



Diagnostic Performance of Serum Asialo α_1 -Acid Glycoprotein Levels to Predict Liver Cirrhosis

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Background/Aims: To date, studies on various noninvasive techniques have been suggested to evaluate the degree of liver fibrosis. We aimed to investigate the diagnostic performance of serum asialo α_1 -acid glycoprotein (AsAGP) in the diagnosis of liver cirrhosis compared with chronic hepatitis for clinically useful result.

Methods: We conducted a case-control study of 96 patients with chronic liver disease. Chronic hepatitis was defined as the presence of chronic liver disease on ultrasonography, with a liver stiffness of less than 5.0 kPa as shown on magnetic resonance elastography (MRE). Liver cirrhosis was defined as liver stiffness of more than 5.0 kPa on MRE. The serum AsAGP concentration was compared between the two groups.

Results: Serum AsAGP levels were significantly higher in patients with cirrhosis than in those with chronic hepatitis (1.83 μ g/mL vs 1.42 μ g/mL, $p < 0.001$). Additionally, when comparing patients in each cirrhotic group (Child-Pugh grades A, B, and C) to those with chronic hepatitis, AsAGP levels were significantly higher in all the cirrhotic groups ($p < 0.05$, $p < 0.01$, $p < 0.001$, respectively). The sensitivity and specificity of AsAGP for detecting cirrhosis were 79.2% and 64.6%, respectively, and the area under the curve value was 0.733. The best diagnostic cutoff to predict cirrhosis was 1.4 μ g/mL. AsAGP and bilirubin were found to be independent risk factors for the prediction of cirrhosis in the logistic regression analysis.

Conclusions: Serum AsAGP showed an acceptable diagnostic performance in predicting liver cirrhosis. (*Gut Liver* 2021;15:109-116)

Key Words: Asialo alpha 1-acid glycoprotein; Liver cirrhosis; Chronic hepatitis; Magnetic resonance elastography

INTRODUCTION

Liver fibrosis is characterized by excessive accumulation of extracellular matrix proteins as a result of sustained hepatic injury.¹ This accumulation can in turn cause distortion of the normal hepatic architecture and ultimately progress to cirrhosis, which is irreversible and causes impaired liver function.^{2,3} Noninvasive tests for the diagnosis of liver fibrosis have been developed. Although many direct and indirect surrogate markers for cirrhosis have been suggested, no single surrogate marker is used widely in clinical practice.

Asialo α_1 -acid glycoprotein (AsAGP) is an acute-phase plasma alpha-globulin glycoprotein, which is mainly biosynthesized in the liver and secreted into the circulation. AsAGP is known to have a major physiological role as a carrier protein in the binding and transport of many drugs, also playing a role in regulating their tissue distribution via a receptor-mediated pathway.⁴ As an acute-phase protein, AsAGP has anti-inflammatory and immunomodulating effects.⁵ AsAGP is glycosylated by various oligosaccharide chains during biosynthesis. When AsAGP is hydrolyzed by sialidase during clearance, the sialic acid residue is removed from the terminal of the oligosaccharide chain.

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This desialylated AsAGP has high affinity for the asialoglycoprotein receptor of the liver.^{6,7} In a previous study, Kim *et al.*⁸ have reported that the serum AsAGP level is elevated in chronic liver disease compared with healthy controls. The serum AsAGP concentration of patients with cirrhosis or hepatocellular carcinoma was significantly higher compared with that of healthy individuals. The area under the curve (AUC) in the receiver operating characteristic (ROC) curve was 0.919 for cirrhosis and 0.946 for hepatocellular carcinoma. However, neither a diagnosis of liver cirrhosis based on clinical judgement nor the diagnostic performance was evaluated to discriminate cirrhosis from chronic liver disease in the previous study.

Recently, many clinical studies related to magnetic resonance elastography (MRE) have been published as a non-invasive imaging test to determine liver fibrosis.^{9,10}

Several studies have reported that MRE could be an alternative to liver biopsy.^{11,12} The U.S. Food and Drug Administration has approved MRE results without liver biopsy in phase IIa clinical trials when developing drugs for nonalcoholic fatty liver disease.

In this study, we investigated the diagnostic performance of AsAGP for detecting cirrhosis from among chronic liver disease. The degree of hepatic fibrosis and diagnosis of cirrhosis were based on MRE. The aim of this study was to evaluate the diagnostic value of serum AsAGP as a novel biomarker specific for liver fibrosis in the diagnosis of liver cirrhosis.

