Factors correlating with acoustic radiation force impulse elastography in chronic hepatitis C

Toru Nishikawa, Senju Hashimoto, Naoto Kawabe, Masao Harata, Yoshifumi Nitta, Michihito Murao, Takuji Nakano, Yuka Mizuno, Hiroaki Shimazaki, Toshiki Kan, Kazunori Nakaoka, Yuka Takagawa, Masashi Ohki, Naohiro Ichino, Keisuke Osakabe, Kentaro Yoshioka

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Department of Liver, Biliary Tract and Pancreas Diseases, Fujita Health University, Aichi 470-1192, Japan
Naohiro Ichino, Keisuke Osakabe, Faculty of Medical Technology, School of Health Sciences, Fujita Health University, Aichi 470-1192, Japan

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Correspondence to: Kentaro Yoshioka, MD, Department of Liver, Biliary Tract and Pancreas Diseases, Fujita Health University, 1-98 Dengakugakubo, Kutsukake, Toyoake, Aichi 470-1192, Japan. kyoshiok@fujita-hu.ac.jp
Telephone: +81-562-932324 Fax: +81-562-938601
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Abstract

AIM: To investigate the factors other than fibrosis stage correlating with acoustic radiation force impulse (ARFI) elastography in chronic hepatitis C.

METHODS: ARFI elastography was performed in 108 consecutive patients with chronic hepatitis C who underwent a liver biopsy. The proportion of fibrosis area in the biopsy specimens was measured by computer-assisted morphometric image analysis.

RESULTS: ARFI correlated significantly with fibrosis stage ($\beta = 0.1865, P < 0.0001$) and hyaluronic acid levels ($\beta = 0.0008, P = 0.0039$) in all patients by multiple regression analysis. Fibrosis area correlated significantly with ARFI by Spearman’s rank correlation test but not by multiple regression analysis. ARFI correlated significantly with body mass index (BMI) ($\beta = -0.0334, P = 0.0001$) in F0 or F1, with $\gamma$-glutamyltranspeptidase levels ($\beta = 0.0048, P = 0.0012$) in F2, and with fibrosis stage ($\beta = 0.2921, P = 0.0044$) and hyaluronic acid levels ($\beta = 0.0012, P = 0.0025$) in F3 or F4. The ARFI cutoff value was 1.28 m/s for $F \geq 2$, 1.44 m/s for $F \geq 3$, and 1.73 m/s for F4.

CONCLUSION: ARFI correlated with fibrosis stage and hyaluronic acid but not with inflammation. ARFI was affected by BMI, $\gamma$-glutamyltranspeptidase, and hyaluronic acid in each fibrosis stage.

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Key words: Acoustic radiation force impulse; Body mass index; Chronic hepatitis C; Computer-assisted morphometric image analysis; Fibrosis stage; Hyaluronic acid; Liver stiffness measurement; Transient elastography; Velocity of shear wave

Core tip: The assessment of liver fibrosis stage is important to estimate prognosis and to identify the patients requiring antiviral treatment in chronic hepatitis C. Liver biopsy is a gold standard for assessing fibrosis, but is invasive. Thus methods for noninvasively assessing fibrosis have been developed. Liver stiffness measurement (LSM) by Fibroscan and acoustic radiation force impulse correlate with fibrosis stage. However, LSM may be affected by factors other than fibrosis, such as edema, steatosis, and inflammation.

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**INTRODUCTION**

The assessment of liver fibrosis stage is important to estimate prognosis and to identify the patients requiring antiviral treatment in chronic hepatitis C.

Methods for noninvasively assessing liver fibrosis have been developed. Liver stiffness measurement (LSM) by transient elastography (TE) with Fibroscan® and velocity of shear wave (Vs) measured by acoustic radiation force impulse (ARFI) correlate with liver fibrosis stage in various liver diseases. However, LSM is affected by factors other than liver fibrosis, such as edema, steatosis, inflammation and necrosis. In particular, inflammation affects LSM; acute or chronic inflammation can result in a high LSM, indicating the presence of falsely higher fibrosis stage than the actual fibrosis stage by both TE and ARFI. However, Rizzo et al. reported that ARFI is not correlated with alanine aminotransferase (ALT) levels.

