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Measurement of Liver Fibrosis in Chronic Hepatitis D: Comparison of Invasive and Non-Invasive Methods

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Objectives: The aim of this study was to compare non-invasive methods in the detection of hepatic fibrosis in patients with chronic hepatitis delta. **Methods:** Twelve patients with chronic hepatitis delta who visited the Gastroenterology Department at the Intermed Hospital, were studied. Clinical and histological data were evaluated and serum indirect fibrosis markers including AST to ALT ratio, AST-to-Platelet Ratio, Fibrosis-4 index scores were calculated. Serum Mac-2 binding protein glycosylation isomer and liver stiffness measurements were performed in all participants. **Results:** Histological scoring showed that 16.7%, 41.7% and 41.7% of participants had F2, F3, and F4 stage of liver fibrosis, respectively. All participants were divided into groups; cirrhotic (F4) and non-cirrhotic (F0-F3). The median AST to ALT ratio in cirrhotic vs. noncirrhotic patients was 1.4 vs. 1.1 (p=.67), AST-to-Platelet ratios were 0.7 vs. 1.1 (p=.48), and Fibrosis-4 index scores were 1.8 vs. 1.6 (p=.82) in non-cirrhotic patients. Median Mac-2 binding protein glycosylation isomer levels in the cirrhotic group 1.3 cut-off index vs. 1.4 cut-off index in the non-cirrhotic group (p=.85). The median liver stiffness was 12.6 kPa in cirrhotic patients while 8.1 kPa in non-cirrhotic patients (p=.05). **Conclusion:** Non-invasive serum markers were less accurate in determining fibrosis in chronic hepatitis delta patients. Liver stiffness measurement was superior to the non-invasive serum markers.

Keywords: Chronic Hepatitis D, Liver Fibrosis, Liver Stiffness, Liver Biopsy, Non-Invasive Fibrosis Marker

Introduction

At present, chronic hepatitis delta virus (HDV) infection still remains a serious health problem in Mongolia. The latest data showed that about 60% of HBsAg carriers were co-infected with HDV in Mongolia[1]. HDV is defective virus that requires hepatitis B virus (HBV) surface antigen to assemble[2]. Chronic HDV infection is considered as the most severe form of viral hepatitis and it progressively develops into liver cirrhosis within a decade[3].

Identification of advanced fibrosis and cirrhosis remains important in chronic viral hepatitis, especially for the purpose of therapeutic decision-making, hepatocellular carcinoma surveillance, and monitoring liver-related complications. Liver biopsy remains the benchmark method for the assessing stage and grade of liver disease. The grade of liver disease is considered to be the degree of inflammation and hepatocellular injury while the stage is the degree of hepatic fibrosis[4]. But liver biopsy has several limitations including that it is expensive and an invasive method with some procedural risks and has the potential for sampling error and intra-observer variation[5].

During the past few decades, three types of non-invasive tests have been introduced into clinical practice to assess hepatic fibrosis in both viral and non-viral liver diseases. The first group of non-invasive tests are indirect serum biomarkers which utilize a combination of simple biochemical, hematological and demographical parameters such as 2-macroglobulin, total bilirubin, gamma-glutamyl transpeptidase (GGT), apolipoprotein A1, haptoglobin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), platelets, age, sex and weight. The AST to ALT Ratio (AAR), AST-to-Platelet Ratio Index (APRI), the Fibrosis-4 (FIB-4) score, Ag-Platelet index (API) and Hui score have been extensively studied[6-10]. These tests have several advantages such as being lower in cost, are easy to implement and reproduce, and are suitable for periodic assessment. The second group of non-invasive tests includes direct serum markers such as procollagen type I carboxy-terminal peptide, procollagen type III amino-terminal peptide, metalloproteinase and tissue inhibitors of matrix metalloproteinase[11]. The Mac-2 binding protein glycosylation isomer (M2BPGi) is a novel serological direct biomarker for liver fibrosis, which is considered as a reliable non-invasive marker for liver fibrosis in patients with chronic hepatitis B, primary biliary cirrhosis and non-alcoholic fatty liver disease[12-15]. In the third group, advanced imaging modalities based on ultrasound or magnetic resonance imaging measure liver stiffness and these are major advances in determining hepatic fibrosis in patients with chronic liver disease. Transient elastography (FibroScan®) renders simple numerical values in order to distinguish the different stages of fibrosis and it is currently becoming the most widely used technique because it is a fast, simple and safe procedure that can be performed at the bedside[16]. Serum and imaging based non-invasive fibrosis markers are well defined in chronic hepatitis B, C, and nonalcoholic fatty liver disease but not in patients with chronic hepatitis delta[17]. In two recently published studies, only non-invasive serum markers were used to assess hepatic fibrosis in chronic hepatitis delta patients while imaging studies were omitted[18,19]. The aim of this study was to assess the accuracy of both non-invasive serum markers and ultrasonic imaging methods of staging hepatic fibrosis in patients with chronic hepatitis delta using liver biopsy histopathological results as the standard.