MATERIALS AND METHODS

1. Study design

This was a single-center case-control study to evaluate the diagnostic accuracy of serum AsAGP levels to predict liver cirrhosis among patients with chronic liver disease. A total of 96 patients were selected at the single center. A total of 48 patients with chronic hepatitis and 48 patients with liver cirrhosis were selected for recruitment (clinical trial: KCT0003648 <https://cris.nih.go.kr/>). The study was approved by the Institutional Review Board (IRB number: 2018-05-006) and performed in accordance with the principles of the Declaration of Helsinki. Written consent was obtained from the selected patients. If the patient withdrew the consent and did not receive the MRE or blood sampling, the patient was regarded as “withdrawal of consent” and was not included in the calculation of the clinical outcome.

2. Inclusion and exclusion criteria

Patients who visited the Department of Hepatology at

Hanyang University Hospital with chronic liver disease who had a persistent elevation of liver enzymes for at least 6 months, and performed MRE were selected for the study. Inclusion criteria were as follows: adults older than 19 years; and patients with chronic liver disease (control group) or patients with liver cirrhosis (test group). Chronic hepatitis was defined as liver stiffness less than 5.0 kPa; and liver cirrhosis was defined as liver stiffness of 5.0 kPa or more on MRE as well as the presence of liver cirrhosis as shown on conventional imaging studies such as ultrasonography or computed tomography. Exclusion criteria were as follows: (1) subjects with contraindications to take magnetic resonance imaging (MRI) due to artificial pacemaker, metallic materials or pregnancy; (2) no completed consent form; (3) technical failure of MRE; (4) screening failure (subjects with cirrhosis diagnosed by conventional imaging but liver stiffness less than 5.0 kPa).

3. Asialo α_1 -acid glycoprotein

Patients who visited to the Department of Hepatology at Hanyang University Hospital were enrolled after completing the consent for clinical trials. On the day of the visit, the MRE was performed and the patient's blood was collected; in some cases, these occurred at the following visit. The patient's blood was centrifuged at 2,000 rpm for 10 minutes in a serum separation tube, and the supernatant was stored in a separate -20°C freezer. When an adequate amount of patient blood was collected, AsAGP concentrations were immediately measured with the AsAGP enzyme-linked immunosorbent assay. To obtain a more accurate analysis result, the serum AsAGP concentration was used for the average value of the results of a triplicate analysis repeated twice.

4. Acquisitions of MRE

Patients were examined in supine position with a 3.0T magnetic resonance scanner (Ingenia, Philips Healthcare, Best, the Netherlands). The patients were asked to hold their breath for 10 seconds, during which two-dimensional MRE was performed to estimate liver stiffness. The MRE parameters were as follows: 60 Hz mechanical frequency, axial image plane, 4 phase offsets, superior-inferior sensitizing direction, 287.4/pixel bandwidth, 50/20 repetition time/echo time, 45×40 cm field of view, 30° flip angle, 10-mm slice thickness, 300×85 matrix size, and 1 mm gap. The active driver outside the scanner room generated vibrations continuously at a fixed frequency (60 Hz), which were delivered through a flexible tube to the passive driver positioned over the body wall anterior to the liver of the patient in the scan room. These transmitted vibrations were then converted to shear waves within the liver. A

gradient-recalled echo MRE sequence was used to acquire images. The source phase images were postprocessed to produce wave displacement images. A curl filter was applied to separate the shear wave data from the longitudinal wave data. The resultant MRI images, called wave images, were further processed automatically on the scanner computer using specialized software (called an inversion algorithm) to create elastograms. Elastogram confidence masks were automatically created that displayed the portions of the elastogram in which the wave data were considered reliable. No contrast agents were used in this study.

5. Liver stiffness measurement

One of two abdominal radiologists independently measured liver stiffness using a magnetic resonance software tool (Philips Intellispace Portal 6.0, Philips Healthcare). Regions of interest were drawn as geographic areas manually at each of the four slices in portions of the liver that had adequate wave amplitude, avoiding areas close to the major blood vessels, liver margins, and artifacts. The mean stiffness value was assessed by averaging the values across the regions of interest, and the result was displayed automatically on each MRE slice in units of kilopascals (kPa). The values measured on the four slices were averaged.