Liver fibrosis is usually semi-quantitatively assessed by the numerical systems of Scheuer or Ishak or Metavir group. Direct measurements of the amount of fibrosis in a biopsy specimen by computer-assisted morphometric image analysis has been reported, in which morphometric collagen content is measured quantitatively; it has been shown to correlate well with liver biopsy assessment numerical systems scores. Isgro et al. reported that fibrosis area has a better relationship with LSM in liver biopsy specimens and the correlation with ARFI was assessed.

**MATERIALS AND METHODS**

**Ethical statement**

This study was performed in strict accordance with the ethical guidelines of the Declaration of Helsinki and was approved by the Fujita Health University ethics committee. All study participants provided written informed consent.

**Patients**

A total of 108 consecutive patients with chronic hepatitis C virus infection who underwent a liver biopsy before treatment with interferon at Fujita Health University Hospital from October 2009 to October 2012 were included (Table 1). Liver biopsy was performed using a 14G disposable true-cut needle under ultrasonographic guidance. Sections were stained with hematoxylin-eosin and azan stain. Liver specimens of at least 1.5 cm length with more than 8 portal tracts were assessed. Liver biopsy specimens were assessed by two hepatologists (Yoshioka K and Nakaoka K) blinded to the clinical data according to Metavir score. Fibrosis was staged as follows: F0, no fibrosis; F1, portal fibrosis without septa; F2, portal fibrosis and few septa; F3, numerous septa without cirrhosis; and F4, cirrhosis. Activity was graded as follows: A0, none; A1, mild; A2, moderate; and A3, severe activity. Steatosis was graded according to the nonalcoholic fatty liver disease activity score as follows: grade 0; < 5% of hepatocytes involved, grade 1, 5%-33%; grade 2, 33%-66%; and grade 3, > 66%. When fibrosis stage, activity grade, or steatosis grade evaluated by the two hepatologists differed, the higher fibrosis stage, activity grade, or steatosis grade was adopted.

**ARFI measurement**

Vs measurement by ARFI was performed with a Siemens ACUSON S2000 (Mochida Siemens Medical Systems Co., Ltd., Tokyo, Japan) within 1 wk of liver biopsy. A region in liver to be examined for elastic properties is targeted with a region-of-interest (ROI) cursor while performing B-mode imaging. Tissue at the ROI is mechanically excited using acoustic push pulses to generate localized tissue displacements. The displacements result in propagation of shear-wave away from the region of excitation which is tracked using ultrasonic correlation-based methods. The maximal displacement is estimated for many ultrasound tracking beams laterally adjacent to the single push-beam. By measuring the time to peak displacement at each lateral location, the shear wave propagation velocity can be reconstructed. The examination was performed on the right lobe of the liver. A measurement depth of 2-3 cm below the liver capsule was chosen. Ten successful acquisitions at different locations were performed on each patient, and the results are expressed in meters/second (m/s), and the median value was calculated. The shear wave propagation velocity is considered to be proportional to the square root of tissue elasticity.

The procedures were performed by two investigators (Nishikawa T and Hashimoto S) who were blind to clinical, serological and histological data. The correlation in Vs measurement between two operators was good ($r = 0.934$).

**Proportion of fibrosis area in the liver biopsy specimens**

The proportion of fibrosis area in the biopsy specimens was measured by computer-assisted morphometric image analysis. Liver biopsy specimens were stained with azan stain. Microscopic images of the entire biopsy specimen were obtained with a digital microscope (BZ-9000, Keyence, Tokyo, Japan). Fibrosis area, which was stained blue with azan, was marked and measured with Image Pro
### Table 1 Characteristics of 108 patients with chronic hepatitis C virus infection

![Table image](image)

1. Data are shown as median (interquartile range); $^a$ Difference of frequency of gender was assessed by $\chi^2$ test. AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; $\gamma$-GT: $\gamma$-glutamyltranspeptidase.

