderate diagnostic value and better than HA, LN, PIIINP and ColIV in identifying those with cirrhosis from AIH patients. Conclusion: AAR, FIB-4 and RDW were independent risk factors of AIH cirrhosis and can be served as reference indices to monitor disease course in AIH.

1. Introduction

Autoimmune hepatitis(AIH) is a chronic progressive liver inflammation characterized by elevated serum level of autoantibodies and aminotransferases as well as liver interface infiltrating with plasma and lymphocytes cells [1]. The etiology and pathogenesis of AIH have not been elucidated, yet there are evidences that heredity, environmental triggers, immunologic unbalance as well certain drugs interactively induce AIH [2]. Long term inflammation causes liver fibrosis and may terminally result in liver dysfunction or cancerization [3], which terribly threatens patients' life. Liver biopsy(LB) remains the gold standard of liver cirrhosis [4], but invasiveness, worse patient acceptance and sample errors limit its application for monitoring disease course largely. As a consequence, simple and noninvasive tools based on routine laboratory tests to substitute LB in cirrhosis diagnosis, not only accurately informing disease course but also reducing the impairments result from LB is of great need clinically. In the resent years, several noninvasive indices based mainly on liver function test as well as peripheral blood cell analysis such as aspartate aminotransferase to alanine aminotransferase ratio(AAR), aspartate aminotransferase to platelet ratio index (APRI), fibrosis index based on the four factors (FIB-4), gamma-glutamyl transferase to platelet ratio (GPR) has been reported to be indicators of liver fibrosis of different causes [5, 6]. Liver chronic inflammation is a leading contributor of cirrhosis in patients with chronic hepatitis, whilst peripheral blood red blood cell distribution width (RDW), neutrophil to lymphocyte ratio (NLR), lymphocyte to monocyte ratio (LMR) and platelet to lymphocyte ratio (PLR) are good indicative marker of systemic inflammation and closely associated with disease severity and prognosis of many disease [7, 8]. However, few literatures have reported the clinical value of the noninvasive

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indices aforementioned in AIH. In the present study, 76 AIH patients undergone LB were enrolled, with AAR, APRI, FIB-4, GPR, RDW, NLR, LMR and PLR calculated from the results of liver function detection and peripheral blood cell counts. And the clinical significance of each index in predicting and diagnosing cirrhosis were assessed in patients with AIH.

2. Material and method

2.1. Patients

A total 76 AIH patients from the Second Affiliated Hospital of Nanchang University who underwent LB between January 2012 and July 2017 were enrolled in the present study, among whom there were 38 patients with liver cirrhosis (AIH cirrhosis group) and the other 38 patients with chronic AIH (chronic AIH group) and 75 age- and gender-matched healthy subjects were enrolled as control group. Individuals fulfilling following criteria were included: (1) with definite diagnosis (AIH patients were diagnosed according to relevant guideline [9], liver cirrhosis diagnosed via LB, and all diagnosis information were confirmed by the attending physicians); (2) with detailed clinical, imaging and laboratory examination data; (3) without infection and inflammation diseases within one month before blood collection; (4) healthy controls were in good condition for all routine tests. Individuals with following criteria were excluded: (1) mingled with liver disease of other causes, such as viral hepatitis, nonalcoholic fatty liver disease (NAFLD) or hepatocellular carcinoma (HCC); (2) mingled with severe disorder in cardiovascular, blood, immune or endocrine system; (3) with a history of long term smoking and excessive drinking; (4) pregnant or lactating women.

