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A prospective study of the correlation between hepatic fibrosis and noninvasively measured fibrosis markers including serum M2BPGi and acoustic radiation force impulse elastography

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Background: Mac-2 binding protein glycosylation isomer (M2BPGi) was introduced as a noninvasively measurable serologic marker for liver fibrosis. Acoustic radiation force impulse imaging (ARFI) elastography is another noninvasive method of measuring hepatic fibrosis. There are limited data about the correlations between histologic fibrosis grade and noninvasively measured markers, including M2BPGi and ARFI.

Methods: This prospective study was conducted among patients admitted consecutively for liver resection, cholecystectomy, or liver biopsy. ARFI elastography, serum M2BPGi levels, and the aspartate aminotransferase to platelet ratio index (APRI) score were evaluated before histologic evaluation. Histologic interpretation was performed by a single pathologist using the METAVIR scoring system.

Results: In patients with high METAVIR scores, M2BPGi levels and ARFI values showed statistically significant differences between patients with fibrosis and those without fibrosis. In 41 patients with hepatocellular carcinoma, as METAVIR scores increased, M2BPGi levels also tended to increase (p=0.161). ARFI values changed significantly as METAVIR scores increased (p=0.039). In 33 patients without hepatocellular carcinoma, as METAVIR scores increased, M2BPGi levels significantly increased (p=0.040). ARFI values also changed significantly as METAVIR scores increased (p=0.033). M2BPGi levels were significantly correlated with ARFI values (r=0.604, p<0.001), and APRI values (r=0.704, p<0.001), respectively.

Conclusions: Serum M2BPGi levels increased with liver fibrosis severity and could be a good marker for diagnosing advanced hepatic fibrosis regardless of the cause of liver disease.

Keywords: Elastography; Histology; Liver fibrosis; M2BPGi

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Introduction

The most important pathologic finding of chronic liver disease is liver fibrosis, which can progress to decompensated liver cirrhosis or hepatocellular carcinoma (HCC). Various kinds of surrogate markers for liver fibrosis have been developed in clinical fields [1,2]. In practice, commonly used indirect markers of liver fibrosis include the aspartate aminotransferase (AST) to platelet ratio index (APRI) and fibrosis-4 [3,4]. Liver fibrosis is traditionally diagnosed with liver biopsy, imaging, and surrogate biomarkers [1,5]. Among them, liver biopsy is the gold standard for diagnosis of liver fibrosis based on histopathological grade [6,7], but the information that can be obtained from a liver biopsy can be inaccurate because of insufficient biopsy tissue and focal sampling [5]. For histological diagnosis, the opinion of an experienced pathologist is very important because differences in diagnosis can occur between observers.

Acoustic radiation force impulse imaging (ARFI) elastography uses ultrasound to evaluate the stiffness of liver tissue. ARFI imaging has been demonstrated in many clinical settings, including hepatobiliary patients [8]. Currently, ARFI elastography is well known as a noninvasive modality to detect hepatic fibrosis mainly in patients with chronic viral hepatitis [9].

In addition, Mac-2 binding protein glycosylation isomer (M2BPGi) has been introduced as a noninvasive serologic marker for liver fibrosis [10,11]. Numerous studies have shown that M2BPGi can predict against liver fibrosis in various liver diseases, such as viral hepatitis, nonalcoholic fatty liver disease, autoimmune hepatitis, primary biliary cirrhosis, and biliary atresia [12].

This prospective study aimed to evaluate the performance of noninvasive hepatic fibrosis markers, including M2BPGi and ARFI point shear wave elastography result, and to compare it with the liver histologic fibrosis grade.

Methods

Ethical statements: This study design was approved by the Institutional Review Board of Kosin University Gospel Hospital (KUGH 2015-06-105). All patients gave written consent for histologic evaluation of the liver at the time of initial consent for study participation.

1. Study protocol

This study was performed prospectively in patients admitted consecutively for liver resection, cholecystectomy, or liver biopsy from September 2015 to April 2020. ARFI elastography, serum M2BPGi measurement, and APRI testing were performed before histologic evaluation.