Materials and Methods

Patients

Twelve HDV patients, who visited to the Department of Gastroenterology at the Intermed hospital, were enrolled in this study. All patients had detectable HBsAg for more than 6 months and they were positive for anti-HDV IgG for more than 6 months and had detectable HDV-RNA.

Laboratory testing

Blood samples were collected and tested for complete blood count and prothrombin time by standard laboratory methods. Liver function tests included aspartate aminotransferase (AST) and alanine aminotransferase (ALT), γ–glutamyl transpeptidase (GGT), alkaline phosphatase (ALP), albumin, total protein, and total bilirubin.

Liver biopsy

Percutaneous liver biopsy was performed using a 16-gauge semi-automatic biopsy needle. All liver specimens were fixed in formalin, embedded in paraffin wax, and stained with hematoxylin and eosin and Masson's trichrome. A liver sample was considered as adequate if its length was 10 mm to 25 mm long and 1 mm wide. All biopsy specimens were analyzed

by an experienced pathologist (ED), who was blinded to the clinical data. Fibrosis was staged on a scale of 0–4 according to the METAVIR classification with F0 indicating no fibrosis; F1, enlarged fibrotic portal tracts; F2, periportal or portal–portal septa but intact architecture with limited septa formation; F3, fibrosis with architectural distortion with numerous septa but no obvious cirrhosis; and F4, probable or definite cirrhosis[20].

Liver stiffness measurement

Ultrasonic liver stiffness measurement was performed by a single experienced operator (SJ), blinded to clinical data and blood tests results, following a validated procedure using an M probe of TE by FibroScan® (EchoSens, Paris, France). The patient was placed in dorsal decubitus with right arm in maximal abduction and probe placed perpendicularly in an intercostal space at the level of the right lobe of the liver. The liver stiffness measurement used was the median of all valid measurements and was expressed in kilopascal (kPa). The liver stiffness measurement was considered reliable when the following criteria had been met: (i) 10 successful measurements were obtained; (ii) the interquartile range (IQR) was lower than 30% of the median value; and (iii) the success rate of more than 80%.

Non-invasive indirect markers

The non-invasive fibrosis markers AST to ALT ratio (AAR), the AST to platelet ratio index (APRI) and Fibrosis-4 (FIB-4) scores were calculated using following equations:

AAR= AST/ALT

$$\text{APRI}=\frac{\text{AST/ULN}}{PLT} * 100\frac{\text{AST/ULN}}{PLT} * 100$$

$$\text{FIB-4}= \frac{Age\,(yr) * AST}{PLT * \sqrt{ALT}} \quad \frac{Age\,(yr) * AST}{PLT * \sqrt{ALT}}$$

In which AST is the aspartate aminotransferase concentration, ULN is the upper limit of normal of AST, PLT is the platelet count (10^9/L), and ALT is the alanine aminotransferase concentration.

Non-invasive direct markers

Serum M2BPGi level was measured by an immune assay based on a chemiluminescent enzyme immune-assay technique with a commercially available kit (HISCL M2BPGi, Sysmex Corporation). M2BPGi level was expressed by a cut-off index (COI).