6. Clinical parameters and proton density fat fraction

The etiology of liver disease, Child-Pugh score, alanine aminotransferase (ALT), aspartate aminotransferase (AST), bilirubin, albumin and prothrombin time (international normalized ratio) were reviewed. Also, an axial three-dimensional multi-echo modified Dixon gradient echo sequence (mDIXON-Quant, Philips) was obtained for evaluation of hepatic steatosis. A total of 27 regions of interest per subject was obtained, and the average of 27 measurements was used for a representative hepatic fat fraction as described previously.^{13,14}

7. Statistical analysis

Baseline characteristics were compared between chronic hepatitis and liver cirrhosis by using the Mann-Whitney U-test for continuous variables and the Fisher exact test for categorical variables and subgroup analysis was also performed. The liver stiffness value was randomly divided into four groups, and the comparison liver function test including AsAGP between them was done. Correlation between liver stiffness value and liver function test were estimated using the Pearson's correlation analysis. The primary efficacy parameter was assessment of AUC for liver cirrhosis as diagnosed by MRE (≥ 5.0 kPa). The secondary validity parameters were sensitivity and specificity of liver cirrhosis as diagnosed by MRE. The ROC plot method was ap-

plied to evaluate the diagnostic accuracy of serum AsAGP for diagnosis of liver cirrhosis. The clinical and imaging parameters were analyzed for possible predictive factors for liver cirrhosis by using multivariate logistic regression analysis. *p*-values < 0.05 considered statistically significant. All statistical analyses were performed with commercially available statistical software, SAS 9.4 software (SAS Institute Inc., Cary, NC, USA).

RESULTS

1. Baseline characteristics

A total of 113 patients (57 with cirrhosis and 56 with chronic liver disease) were screened for inclusion. After exclusion of 17 patients, the remaining 96 (48 with cirrhosis and 48 with chronic liver disease) were included (Fig. 1). The study population consisted of 61 men and 35 women. Among the baseline characteristics, the following parameters showed significant differences between two groups: MRE ($p < 0.001$), MRI-proton density fat fraction ($p = 0.004$), AST ($p = 0.028$), AST/ALT ratio ($p < 0.001$), bilirubin ($p < 0.001$), albumin ($p < 0.001$), prothrombin time ($p < 0.001$), and AsAGP ($p < 0.001$). Serum AsAGP levels were significantly higher in the patients with liver cirrhosis (1.83 ± 0.64 $\mu\text{g/mL}$) compared with the patients with chronic hepatitis (1.42 ± 0.29 $\mu\text{g/mL}$, $p < 0.001$) (Table 1, Fig. 2A). Detailed baseline characteristics of the study population are shown in Table 1.

2. Clinical parameters and serum AsAGP level according to disease severity

The serum AsAGP level was significantly higher in cirrhosis group compared with chronic liver disease ($p < 0.001$) (Table 2). As a serum biomarker for predicting liver cirrhosis, serum albumin, prothrombin time, and bilirubin concentration were normal, but only serum AsAGP concentration was significantly high in the Child-Pugh grade A group. The serum AsAGP concentration according to disease severity is shown in Fig. 2B. AsAGP concentrations tended to increase with progression of liver cirrhosis.

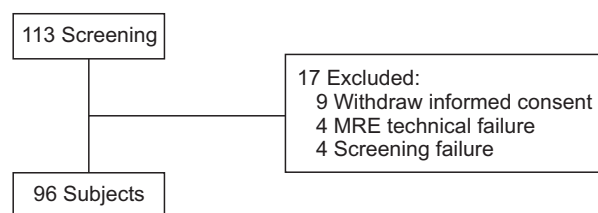


Fig. 1. Flowchart. MRE, magnetic resonance elastography.

Table 1. Baseline Patient Characteristics (n=96)

Variable	CH (n=48)	LC (n=48)	p-value
Age, yr	53.0±11.6	58.5±10.7	0.017
Sex, male/female	24 (50)/24 (50)	37 (77)/11 (23)	0.006
MRE, kPa	2.60±0.65	6.62±1.34	<0.001
MRI-PDFF, %	9.43±9.57	4.69±5.78	0.004
ALT, U/L	54.98±76.24	32.40±28.23	0.059
AST, U/L	54.48±47.24	77.27±52.36	0.028
AST/ALT ratio	1.6±0.9	3.0±2.5	<0.001
Bilirubin, mg/dL	0.8±0.3	2.5±2.1	<0.001
Albumin, mg/dL	4.3±0.4	3.4±0.7	<0.001
PT, INR	1.0±0.1	1.4±0.3	<0.001
Platelet, ×10 ³ /mm ³	224.33±67.43	110.02±55.92	<0.001
AsAGP, µg/mL	1.42±0.29	1.83±0.64	<0.001

Data are presented as mean±SD or number (%).