#### Statistical analysis

Patients were categorized according to fibrosis stage. The groups were compared with the $\chi^2$ test and Mann-Whitney U test. Factors correlated with ARFI were estimated by Spearman's rank correlation test. Factors independently correlated with ARFI were assessed by multiple regression analysis. The diagnostic performance of ARFI and fibrosis area was determined in terms of sensitivity, specificity, positive and negative predictive value, positive likelihood ratio, diagnostic accuracy, and area under the receiver operating characteristics (ROC) curve. Optimal cutoff values between fibrosis categories were determined at maximum sum of sensitivity and specificity. Data were analyzed using StatFlex version 5.0 for Windows (Stat Flex, Osaka, Japan). A two-sided P value of $< 0.05$ indicated statistical significance.

### RESULTS

#### Semiquantitative histological assessment using the Metavir system

The liver biopsies of the 108 patients were assessed by the Metavir system. Fibrosis stage was F0 in 14 patients, F1 in 17, F2 in 32, F3 in 31 and F4 in 14 (Table 1).

#### ARFI measurement

ARFI was significantly correlated with fibrosis stage ($\rho = 0.732, P < 0.0001$) (Figure 1A). ARFI values differed significantly between stages F1 and F2 ($P = 0.0010$), between F2 and F3 ($P = 0.0009$), between F3 and F4 ($P = 0.0008$), and between F4 and F0 ($P = 0.0105$).

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Plus 4.0 imaging software (Nippon Roper Co., Ltd., Tokyo, Japan).
The ARFI cutoff values for different fibrosis stages determined by ROC analysis were 1.28 m/s for $F \geq 1$, and 1.16 m/s for $F = 3$ ($P = 0.0014$), and between $F = 3$ and $F = 4$ ($P = 0.0008$) (Table 1).

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### Table 2  Optimal cutoff value of velocity of shear wave for each fibrosis stage was determined at maximum sum of sensitivity and specificity

| Stage | Cutoff value (m/s) | Sensitivity | Specificity | AUROC | Standard error of AUROC |
|-------|-------------------|-------------|-------------|-------|-------------------------|
| F1    | 1.28              | 96.3%       | 86.2%       | 0.869 | 0.036                   |
| F2    | 1.28              | 96.3%       | 86.2%       | 0.869 | 0.036                   |
| F3    | 1.28              | 96.3%       | 86.2%       | 0.869 | 0.036                   |
| F4    | 1.28              | 96.3%       | 86.2%       | 0.869 | 0.036                   |

AUROC: Area under receiver operating characteristic curve

1.28 m/s for F ≥ 1, 1.44 m/s for F ≥ 3, and 1.73 m/s for F4 (Table 2).

### Fibrosis area in liver biopsy specimens

The proportion of fibrosis area was significantly correlated with fibrosis stage as assessed by the Metavir system (p = 0.872, P < 0.0001) (Figure 1B). The fibrosis area values differed significantly between stages F0 and F1 (P = 0.0111), F1 and F2 (P = 0.0022), F2 and F3 (P < 0.0001), and between F3 and F4 (P < 0.0001) (Table 1).

The fibrosis area cutoff values for the different fibrosis stages determined by ROC analysis were 1.17% for F ≥ 1, 1.80% for F ≥ 2, 3.71% for F ≥ 3, and 7.32% for F4 (Table 3).