Statistical analysis

Statistical analyses were performed with the SPSS 16.0 software package (SPSS Inc. Chicago, IL, USA). The median, range, mean and standard deviation were calculated for numerical data. Differences between groups were analyzed using Mann-Whitney U-test and Fisher's exact test with $p < .05$ considered statistically significant.

Ethical statements

The Ethical Review Committee of the Mongolian National University of Medical Sciences approved the current study protocol. The written consent forms were obtained from all study subjects prior to blood sampling and liver biopsy.

Results

Twelve chronic hepatitis delta patients were studied. Their baseline characteristics are presented in Table 1. The mean age for all subjects was 40.6±8.8 years with a predominance of male sex (n=8, 66%). Mean ALT and AST were 90.1 U/L and 70.7 U/L while the mean albumin, total bilirubin levels were 43 g/L and 9.3 mmol/L. One subject (8.3%) was positive for HBeAg.

The mean fibrosis score of all 12 patients using the METAVIR scoring system was 3.3 (Table 2). Histological results showed that two patients (16.7%) had F2 fibrosis with periportal or portal–portal septa but intact architecture with limited septa formation (Figure 1) and five patients (41.7%) had significant fibrous septa with architectural distortion but no fully developed cirrhosis (Figure 2). Five patients (41.7%) had cirrhosis (Figure 3). The mean AAR, APRI and FIB-4 scores for all patients were 1.2, 0.85 and 1.68 while mean liver stiffness was 10.3 kPa. The mean M2BPGi level for all patients was 1.3 COI.

To compare the accuracy of serum markers to ultrasonic liver stiffness measurements we compared their results in cirrhotic patients (F4) and non-cirrhotic patients (F0-3) (Table 3). The mean age of cirrhotic patients was 39.4 vs. 41.3 years in non-cirrhotic patients (p=.24). There was no significant difference in gender distribution. Cirrhotic patients had lower mean PLT counts compared with non-cirrhotic HDV patients (169 x10^9/L vs. 222 x10^9/L, p=.02). Mean AST (48.6 U/l vs. 86.5 U/L, p= .82) and ALT (125.3 U/L vs. 40.6 U/L, p=.29) levels in cirrhotic patients were not significantly different from non-cirrhotic patients. The mean albumin (43 g/L vs. 42.7 g/L, p=.78) and total bilirubin

Table 1. Baseline characteristics of patients

Variables	HDV patients (n = 12)
Males, n (%)	8 (66.7%)
Females, n (%)	4 (33.3%)
Mean age ± SD	40.5±8.8
Laboratory data	
WBC (x 10^6/L), mean±SD	5.4±1.4
PLT (*10^9/L), mean±SD	200±35
AST (U/L), mean±SD	70.7±60.7
ALT (U/L), mean±SD	90.1±116.1
Serum albumin (g/L), mean±SD	43±3.4
Total bilirubin (μmol/L), mean±SD	9.1±3.3
HBeAg positive, n (%)	1 (8.3%)

ALT, alanine aminotransferase; AST, aspartate aminotransferase; HBeAg, hepatitis B e antigen; HDV, hepatitis Delta virus; PLT, platelet count; SD, standard deviation; WBC, White blood cell;

Table 2. Fibrosis tests results

Variables	HDV patients (n = 12)
Histological fibrosis score (METAVIR scoring system), mean ±SD	3.3±0.7
F2	2 (16.7%)
F3	5 (41.7 %)
F4	5 (41.7%)
Non-invasive indirect fibrosis scores, mean±SD	
AAR	1.2±0.7
APRI	0.8±0.6
FIB-4	1.7±0.7
Non-invasive direct fibrosis marker, mean±SD	
M2BPGi COI	1.3±0.8
Non-invasive imaging (FibroScan®) test	
Liver stiffness, kPa	10.3±3.4

AAR, the AST to ALT ratio; APRI, the AST to platelet ratio index; COI, cut-off index; FIB-4 score, and Fibrosis 4 index; HDV, hepatitis Delta virus; kPa, kilopascal; M2BPGi, Mac-2 binding protein glycosylation isomer; SD, standard deviation

levels (8.4 mmol/L vs. 9.6 mmol/L, p=.82) were not significantly different in cirrhotic and non-cirrhotic groups.