CH, chronic hepatitis; LC, liver cirrhosis; MRE, magnetic resonance elastography; MRI-PDFF, magnetic resonance imaging proton density fat fraction; ALT, alanine aminotransferase; AST, aspartate aminotransferase; PT, prothrombin time; INR, international normalized ratio; AsAGP, asialo α₁-acid glycoprotein.

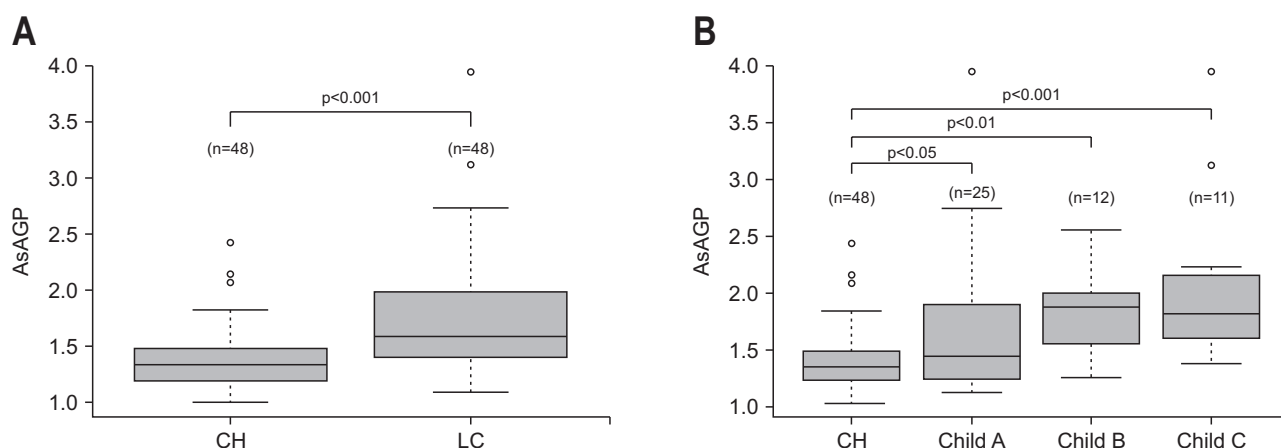


Fig. 2. (A) Comparison of AsAGP concentrations between patients with chronic hepatitis (CH) and those with liver cirrhosis (LC). (B) Comparison of AsAGP concentrations according to the Child-Pugh grade of LC.

AsAGP, asialo α₁-acid glycoprotein; Child A, Child-Pugh grade A of LC; Child B, Child-Pugh grade B of LC; Child C, Child-Pugh grade C of LC.

Table 2. Comparison between the Chronic Hepatitis and Cirrhosis Groups

Variable	Normal range	CH (n=48)	LC			
			LC total (n=48)	Child-Pugh A (n=25)	Child-Pugh B (n=12)	Child-Pugh B&C (n=23)
AsAGP, µg/mL	<1.33	1.42±0.29	1.83±0.64	1.68±0.66	1.88±0.40	1.98±0.61
MRE, kPa	<2.0	2.60±0.65	6.62±1.34	6.17±1.14	7.43±1.55	7.11±1.41
MRI-PDFF, %	-	9.43±9.57	4.69±5.78	2.74±1.40	5.88±6.11	6.80±7.77
AST/ALT ratio	-	1.58±0.89	3.02±2.53	2.10±0.91	2.90±1.49	4.02±3.27
Bilirubin, mg/dL	0.2–1.4	0.75±0.30	2.45±2.14	1.22±0.49	3.23±2.38	3.79±2.44
Albumin, mg/dL	3.5–5.0	4.33±0.37	3.45±0.67	3.92±0.40	3.07±0.65	2.93±0.52
PT, INR	<1.7	1.05±0.07	1.37±0.35	1.15±0.13	1.53±0.35	1.61±0.35
Platelet, ×10 ³ /mm ³	150–450	224.33±67.43	110.02±55.92	127.4±54.24	90.33±31.77	92.00±58.09

Data are presented as mean±SD.