2. Measurement of M2BPGi

Preoperative serum samples were collected before histologic evaluation. Serum M2BPGi was measured at baseline using an automated immunoanalyzer (HISCL-800; Sysmex, Kobe, Japan). The measured result was presented as a cutoff index calculated as follows:

$$\text{WFA-M2BP}=(\text{WFA-M2BPsample}-\text{WFA-M2BPnc})/(\text{WFA-M2BPpc}-\text{WFA-M2BPnc}),$$

where WFA-M2BPsample is the measured value of the patient serum sample; WFA-M2BPnc is the negative control value; and WFA-M2BPpc is the positive control provided by the manufacturer.

3. ARFI imaging

Liver stiffness was measured using an ARFI elastography machine (ACUSON S3000; Siemens, Munich, Germany) at the Liver Clinic of Kosin University Gospel Hospital. For the ARFI examination of the liver, the patient lay in a supine position with abduction of the right arm. The liver was evaluated with grayscale ultrasound before ARFI, which was performed at 2–3 cm below the liver capsule, away from large vessels. For each patient, the ARFI value was obtained by repeating measurement more than three times, and then the average value was used in this study.

4. Histologic assessment of hepatic fibrosis

All liver histology interpretations were performed by a single pathologist well experienced in hepatobiliary pathology. A tissue sample was stained and scored for degree of fibrosis according to the METAVIR scoring system, which specifies a fibrosis score from 0–4 points; no portal fibrosis (stage F0), portal fibrosis without septa (stage F1), portal fibrosis with few septa (stage F2), septal fibrosis without cirrhosis (stage F3), and cirrhosis (stage F4) [13].

5. Laboratory examination

Laboratory data were collected at the time of the initial admission to the hospital. Complete blood count results, including hemoglobin concentration, white blood cell count, platelet count, and prothrombin time, and blood chemistry data were recorded. The APRI score was calculated using laboratory data as follows [14]:

$$\text{APRI}=([\text{AST/upper limit of the normal range of AST}]\times 100)/\text{platelet}\times 10^{9}/\text{L}$$

6. Statistical analysis

Demographic data and baseline characteristics are presented as mean and standard deviation values for continuous variables. To compare the three or four groups according to histologic fibrosis grade, one-way analysis of variance or the Kruskal-Wallis test was performed with continuous variables, and linear-by-linear association was performed with categorical variables. Statistical significance was determined as $p<0.05$ using SPSS software version 23 (IBM Corp., Armonk, NY, USA).

Results

1. Baseline characteristics

A total of 74 patients were included in this study. The mean age was 59.2±9.0 years, and 55 of the patients (74.3%) were male. The mean body weight was 65.2±11.0 kg, 19 patients (25.7%) had diabetes, and 26 patients (35.1%) had hypertension. Hepatitis B surface antigen positivity was found in 37 patients (50.0%), and anti-hepatitis C virus positivity was found in nine (12.2%). Thirteen patients had alcoholic liver disease, and 41 (55.4%) had HCC. Liver tissue was acquired through liver resection (68.9%), metastasectomy (8.1%), cholecystectomy (5.4%), liver transplantation (9.5%), and needle biopsy (8.1%). Histologic fibrosis grades were identified as F0/1 (35.1%), F2 (14.9%), F3 (12.2%), and F4 (37.8%) based on the METAVIR system (Table 1).

2. M2BPGi and ARFI correlated with METAVIR score

In all 74 patients, as the METAVIR score increased, there was a statistically significant difference between histologic fibrosis and both the M2BPGi (Fig. 1A) and ARFI (Fig. 1B) values. The M2BPGi result showed no statistical difference depending on the cause of liver disease, including hepatitis B virus, hepatitis C virus, or alcohol consumption ($p=0.884$). The APRI value also showed no significant difference according to the cause of liver disease ($p=0.066$) (Table 1).

1) M2BPGi and ARFI correlated with METAVIR score in HCC

Forty-one patients were diagnosed with HCC. As the METAVIR score increased, the M2BPGi level also tended to increase, but there was no statistical significance ($p=0.161$) (Fig. 2A). However, the ARFI value elevated significantly as the METAVIR score increased ($p=0.039$) (Fig. 2B).