Mean AAR, APRI, and FIB-4 scores were 1.4, 0.7 and 1.8 in the cirrhotic patients vs. 1.1, 0.9 and 1.6 in the non-cirrhotic patients. Mean M2BPGi level in cirrhotic group was 1.3 COI vs. 1.4 COI in non-cirrhotic group (p=.85). The mean liver stiffness was 12.6 kPa in cirrhotic patients while 8.6 kPa in non-cirrhotic patients (p=.18).

We then compared our liver stiffness measurements to the histological stage. The mean liver stiffness was 8.1 kPa, 8.9 kPa, and 12.6 kPa in F2, F3 and F4 histology fibrosis groups, respectively (Figure 1). Comparing F2 group, patients in the F4 group had significantly higher levels of liver stiffness (8.1 vs. 12.6, p=.005). There was only one patient with liver cirrhosis (F4 stage) who had a lower result (9.1 kPa). On the other hand, one non-cirrhotic patient (F3 stage) had a higher level of liver

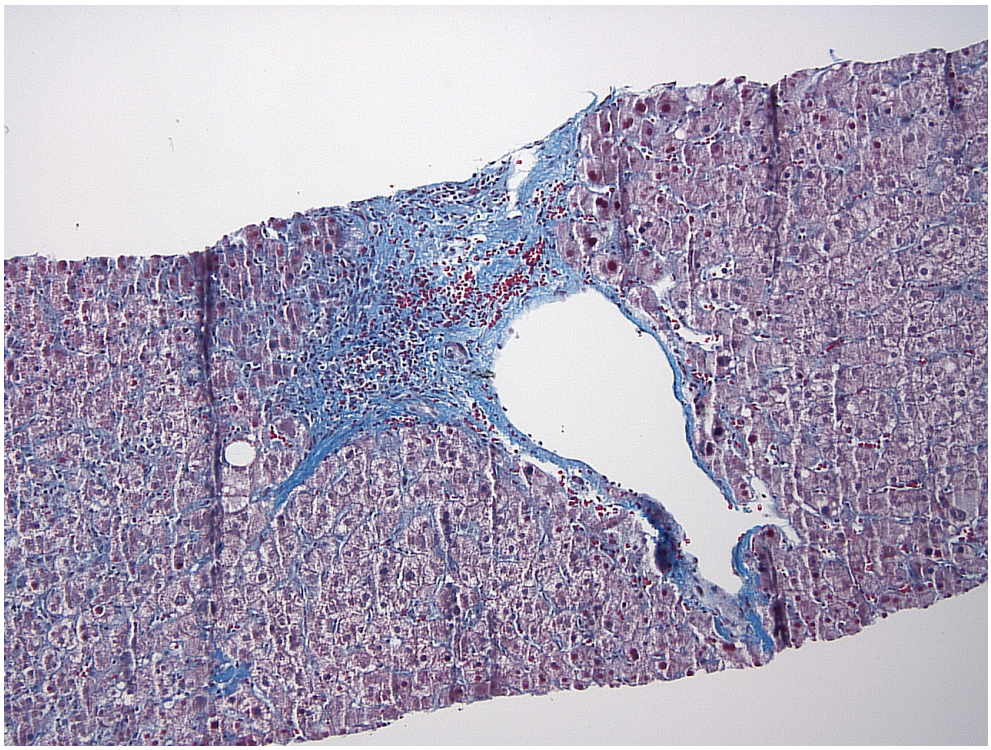

Figure 1. Liver biopsy image with F2 stage liver disease by the METAVIR scoring system in a 39-year-old female. There were pe riportal or portal–portal septa but intact architecture with limited septa formation. (Masson trichrome stain, original magnification x100)