CH, chronic hepatitis; LC, liver cirrhosis; AsAGP, asialo α₁-acid glycoprotein; MRE, magnetic resonance elastography; MRI-PDFF, magnetic resonance imaging proton density fat fraction; AST, aspartate aminotransferase; ALT, alanine aminotransferase; PT, prothrombin time; INR, international normalized ratio.

There was a significant difference between the patients with chronic hepatitis and the patients with a Child-Pugh score of A, B, and C ($p<0.05$, $p<0.01$ and $p<0.001$, respectively).

3. Clinical parameters and serum AsAGP level according to hepatic fibrosis

As the MRE level increased, the concentration of serum AsAGP also increased (Table 3). And serum AsAGP concentration according to etiology is shown in Table 4. The sensitivity and specificity of diagnosing liver fibrosis in the patients with chronic hepatitis were 80% and 37%, respectively, based on MRE 3.0 kPa and a serum AsAGP concentration of 1.33 $\mu\text{g/mL}$ or more.

4. Correlation between AsAGP and other liver function test including MRE

The Pearson's correlation coefficient between serum AsAGP concentrations and other major liver function

indices is shown in Table 5. The AsAGP level was positively correlated with liver stiffness by MRE ($r=0.333$, $p<0.001$), bilirubin level ($r=0.254$, $p=0.012$), prothrombin time ($r=0.300$, $p=0.003$), and AST to platelet ratio index ($r=0.214$, $p=0.036$). The AsAGP level was negatively correlated with serum albumin level ($r=-0.353$, $p<0.001$).

5. Diagnostic performance of AsAGP for diagnosis of liver cirrhosis

The AUC of the ROC for the diagnosis of liver cirrhosis was 0.733 (Fig. 3). As the secondary validity parameter, sensitivity and specificity were 79.2% and 64.6%, respectively, when the cutoff value of serum AsAGP concentration was 1.4 $\mu\text{g/mL}$. In the multivariate logistic regression analysis, only AsAGP and bilirubin were independent risk factors for diagnosis of liver cirrhosis (Table 6). We compared AsAGP with other fibrosis markers (AST/ALT ratio, AST to platelet ratio index, and fibrosis-4). The AUC of AST/ALT ratio, AST to platelet ratio index and fibrosis-4

Table 3. Comparison between AsAGP Concentrations and Other Liver Function Tests

Variable	MRE (kPa)				p for trend
	<3 (n=38)	3–5 (n=10)	5–6 (n=20)	>6 (n=28)	
AsAGP, $\mu\text{g/mL}$	1.42 \pm 0.3	1.46 \pm 0.27	1.81 \pm 0.65	1.84 \pm 0.65	0.003
Age, yr	52.74 \pm 11.12	54.00 \pm 13.99	61.60 \pm 9.40	56.32 \pm 11.14	0.040
Sex, male/female	17/21	7/3	15/5	22/6	
MRI-PDFF, %	8.41 \pm 9.08	13.30 \pm 10.86	3.66 \pm 5.27	5.42 \pm 6.11	0.008
ALT, U/L	50.71 \pm 73.87	71.2 \pm 86.87	27.3 \pm 38.12	36.04 \pm 18.20	0.184
AST, U/L	48.89 \pm 47.71	75.7 \pm 40.79	51.85 \pm 40.78	95.43 \pm 52.75	0.001
AST/ALT ratio	1.52 \pm 0.87	1.77 \pm 0.98	2.58 \pm 1.49	3.33 \pm 3.05	0.002
Bilirubin, mg/dL	0.76 \pm 0.33	0.72 \pm 0.16	2.04 \pm 2.30	2.74 \pm 2.01	<0.001
Albumin, mg/dL	4.32 \pm 0.39	4.35 \pm 0.31	3.77 \pm 0.63	3.21 \pm 0.62	<0.001
PT, INR	1.04 \pm 0.06	1.08 \pm 0.08	1.29 \pm 0.32	1.42 \pm 0.36	<0.001

Data are presented as mean \pm SD or number.

AsAGP, asialo α_1 -acid glycoprotein; MRE, magnetic resonance elastography; MRI-PDFF, magnetic resonance imaging proton density fat fraction; ALT, alanine aminotransferase; AST, aspartate aminotransferase; PT, prothrombin time; INR, international normalized ratio.