2.2. Data collection and laboratory detection

Basic and medical history information of each patient were collected via the medical record reviewing and telephone follow up including age, gender, history of smoking and drinking as well as infection and drug-taking history within one month before blood collection. Serum were obtained from 3 ml coagulated peripheral blood after a 1026 *g* centrifugation for 5 min to detect total protein(TP), albumin (Alb), globulin, (Glo), total bilirubin(TB), aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP) and gamma-glutamyl transferase (GGT) using OLYMPUS AU5800 machine (Beckman Coulter, Tokyo, Japan), with hyaluronic acid (HA), laminin (LN), procollagen III N terminal peptide (PIIINP) and type IV collagen (ColIV)detected by chemiluminescent immunoassay using MAGLUMI 2000 machine provided by Shenzhen New Industries Biomedical Engineering Ltd.(Shenzhen, China); anther 2 ml EDTA anticoagulated blood sample were collected, using Sysmex XN20 A1 machine(Sysmex, Tokyo, Japan) to determine peripheral white blood cell (WBC) count, platelet (PLT) count, neutrophil count, lymphocyte count, monocyte count and RDW, and then calculated albumin to globulin ratio(AGR), AAR, APRI, FIB-4[FIB4 = age(yr) × AST(U/L)/(PLT(10^9/L) × ALT(U/L)$^{1/2}$)], GPR, NLR, LMR and PLR. All measurements were run in duplicate for each sample and included blinded quality controlled samples, with inter and intra-batch CVs < 5%. All assays were performed in strict accordance with manufactures' protocols and the standard operating procedure(SOP) of the Second Affiliated Hospital of Nanchang University. This study was approved by ethics committee of the Second Affiliated Hospital of Nanchang University and in accordance with the 1964 Helsinki declaration as well as its later amendments, with written informed consents obtained from all eligible participants.

2.3. Statistical analysis

IBM SPSS statistical 22.0 (SPSS inc. Chicago, IL, USA) was utilized for statistical analysis. Kolmogorov-Smirnov test and Levene's test were selected to assess the normality and equality of measurement parameters. Variables of normal distribution were expressed as mean ± SD, as median (interquartile range) if abnormal distributed. Differences of normal distributed and equal-variance variables between groups were tested by Student test or use Mann-Whitney *U* test otherwise. Differences of quantitative data among groups were tested with Chi-square test. Binary logistic regression analysis was used to access the correlations between indices and liver cirrhosis. The "Enter" method was utilized to conduct a univariate logistic regression analysis, with variables statistically significant selected into multivariate unconditional logistic regression analysis. Furthermore, collinearity diagnostics were conducted to determine the multicollinearity among variables. Receiver operating characteristic(ROC) curves were performed to evaluate the diagnostic performance of each index for cirrhosis via comparing the area under ROC curve (AUC). *P*-value < .05 denoted statistically significant.

3. Result

3.1. Comparison of parameters between AIH patients and healthy controls

Demographics and laboratory examination results of AIH patients and healthy controls were illustrated in Table 1. Enrolled 76 AIH patients included 60 females (78.95%) and 16 males (21.05%), mean age was 56.83 ± 12.58; while among 75 healthy subjects, there were 58 females (76.32%) and 17 males (22.37%) and the mean age was 57.04 ± 12.20. As two group were age- and gender-matched, there was no statistically significant difference in age and gender between groups. After tested by Mann-Whitney *U* test, TP and Alb were significantly lower in AIH group and aminotransferase levels elevated remarkably compared with healthy controls; RDW and NLR levels were higher yet LMR were lower in AIH group compared to healthy control group with $P < .001$. PLR levels between AIH patients and healthy controls were not different statistically, $P = .796$, as shown in Table 1.

4. Comparison of laboratory results between AIH cirrhosis and chronic AIH patients

All 76 included AIH patients were classified into AIH cirrhosis group and chronic AIH group by LB, and there were 38 patients for each group. There were 32 (84.21%) females and 6 (15.79%) males in the AIH cirrhosis group, with mean age of 57.13 ± 10.27; and in the chronic AIH group, there were 28 (73.68%) females and 10 (26.32%) males, with mean age of 56.53 ± 14.65; there was no statistically significant differences in gender and age between groups. After tested by Mann-Whitney *U* test and Student-test (t-test), levels of indices related to liver fibrosis status including AAR, APRI, FIB-4, GPR, HA, LN, PIIINP and ColIV as well as inflammation-related indices (RDW and NLR) significantly higher in AIH cirrhosis group than chronic AIH group, as shown in Table 2.

4.1. Analysis of risk factors associated with AIH cirrhosis

Binary logistic regression analysis was performed to explore risk factors associated with the presence of liver cirrhosis in patients with AIH. In univariate logistic regression analysis (shown in Table 3.), AAR, FIB-4, RDW, NLR, HA, LN, PIIINP and ColIV were associated with liver cirrhosis, yet after multivariate stepwise logistic regression, AAR, FIB-4 and RDW were identified independently associated with AIH cirrhosis OR (95% CI) were 3.517(1.300–9.514), 1.247(1.032–1.506) and 1.414(1.086–1.842) respectively.

4.2. Diagnostic performance of indices comparison

ROC curves were performed to evaluate the performance of indices in identifying cirrhosis patients from chronic AIH patients, as shown in