2) M2BPGi and ARFI correlated with METAVIR score without HCC

Thirty-three patients did not have HCC. As the METAVIR score increased, the M2BPGi level also significantly increased ($p=0.040$) (Fig. 3A), and the ARFI value elevated significantly ($p=0.033$) (Fig. 3B).

3. Correlation among noninvasive fibrosis markers

The M2BPGi level was found to have a significant correlation with the ARFI value ($r=0.604$, $p<0.001$) (Fig. 4A) and the APRI value ($r=0.704$, $p<0.001$) (Fig. 4B).

Discussion

This prospective study confirmed a significant relationship between hepatic fibrosis grade and serum M2BPGi. Even in HCC patients, the M2BPGi level showed a tendency to infer hepatic fibrosis. M2BPGi showed a significant association with both the ARFI value as an elastography marker and APRI as a serologic marker.

M2BPGi, a secreted glycoprotein present in the extracellular matrix, correlates with liver fibrosis [15]. M2BPGi was chosen as a biomarker of liver fibrosis using serum from chronic hepatitis C patients, in whom it is currently used in hepatic fibrosis evaluation [16,17]. In addition, the M2BPGi level in patients with chronic hepatitis B increased as liver fibrosis progresses. However, the M2BPGi level in chronic hepatitis B patients was slightly lower than that in chronic hepatitis C patients [18]. In addition, the M2BPGi level for diagnosing liver fibrosis in nonalcoholic fatty liver disease patients was lower than that in chronic hepatitis C patients. Therefore, it is necessary to consider the cause of the underlying liver disease when interpreting the M2BPGi results [19]. According to the results of the present study, the M2B-

Table 1. Baseline characteristics, M2BPGi levels, and laboratory data of patients by cause of liver disease