### Factors correlating with ARFI in all 108 patients

ARFI was significantly correlated with fibrosis stage (P < 0.0001) (Figure 1A), inflammatory grade (P < 0.0001), aspartate aminotransferase (AST) levels (P < 0.0001), ALT levels (P = 0.0008), γ-glutamyltranspeptidase (γ-GTP) levels (P < 0.0001), platelet count (P < 0.0001), prothrombin time (INR) (P = 0.0003), albumin levels (P = 0.0002), total cholesterol levels (P = 0.0004), γ-globulin levels (P = 0.0087), hyaluronic acid levels (P < 0.0001), and fibrosis area (P < 0.0001) (Figure 1) by Spearman’s rank correlation test (Table 4). ARFI tended to be higher in genotype 1 [median, 1.49 (interquartile range, 1.22-1.75) m/s] than in genotype 2 [1.30 (1.17-1.46)] (P = 0.0728).

The multiple regression analysis selected fibrosis stage (β = 0.1865, P < 0.0001) and hyaluronic acid levels (β = 0.0008, P = 0.0039) as factors that independently correlated with ARFI, whereas inflammatory grade, AST, ALT and fibrosis area were not selected (Table 4).

### Factors correlating with ARFI in stage F0 or F1 patients

To elucidate the factors affecting ARFI other than fibrosis stage, patients with stage F0 or F1, those with F2, and those with F3 or F4 were analyzed separately.

Body mass index (BMI) was significantly correlated with ARFI (P = 0.0003) (Figure 1D) and ALT levels (P = 0.0593) and γ-GTP levels (P = 0.0614) tended to be correlated with ARFI by Spearman’s rank correlation test in the 31 patients with stage F0 or F1 (Table 4).

### DISCUSSION

The assessment of fibrosis stage is important to estimate prognosis and to identify the patients requiring antiviral treatment in chronic hepatitis C. A lot of noninvasive methods to assess liver fibrosis stage other than liver biopsy are available, for example, ARFI, TE, real-time elastography, and algorithm of serum fibrosis markers such as FibroTest and APRI. They provide good performances in estimation of fibrosis stage, while there are problems such as influence of inflammation. In the present study, factors other than fibrosis stage that affect ARFI were investigated in patients with chronic hepatitis C.

The present study confirmed findings previously that ARFI correlates with fibrosis stage. ARFI cutoff values for different fibrosis stages were 1.28 m/s for F ≥ 1, 1.28 m/s for F ≥ 2, 1.44 m/s for F ≥ 3, and 1.73 m/s for F4. This result suggests that distinguishing between F0 and F1 is impossible, as the cutoff was correlated with ARFI by multiple regression analysis (β = 0.0334, P = 0.0001).

### Factors correlating with ARFI in the stage F2 patients

γ-GTP levels were significantly correlated with ARFI (P = 0.0013) (Figure 1E) and γ-globulin levels (P = 0.0581) tended to be correlated with ARFI in the 32 patients with stage F2 by Spearman’s rank correlation test (Table 4). The multiple regression analysis only selected γ-GTP levels as a factor correlating with ARFI (β = 0.0048, P = 0.0012).

### Factors correlating with ARFI in the stage F3 or F4 patients

In the patients with stage F3 or F4, fibrosis stage (P = 0.0004), platelet count (P = 0.0036), prothrombin time (INR) (P = 0.0080), albumin levels (P = 0.0015), hyaluronic acid levels (P = 0.0003) (Figure 1F), and fibrosis area (P = 0.0481) were significantly correlated with ARFI by Spearman’s rank correlation test (Table 4). The multiple regression analysis selected fibrosis stage (β = 0.2921, P = 0.0044) and hyaluronic acid levels (β = 0.0012, P = 0.0025) as factors correlating with ARFI.
Table 4  Factors correlating with velocity of shear wave in 108 patients with chronic hepatitis C virus infection