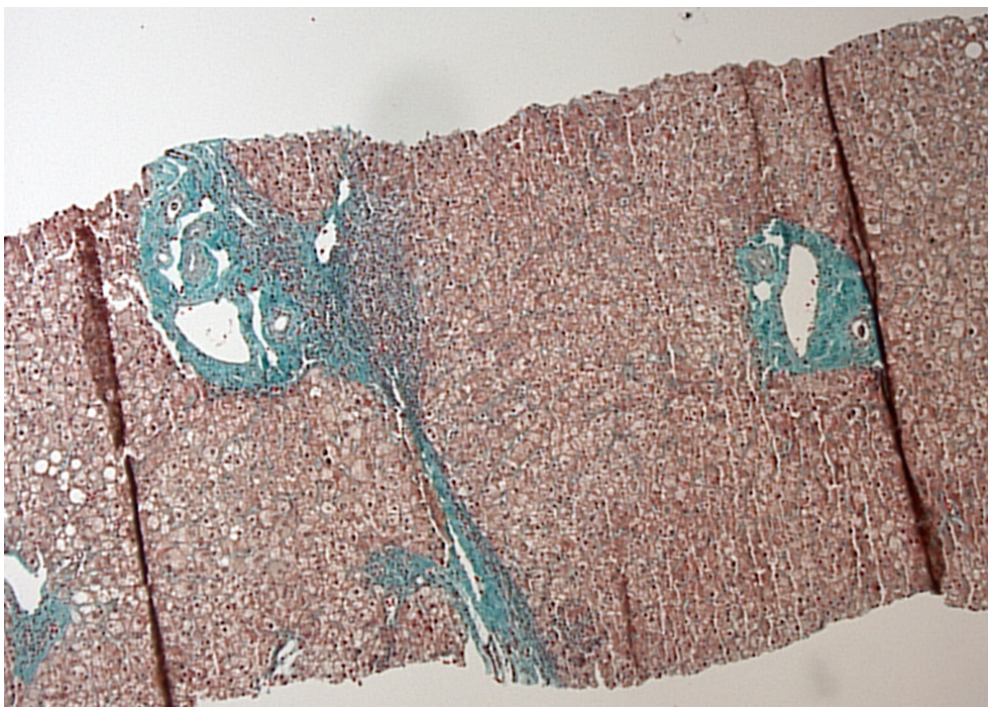

Figure 2. Liver biopsy image with METAVIR stage F3 in a 52-year-old female. Fibrous septa with architectural distortion but no fully developed or extended into lobular area & limited in portal region. (Masson trichrome stain, original magnification x100)