Characteristics	All (n=74)	Cause of disease				*p*-value
		HBV (n=37)	HCV (n=9)	Alcohol (n=13)	Unknown (n=15)	
Age (yr), median (IQR)	58.5 (54.0–66.0)	57.0 (52.5–63.0)	57.0 (55.5–62.5)	59.0 (52.0–67.5)	65.0 (55.0–71.0)	0.246
Sex, no. (%)						0.002
Male	55 (74.3)	32 (86.5)	7 (77.8)	10 (76.9)	6 (40.0)	
Female	19 (25.7)	5 (13.5)	2 (22.2)	3 (23.1)	9 (60.0)	
Body scale, median (IQR)						
Body weight (kg)	64.80 (57.20–70.60)	68.00 (58.25–75.20)	60.40 (55.80–77.10)	64.00 (54.75–68.50)	64.80 (54.00–69.60)	0.490
Height (cm)	165.4 (159.7–168.0)	166.0 (160.4–169.5)	166.7 (160.5–169.7)	165.0 (158.0–169.0)	160.0 (155.1–165.0)	0.103
Co-morbidity, no. (%)						
Diabetes mellitus	19 (25.7)	7 (18.9)	4 (44.4)	4 (30.8)	4 (26.7)	0.452
Hypertension	26 (35.1)	11 (29.7)	3 (33.3)	6 (46.2)	6 (40.0)	0.331
Hepatocellular carcinoma, no. (%)	41 (55.4)	28 (75.7)	8 (88.9)	4 (30.8)	1 (6.7)	<0.001
Noninvasive marker, median (IQR)						
ARFI	1.50 (1.25–1.88)	1.52 (1.39–1.84)	1.82 (1.59–2.46)	1.44 (1.24–2.11)	1.23 (1.12–1.50)	0.011
M2BPGi	1.12 (0.62–1.99)	1.08 (0.68–1.84)	1.26 (0.53–7.59)	1.12 (0.42–2.33)	1.21 (0.54–2.25)	0.884
APRI	23.86 (13.53–51.44)	28.69 (15.97–56.07)	36.59 (15.31–81–81)	16.24 (9.99–29.20)	16.49 (8.82–45.00)	0.066
Tissue acquisition, no. (%)						0.183
Liver resection	51 (68.9)	27 (73.0)	8 (88.9)	8 (61.5)	8 (53.3)	
Cholecystectomy	4 (5.4)	3 (8.1)	0	0	1 (6.7)	
Metasectomy	6 (8.1)	0	1 (11.1)	1 (7.7)	4 (26.7)	
Liver transplantation	7 (9.5)	5 (13.5)	0	2 (15.4)	0	
Needle biopsy	6 (8.1)	2 (5.4)	0	2 (15.4)	2 (13.3)	
METAVIR						0.001
F 0/1	26 (35.1)	8 (21.6)	1 (11.1)	6 (46.2)	11 (73.3)	
F2	11 (14.9)	6 (16.2)	1 (11.1)	2 (15.4)	2 (13.3)	
F3	9 (12.2)	7 (18.9)	0	1 (7.7)	1 (6.7)	
F4	28 (37.8)	16 (43.2)	7 (77.8)	4 (30.8)	1 (6.7)	
Laboratory result, median (IQR)						
WBC ($\times 10^3/\mu L$)	5.08 (4.00–6.19)	4.82 (3.59–6.04)	4.45 (2.94–5.09)	5.96 (5.22–7.45)	5.18 (4.41–6.98)	0.038
Platelet ($\times 10^3/\mu L$)	157.11 (111.50–214.75)	131.00 (111.00–183.50)	116.00 (71.50–141.00)	234.00 (142.50–282.50)	204.00 (116.00–247.00)	0.004
PT (INR)	1.03 (0.98–1.11)	1.02 (0.99–1.17)	1.03 (0.94–1.08)	1.02 (0.97–1.35)	1.03 (0.97–1.09)	0.844
Protein total (g/dL)	7.10 (6.70–7.50)	7.15 (6.80–7.50)	7.30 (7.10–7.85)	6.90 (6.55–7.35)	7.10 (6.60–7.70)	0.317
Albumin (g/dL)	4.10 (3.80–4.42)	4.30 (3.85–4.45)	4.00 (3.65–4.55)	3.80 (3.75–4.30)	4.10 (3.70–4.50)	0.526
Total bilirubin (mg/dL)	0.83 (0.60–1.31)	0.93 (0.66–1.49)	0.75 (0.60–1.17)	0.76 (0.56–3.57)	0.67 (0.47–0.90)	0.316
Direct bilirubin (mg/dL)	0.31 (0.21–0.50)	0.34 (0.23–0.53)	0.34 (0.25–0.38)	0.25 (0.20–1.71)	0.27 (0.19–0.43)	0.423
AST (U/L)	35.00 (23.75–54.50)	35.00 (27.00–55.50)	36.00 (22.05–60.50)	38.00 (22.50–64.00)	31.00 (20.00–45.00)	0.862
ALT (U/L)	26.00 (16.75–38.25)	28.00 (19.00–40.50)	23.00 (15.50–28.50)	17.00 (12.00–42.50)	26.00 (16.00–39.00)	0.335
Creatinine (mg/dL)	0.69 (0.57–0.87)	0.74 (0.63–0.86)	0.79 (0.59–0.90)	0.68 (0.58–0.92)	0.56 (0.47–0.90)	0.281
hs-CRP (mg/dL)	0.13 (0.03–0.90)	0.13 (0.02–0.51)	0.03 (0.02–0.18)	0.83 (0.16–2.63)	0.10 (0.04–0.97)	0.023

M2BPGi, Mac-2 binding protein glycosylation isomer; HBV, hepatitis B virus; HCV, hepatitis C virus ; IQR, interquartile range; ARFI, acoustic radiation force impulse; APRI, aspartate aminotransferase to platelet ratio index; WBC, white blood cell; PT (INR), prothrombin time (international normalized ratio); AST, aspartate aminotransferase; ALT, alanine aminotransferase; hs-CRP, high-sensitivity C-reactive protein.

PGi level does not appear to change significantly depending on the cause of liver disease. It was also revealed to be able to predict hepatic fibrosis without being significantly affected by the presence or absence of HCC. This result will be helpful in evaluating the degree of hepatic fibrosis using M2BPGi easily and conveniently in clinical practice.