Table 4. Serum AsAGP Concentrations According to Etiology

Etiology	MRE (kPa)			
	<3 (n=38)	3–5 (n=10)	5–6 (n=20)	>6 (n=28)
ASH (n=3)	1.45 \pm 0.38	1.27*	-	-
HBV (n=13)	1.38 \pm 0.20	1.33*	-	-
HCV (n=2)	1.43 \pm 0.45	-	-	-
NAFLD (n=26)	1.49 \pm 0.35	1.49 \pm 0.28	-	-
Unknown hepatitis (n=4)	1.16 \pm 0.14	-	-	-
LC (n=41)	-	-	1.68 \pm 0.44	1.82 \pm 0.67
LC, hHCC (n=2)	-	-	3.95*	1.82*
LC, HCC (n=5)	-	-	1.78 \pm 0.33	2.07 \pm 0.68

Data are presented as mean \pm SD.

AsAGP, asialo α_1 -acid glycoprotein; MRE, magnetic resonance elastography; ASH, alcoholic steatohepatitis; HBV, hepatitis B virus; HCV, hepatitis C virus; NAFLD, nonalcoholic fatty liver disease; LC, liver cirrhosis; HCC, hepatocellular carcinoma; hHCC, historical HCC.

*(n=1).

Table 5. Correlation between AsAGP and Other Liver Function Tests

Variable	Pearson correlation coefficient (r)	p-value
Age, yr	0.097	0.348
MRE, kPa	0.333	<0.001
MRI-PDFF, %	-0.049	0.656
ALT, U/L	-0.044	0.667
AST, U/L	0.112	0.277
AST/ALT ratio	0.112	0.275
Bilirubin, mg/dL	0.254	0.012
Albumin, mg/dL	-0.353	<0.001
PT, INR	0.300	0.003
FIB-4	0.131	0.204
APRI	0.214	0.036

AsAGP, asialo α₁-acid glycoprotein; MRE, magnetic resonance elastography; MRI-PDFF, magnetic resonance imaging proton density fat fraction; ALT, alanine aminotransferase; AST, aspartate aminotransferase; PT, prothrombin time; INR, international normalized ratio; FIB-4, fibrosis-4; APRI, AST to platelet ratio index.

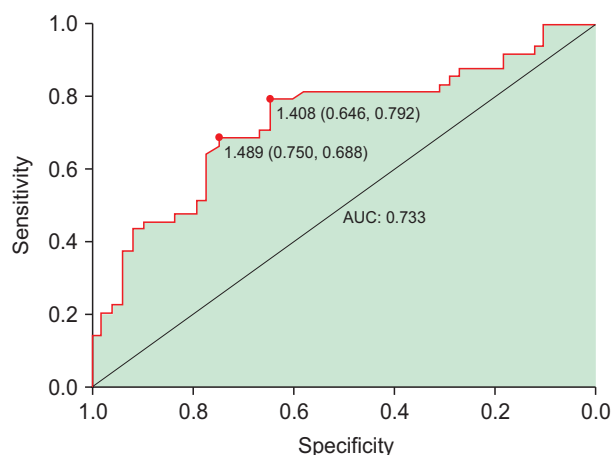


Fig. 3. The AUC (area under the curve) of the receiver operating characteristic curve. The best diagnostic cutoff to predict cirrhosis was 1.4 μg/mL. The values in parentheses mean specificity and sensitivity, respectively.

was 0.748, 0.822 and 0.935, respectively. AsAGP had the lowest AUC compared to other fibrosis markers. Because AsAGP showed relatively low diagnostic accuracy, we created a scoring system that includes albumin and bilirubin [$p = \exp(f) / (1 + \exp(f))$, $f = 4.38 + 1.38 \text{AsAGP} - 2.45 \text{alb} + 3.32 \text{T. bil}$]. If $p > 0.4$, it can be determined as liver cirrhosis, otherwise as chronic hepatitis. When applied to the diagnosis of cirrhosis, the AUC was 0.926 and the prediction performance was improved compared to AsAGP alone.