|                        | All patients (n = 108) | Patients with F0 or F1 (n = 31) | Patients with F2 (n = 32) | Patients with F3 or F4 (n = 45) |
|------------------------|------------------------|---------------------------------|--------------------------|--------------------------------|
|                        | Spearman’s rank        | Multiple regression analysis    | Spearman’s rank          | Multiple regression analysis    |
|                        | ρ                      | p value                         | β                        | p value                         |
| Age (yr)               | NS                     | NS                              | NS                       | NS                              |
| Gender (female/male)   | NS                     | NS                              | NS                       | NS                              |
| BMI                    | NS                     | NS                              | NS                       | NS                              |
| Fibrosis stage         | 0.732                  | < 0.0001                        | 0.187                    | 0.001                           |
| Inflammatory grade     | 0.612                  | < 0.0001                        | NS                       | NS                              |
| Steatosis grade        | NS                     | NS                              | NS                       | NS                              |
| AST (IU/L)             | 0.430                  | < 0.0001                        | NS                       | NS                              |
| ALT (IU/L)             | 0.738                  | 0.0008                          | 0.343                    | 0.0593                          |
| γ-GTP (IU/L)           | 0.407                  | < 0.0001                        | NS                       | NS                              |
| Platelet count (× 10^9/μL) | 0.441                | < 0.0001                        | NS                       | NS                              |
| Prothrombin time (INR) | 0.344                  | 0.0003                          | NS                       | NS                              |
| Albumin (g/dL)         | 0.347                  | 0.0002                          | NS                       | NS                              |
| Total cholesterol (mg/mL) | 0.337                 | 0.0004                          | NS                       | NS                              |
| γ-glutamyltranspeptidase (g/dL) | 0.252                 | 0.0087                          | NS                       | NS                              |
| Hyaluronic acid (ng/mL) | 0.576                  | < 0.0001                        | 8.00E-4                  | 0.0039                          |
| HCV genotype (1/2)     | 0.428                  | 0.072                           | NS                       | NS                              |
| HCV RNA (logIU/mL)     | 0.252                  | 0.0087                          | NS                       | NS                              |
| Fibrosis area (%)      | 0.656                  | < 0.0001                        | NS                       | NS                              |
| R                      | 0.707                  | 0.645                           | 0.546                    | 0.634                           |
| Adjusted R             | 0.490                  | 0.396                           | 0.275                    | 0.375                           |
| F                      | 51,800                 | 20,700                          | 12,700                   | 14,100                          |
| P value                | < 0.0001               | 0.0001                          | 0.0012                   | < 0.0001                        |

1Difference of frequency of gender or genotype was assessed by Mann-Whitney U test. AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; γ-GTP: γ-glutamyltranspeptidase.

value for $F \geq 1$ and that for $F \geq 2$ are the same. However, Sporea et al. reported that the cutoff value is 1.19 m/s for $F \geq 1$, 1.33 m/s for $F \geq 2$, 1.43 m/s for $F \geq 3$, and 1.55 m/s for $F \geq 4$. Rizzo et al. reported that the cutoff value is 1.3 m/s for $F \geq 2$, 1.7 m/s for $F \geq 3$ and 2.0 m/s for $F \geq 4$. Thus, discrepancies are apparent among the cutoff values reported in different studies. The discrepancies are probably attributed to the difference in the population studied. Further studies should be conducted to establish standard ARFI cutoff values for staging fibrosis.

In the present study, AST, ALT and inflammatory grade were correlated with ARFI in the univariate analysis that included all patients, but were not selected as factors independently correlating with ARFI in the multiple regression analysis. In addition, inflammatory factors did not correlate with ARFI when patients with different fibrosis stages were analyzed separately. These results suggest that inflammatory activity does not affect ARFI in patients with chronic hepatitis C. Rizzo et al. also reported that ARFI is not associated with ALT, BMI, Metavir grade, or liver steatosis, whereas TE is significantly correlated with ALT. Bota et al. reported that discordance of at least two fibrosis stages between ARFI and histologic assessment were associated with female sex, interquartile range interval (IQR) $\geq 30\%$, high AST and high ALT in univariate analysis, while, in multivariate analysis, the female gender and IQR $\geq 30\%$ ($P = 0.004$) were associated with the discordances. In contrast, Yoon et al. reported that the optimum ARFI cutoff values are 1.13 m/s for $F \geq 2$ and 1.98 m/s for $F4$, whereas these values decreased to 1.09 m/s for $F \geq 2$ and 1.81 m/s for $F4$ when patients with normal ALT levels were selected. Chen et al. reported that ALT, ActiTest A score, Metavir activity (A) grade, Metavir F stage, BMI, and platelet count are independently associated with ARFI and suggested that a 100 IU/L increase in serum ALT levels augmented ARFI by approximately 0.155 m/s. In the present study, only 25 patients had ALT levels of 100 IU/L.
or higher. The low ALT levels among the patients studied may be a reason why ALT was not correlated with ARFI.