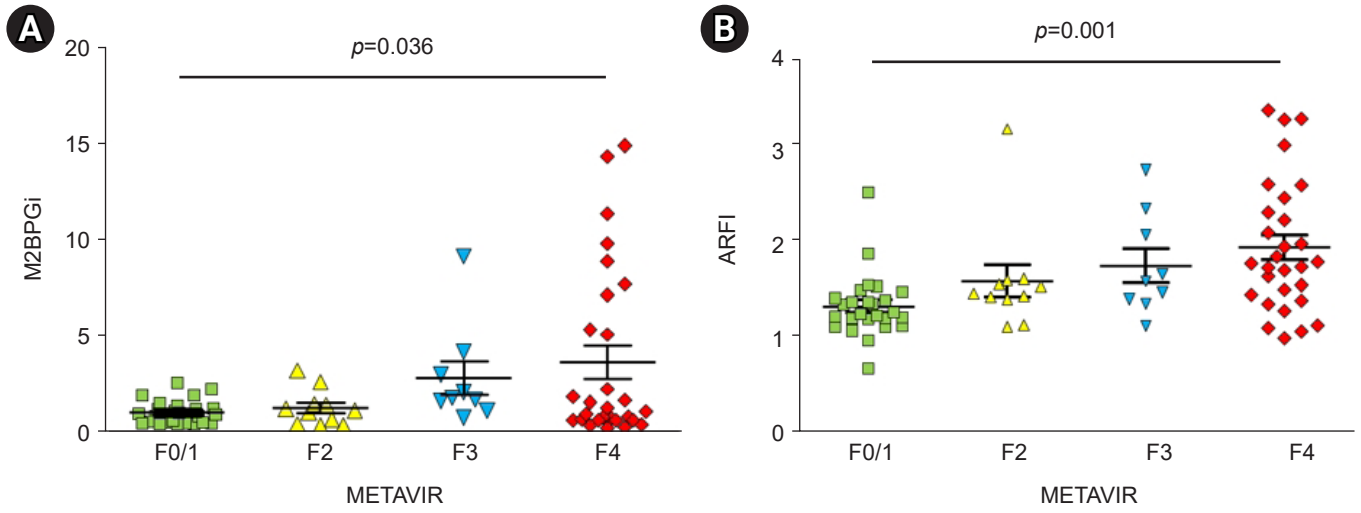

Fig. 1. M2BPGi levels and ARFI values correlated with METAVIR scores in all patients. As METAVIR scores increased, there were statistically significant differences in M2BPGi (A) and ARFI (B) values. M2BPGi, Mac-2 binding protein glycosylation isomer; ARFI, acoustic radiation force impulse imaging.