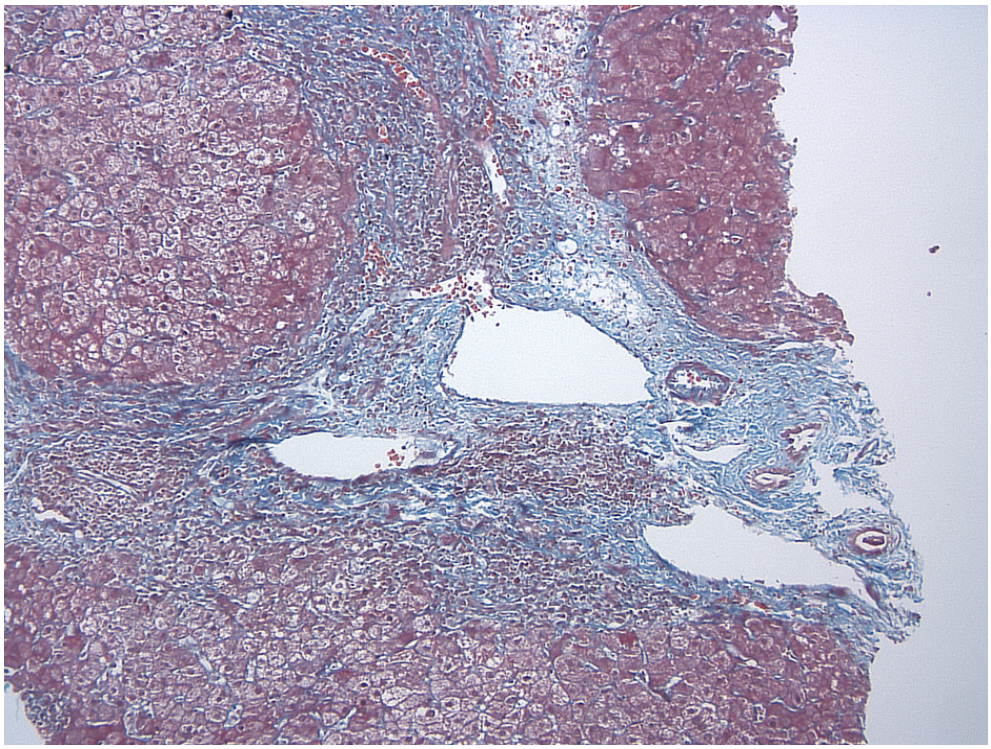

Figure 3. Liver biopsy image with METAVIR stage F4 in a 40-year-old female. Note the presence thick fibrous septa and big cluster of hepatocytes within split septa. Well demarcated cirrhotic nodules are visible. (Masson trichrome stain, original magnification x100).

Table 3. Comparison of demographic characteristics and non-invasive methods in detection of hepatic fibrosis in cirrhotic and non-cirrhotic patients with chronic hepatitis delta.

	Cirrhotic patients (n=5)	Non cirrhotic patients (n=7)	p-value
Age, mean± SD	39.4±10.4	41.3 ±7.8	.53
Male gender, n (%)	2 (40%)	5 (85.7%)	.54
PLT ($*10^9$/L), mean±SD	169±24	222±23	.02
AST (U/L), mean±SD	48.6±19.6	86.5±76.2	.82
ALT (U/L), mean±SD	40.6±14.3	125.3±145.3	.29
Serum albumin (g/L), mean±SD	43±2.3	42.7±4.2	.78
Total bilirubin (μmol/L), mean±SD	8.4±3.4	9.6±3.5	.82
AAR, mean±SD	1.4±0.8	1.1±0.6	.67
APRI, mean±SD	0.7±0.2	1.1±0.6	.48
FIB-4, mean±SD	1.8±0.8	1.6±0.6	.82
Liver stiffness (kPa), mean±SD	12.6±3.1	8.6±2.7	.18
M2BPGi (COI), mean±SD	1.3±0.7	1.4±0.8	.85

AAR, the AST to ALT ratio; ALT, alanine aminotransferase; AST, aspartate aminotransferase; APRI, the AST to platelet ratio index; COI, cut-off index; FIB-4, Fibrosis 4 index; kPa, kilopascal; M2BPGi, Mac-2 binding protein glycosylation isomer; PLT, platelet count; SD, standard deviation

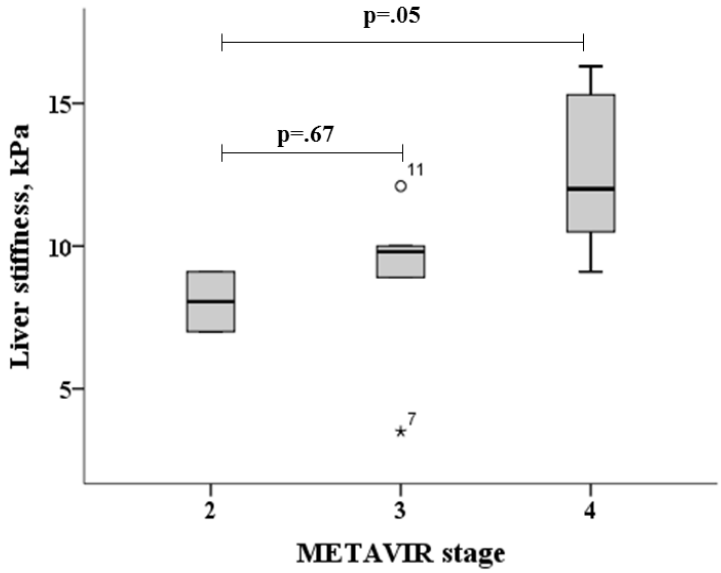

Figure 4. Liver stiffness measurements by fibrosis stage

stiffness (12.1 kPa). This patient had a moderate degree of steatosis by both histology and FibroScan® test.