DISCUSSION

AsAGP showed acceptable discriminative performance for cirrhosis in patients with chronic liver disease. Serum AsAGP levels showed a favorable correlation with the de-

Table 6. Multivariable Analysis for the Diagnosis of Cirrhosis

Variable	Regression coefficient	Standard error	p-value
AsAGP, μg/mL	3.115	1.518	0.040
Age, yr	0.067	0.053	0.211
Sex	0.976	0.562	0.083
MRI-PDFF, %	-0.510	0.283	0.071
ALT, U/L	-0.072	0.051	0.156
AST, U/L	0.041	0.039	0.296
AST/ALT ratio	-0.825	0.871	0.344
Bilirubin, mg/dL	4.352	2.028	0.032
Albumin, mg/dL	-2.279	1.380	0.099
PT, INR	10.628	7.122	0.136

AsAGP, asialo α₁-acid glycoprotein; MRI-PDFF, magnetic resonance imaging proton density fat fraction; ALT, alanine aminotransferase; AST, aspartate aminotransferase; PT, prothrombin time; INR, international normalized ratio.

gree of liver stiffness using MRE. Our study distinguished cirrhosis based on MRE results and tried to find out the predictability of liver fibrosis through AsAGP. We also investigated the difference of AsAGP concentration according to the progression of cirrhosis, and aimed to evaluate the clinical usefulness of AsAGP in the diagnosis of early stage of cirrhosis compared with chronic hepatitis group. To our knowledge, this is first study to investigate diagnostic performance for detecting early-stage cirrhosis using AsAGP in patients with chronic liver disease. In this study, AsAGP and bilirubin were independent risk factors for cirrhosis. AsAGP concentration did not correlate with ALT, AST, or degree of hepatic fat fraction. This finding might suggest an advantage of determining AsAGP levels in the acute stage. The reliability of most noninvasive markers (e.g., FibroScan) decreases when ALT or AST are elevated. The other advantage of determining the AsAGP level is that it showed a positive correlation with hepatic fibrosis burden.

We also aimed to evaluate the clinical usefulness of AsAGP in the diagnosis of early-stage cirrhosis compared with the chronic hepatitis group. Only AsAGP level elevated in Child-Pugh A group compared with chronic liver disease whereas serum bilirubin, albumin, and prothrombin time were not different between them. When the diagnosis of cirrhosis was based on a serum AsAGP concentration of 1.4 μg/mL, the sensitivity and specificity were 79.2% and 64.6%, respectively, and the AUC value was 0.733, compared with the patients with chronic hepatitis. The reason for the relatively low specificity and AUC is presumably because the control group was selected for patients with chronic hepatitis including nonalcoholic fatty liver disease, not healthy individuals.

Changes in liver function in patients with liver cir-

rhosis, which is the last stage of structural change, are not necessarily consistent with the structural changes. In this study, however, approximately 68% (17/25) of Child-Pugh A patients had serum AsAGP levels above 1.4 $\mu\text{g/mL}$. We performed a logistic regression analysis using AST, ALT, albumin, bilirubin, prothrombin time, and AsAGP as predictive factors. When scoring system using AsAGP, albumin and bilirubin was applied to detect liver cirrhosis, the AUC value of the ROC curve for predicting cirrhosis on MRE >5.0 kPa was 0.926.

There are several hypotheses as to why serum AsAGP levels increase with the degree of liver fibrosis.⁸ First, when the liver fibrosis occurs, some asialoglycoprotein receptors on the hepatic cell surface can be damaged. In addition, extra neuraminidase is released into the circulating blood during cellular transformation, which can in turn promote desialylation of AsAGP. Finally, the onset of extensive fibrosis triggers the production or release of incomplete asialoglycoproteins into the blood circulation by hepatic cells.

Our study has several limitations. First, there are several noninvasive biomarkers to detect cirrhosis, including the Mac-2 binding protein glycosylation isomer and the enhanced liver fibrosis test. Head-to-head direct comparison studies are needed. Second, longitudinal studies of AsAGP are needed to enable the tracking of disease progression and to predict major clinical outcomes.

In conclusion, the measurement of serum AsAGP levels could be useful for predicting the degree of liver fibrosis in patients with chronic hepatitis and for distinguishing cirrhosis. It is considered a noninvasive blood test that can detect high-risk patients with an MRE of 5.0 kPa or more.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

AUTHOR CONTRIBUTIONS

Study concept and design: D.W.J. Acquisition of data: D.H.L., M.K. Analysis and interpretation of data: D.H.L., M.K., D.W.J. Drafting of the manuscript: D.H.L. Critical revision of the manuscript: D.W.J., H.S.C. Statistical analysis: M.J.K., B.K.K. Study supervision: D.W.J., J.H.Y., K.N.L., H.L.L., O.Y.L., B.C.Y. Approval of final manuscript: all authors.

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