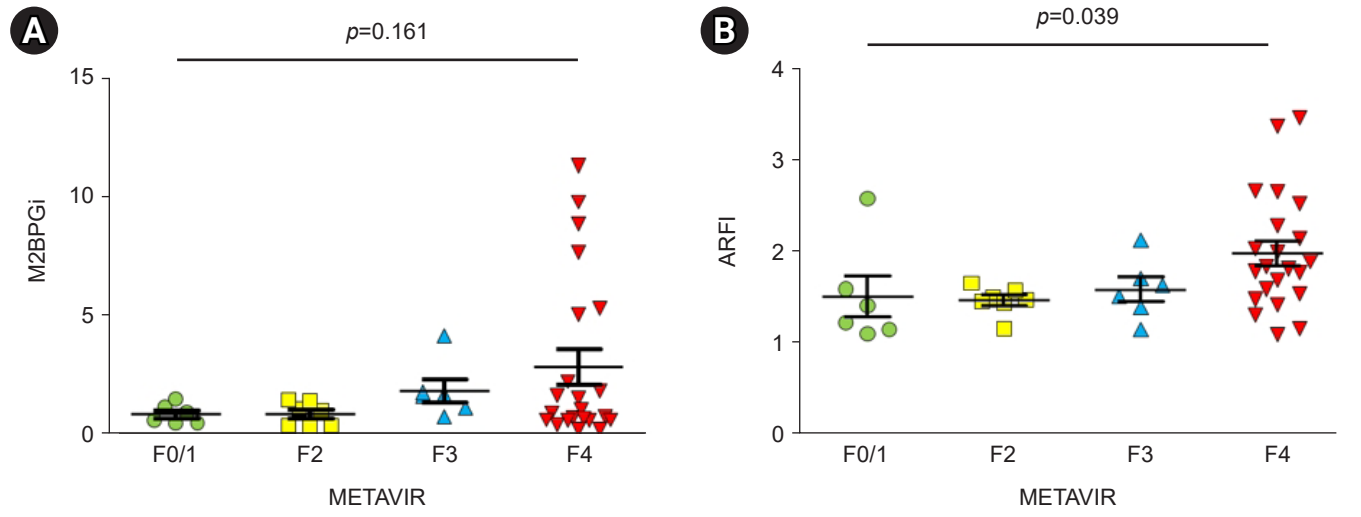

Fig. 2. M2BPGi levels and ARFI values correlated with METAVIR scores in hepatocellular carcinoma. (A) As METAVIR scores increased, M2BPGi levels tended to increase, but without statistical significance. (B) ARFI values changed significantly as METAVIR scores increased. M2BPGi, Mac-2 binding protein glycosylation isomer; ARFI, acoustic radiation force impulse imaging.

ARFI elastography uses ultrasound to visualize liver stiffness. In many studies, ARFI elastography was capable of detecting hepatic fibrosis, especially in patients with chronic viral hepatitis [9]. Recently, a meta-analysis of noninvasive imaging modalities in four ARFI elastography studies (6 cohorts) with 486 patients [20-23] revealed that the overall sensitivity and specificity were 0.92 (95% confidence interval, 0.81–0.97) and 0.72 (95% confidence interval, 0.62–0.81), respectively [24]. In addition, APRI is an indirect marker of hepatic fibrosis based on routine laboratory examinations. In a meta-analysis of 40 studies, investigators concluded that an APRI score >1.0 point had a sensitivity of 76% and a specificity of 72% for predicting advanced hepatic fibrosis [25]. In our study, M2BPGi level showed a significant correlation with both the APRI and ARFI values. In particular, M2BPGi level had a high correlation with noninvasive markers even when analyzed separately based on the presence or absence of HCC.

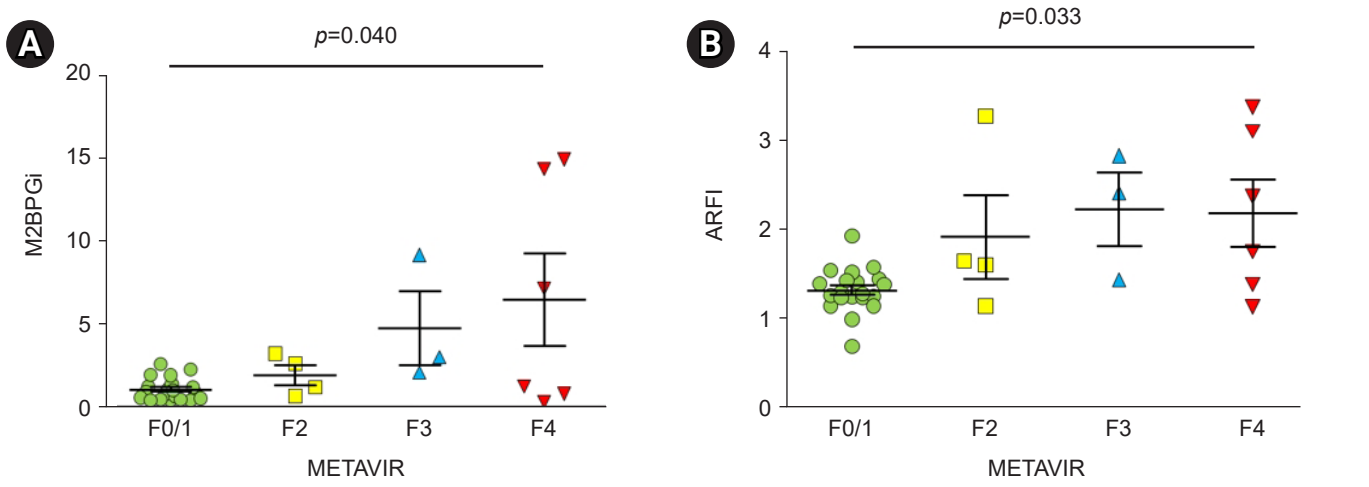

Fig. 3. M2BPGi levels and ARFI values correlated with METAVIR scores in the absence of hepatocellular carcinoma. (A) As METAVIR scores increased, M2BPGi levels significantly increased, as did (B) ARFI values. M2BPGi, Mac-2 binding protein glycosylation isomer; ARFI, acoustic radiation force impulse imaging.