A multiple linear regression analysis in our previous study on TE selected fibrosis area, ALT levels, γ-GTP levels, prothrombin time, and hyaluronic acid levels as factors correlating with TE. Many studies on TE have reported that LSM is affected by ALT levels. Franquelli et al. reported that TE fibrosis staging was overestimated by necroinflammatory activity and steatosis. Coco et al. found that LSM is higher in patients with an elevated ALT than in those with either spontaneous biochemical remission or after antiviral therapy. Thus, it is probable that ALT or inflammatory activity affects TE. However, it is still unclear whether they also affect ARFI. Further studies are needed to clarify factors that affect ARFI other than fibrosis stage.

ARFI was significantly correlated with BMI in the 31 patients with stage F0 or F1; the higher the BMI, the lower the ARFI. However, ARFI was not associated with steatosis grade. Motosugi et al. reported that fat deposition in the liver does not affect ARFI. Thus, the negative correlation between BMI and ARFI could not be attributed to steatosis, which accompanies higher BMI. Actually, BMI and steatosis grade were not correlated in patients with stage F0 or F1 in the present study (data not shown). The mechanism of the association between higher BMI and lower ARFI is unclear. Because a higher BMI is associated with lower ARFI, and may cause an underestimation of fibrosis staging, careful attention should be paid to BMI during ARFI staging of fibrosis in patients with stage F0 or F1 disease.

ARFI significantly correlated with γ-GTP levels in patients with F2 and with fibrosis stage and hyaluronic acid levels in patients with stage F3 or F4. γ-GTP and hyaluronic acid levels have been regarded as the most informative fibrosis markers. Thus, it is reasonable that γ-GTP and hyaluronic acid levels independently correlated with ARFI.

Isgro et al. showed that the collagen proportional area has a better relationship with TE and with hepatic venous pressure gradient compared with Ishak stage. In the present study, fibrosis area was correlated significantly with fibrosis stage, but only fibrosis stage and hyaluronic acid levels were selected as factors independently correlating with ARFI. Our previous study demonstrated a better correlation of TE with fibrosis stage than with fibrosis area in patients with chronic hepatitis C. The Metavir stages represent categories of increasing fibrosis severity based on a combination of location and quantity of scarring as well as whether the fibrous tissue forms septa, bridges, or nodules. Fibrosis area represents only the quantity of fibrosis in liver tissues. Our results indicate that not only the quantity of fibrosis but also other histological factors such as patterns of fibrosis also affect ARFI.

The present study demonstrated that ARFI correlated with fibrosis stage but was not associated with inflammation. BMI negatively correlated with ARFI in the patients with stage F0 or F1. γ-GTP and hyaluronic acid levels were positively correlated in those with stage F2 and in those with F3 or F4, respectively. Thus, careful attention should be paid to BMI, γ-GTP levels, and hyaluronic acid levels when estimating fibrosis stage by ARFI. Fibrosis stage showed a better correlation with ARFI than fibrosis area, indicating that not only the quantity of fibrosis but also other factors such as patterns of fibrosis also affect ARFI. Since the number of the patients studied is small, further studies are needed to confirm the conclusion of the present study.

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