Discussion

Chronic hepatitis delta is considered the most severe form of viral hepatitis with progressive liver disease, which leads to liver cirrhosis within 5-10 years and three-fold increased risk of hepatocellular carcinoma[21]. Assessment of hepatic fibrosis is crucial to identify patients with advanced fibrosis who need immediate antiviral treatment. Chronic hepatitis delta is a progressive disease, as evident by our finding that most of our patients had advanced fibrosis (F3-F4).

In our study, we compared non-invasive serum markers (AAR, APRI, FIB-4, and M2BPGi) to non-invasive imaging method (FibroScan®) to determine liver fibrosis in chronic HDV patients using liver biopsy histopathological results as the benchmark. Non-invasive fibrosis markers have been well validated in patients with chronic hepatitis B and C, but not in chronic hepatitis D. Recently, studies compared non-invasive indirect serum markers to the invasive method in chronic hepatitis delta patients. Takyar et al. assessed non-invasive serum markers including FIB-4, AAR, API and APRI in 62 HDV patients and found that area under the receiver operator curve for detecting cirrhosis was 0.83, 0.7, 0.8 and 0.75, respectively[19]. Lutterkort et al. retrospectively assessed 8 non-invasive serum markers among 100 HDV patients from HIDIT-2 multicenter trial[12]. The area under the receiver operator curve when detecting cirrhosis using AAR, APRI, and FIB-4 in HDV patients was 0.62, 0.60 and 0.65, respectively. Both researchers concluded that non-invasive indirect serum biomarkers were less accurate in determining liver fibrosis in HDV patient. This is parallels our results. There are several reasons that may explain the poor performance of indirect serum markers in HDV patients. First, most indirect serum markers were calculated using age, platelet counts, and transaminase levels. Advanced age, higher transaminase levels, and lower platelet counts are often associated with more advanced fibrosis. But in chronic hepatitis delta, patients may have liver cirrhosis even in their 30s. Also as mentioned previously, HDV is a progressive disease and it has higher transaminase levels and greater thrombocytopenia compared to HBV or HCV mono-infection[19].

To our knowledge, this is the first report compares serum M2BPGi levels in stages of different liver fibrosis in patients with chronic hepatitis D. Studies from Japan found that serum M2BPGi was independently associated with liver fibrosis stage and the cut-off values were calculated in each fibrosis stage in chronic liver disease such as chronic hepatitis B, primary biliary cirrhosis, and non-alcoholic fatty liver disease[12,13,15]. The low serum M2BPGi level in HBV mono-infected patients versus HDV patients was reported in our previous study[22]. Our small sample

size may be the reason why we did not show a significant difference in M2BPGi levels in this study.

Transient elastography is well validated in chronic hepatitis B, C, alcoholic, and nonalcoholic fatty liver disease[16,23,24]. To best of our knowledge, this is the first study to assessing liver stiffness measurement in liver fibrosis stages among chronic hepatitis D patients. We found that liver stiffness measurements were significantly higher in patients with advanced fibrosis than those who have not cirrhosis. But there were two cases, in which the liver stiffness measurement and histology fibrosis score were not concordant. That may be explained two ways. First, liver stiffness measurements have lower reliability in patients who are obese or have a large amount of chest wall fat[25]. On the other hand, liver biopsy has several limitations including the possibility of sampling error (1/50000 biopsies) and inter-observer differences in determining the stage[5].

Our study has several limitations. The small sample size is a major weakness. Molecular biology tests including HBV DNA and HDV RNA level were not tested. Additionally, the patient's antiviral treatment status was not been considered in this study. Further studies with a larger sample size are necessary to confirm the accuracy of liver elastography and M2BPGi levels for assessing the fibrosis among patients with HDV infection.

In conclusion, non-invasive serum markers were less accurate than liver stiffness measurements in determining fibrosis in patients with chronic hepatitis delta.

Conflict of Interest

The authors state no conflict of interest.

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