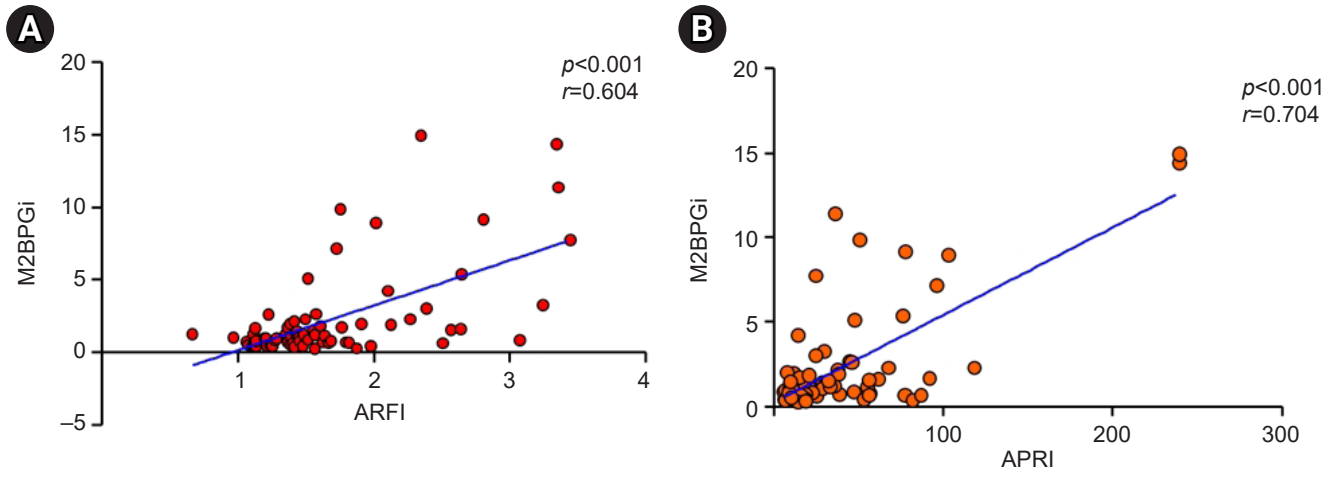

Fig. 4. Correlations among noninvasive fibrosis markers. (A) M2BPGi levels showed a significant correlation with ARFI values and (B) with APRI values. M2BPGi, Mac-2 binding protein glycosylation isomer; ARFI, acoustic radiation force impulse imaging; APRI, aspartate aminotransferase to platelet ratio index.

The main limitations of this study are its relatively small sample size (n=74) and lack of prognostic analysis for predicting deterioration of liver function or development of HCC. In addition, elastography study was performed with ARFI not FibroScan, which is more highly validated in real life. However, this study prospectively analyzed the correlation between liver histology and M2BPGi level and will be of great help in clinical practice. In conclusion, the serum M2BPGi level increased with liver fibrosis severity and could be a good marker for diagnosing advanced hepatic fibrosis regardless of the cause of liver disease.

Article information

Conflicts of interest

Hyunyong Hwang and Young Il Choi are editorial board members of the journal but were not involved in the peer reviewer selection, evaluation, or decision process of this article. No other potential conflicts of interest relevant to this article were reported.

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Author contributions

Conceptualization: KIS, HH. Data curation: BCY, HHM, YIC, DHS, MY. Formal analysis: KIS, HH. Funding acquisition: KIS, HH. Investigation: BCY, HHM, YIC, DHS, MY. Methodology: KIS, HH, BCY, HHM, YIC. Project administration: HH. Resources: HH. Supervision: BCY, DHS, MY. Visualization: KIS, HH. Writing - original draft: KIS. Writing - review & editing: HH. Approval of final manuscript: all authors.

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