

Ultrasound Elastography Correlates Treatment Response by Antiviral Therapy in Patients with Chronic Hepatitis C

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Key Words

Antiviral therapy · Liver stiffness · Liver fibrosis ·
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Abstract

Objective: To investigate the relationship between tissue elasticity before and after antiviral therapy and shear wave as well as strain elastography. **Methods:** FibroScan and real-time tissue elastography were performed before and after antiviral therapy for chronic hepatitis C, and treatment efficacy and elastographic findings were comparatively analyzed. Elasticity was evaluated by measuring liver stiffness (LS) in kilopascals using FibroScan, and the liver fibrosis index (LFI) was assessed by real-time tissue elastography. **Results:** LS and LFI correlated well before and after therapy ($r = 0.567$, $p = 0.003$ and $r = 0.576$, $p = 0.002$, respectively). In the group without a sustained virological response (SVR), LS increased in 4 of 5 patients. Patients with an increase in both LS and LFI were all in the non-SVR group (3/3, 100%). In addition, LS increased in all patients except 1 in the non-SVR group (4/5, 80%). In the SVR group, both LS and LFI decreased in all patients except 1 (18/19, 94.7%). In the patient with an increase in LS despite achieving SVR, LS decreased quickly after alcohol cessation. **Conclusions:** With a few exceptions, SVR im-

proved LS. All patients with an increase in LFI were in the non-SVR group, even though LFI decreased in 2 patients. Our findings suggest that an LFI increase indicates lack of treatment efficacy with antiviral therapy. LFI may be useful for the assessment of treatment efficacy in patients with worsening of LS despite achieving SVR with antiviral therapy.

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Introduction

Chronic hepatitis patients have a high risk of developing cancer, and their prognosis depends largely on the early detection of liver cancer during routine medical screenings [1–3] because of the higher chance of receiving curative therapy [4–6]. Previous studies have shown that once a sustained virological response (SVR) with antiviral therapy has been achieved, liver fibrosis improves gradually, lowering the risk for liver cancer [3, 7, 8]. Despite its status as the gold standard for the diagnosis of liver fibrosis, liver biopsy is invasive and associated with sampling errors; therefore, a noninvasive diagnostic technique that utilizes, for example, serum markers or ultrasound (US) elastography for the assessment of liver fibrosis over time is desirable.

US elastography is broadly divided into shear wave elastography, in which an US device such as FibroScan generates shear waves and measures the velocity of waves propagating through the liver, and strain elastography, in which slight tissue deformation or strain caused by heartbeats is visualized in real-time tissue elastography (RTE) [9–11]. In shear wave elastography, the measurement of liver stiffness (LS) is affected greatly by the severity of inflammation, jaundice and congestion besides liver fibrosis [12–16]. In addition, LS is highly correlated with the risk of liver cancer in chronic hepatitis patients [17–19]. Although a study using shear wave elastography with the employment of FibroScan reported that LS was improved by interferon (IFN) therapy [20], the association between strain elastography and antiviral therapy has not been clarified. We therefore performed RTE and FibroScan measurement concurrently and investigated the association between the efficacy of IFN therapy and the differences in LS and liver fibrosis index (LFI) between pre- and posttreatment measurements.

Patients and Methods

Patients

The study included 26 patients with chronic hepatitis C who underwent US elastography before (pretreatment, PT) and 2 years after therapy initiation (after treatment, AT) at Kinki University Hospital between October 2010 and July 2013.

IFN Therapy

In accordance with the Japan Society of Hepatology Guidelines for the Management of Hepatitis C Virus (HCV) Infection, the treatment strategy was determined based on HCV serotype and the amount of HCV-RNA.

Patients with serotype 2 and <5 log IU/ml HCV-RNA underwent pegylated IFN alpha (PEG) monotherapy for 24 weeks. Patients with serotype 1 and <5 log IU/ml HCV-RNA as well as patients with serotype 2 and ≥ 5 log IU/ml HCV-RNA underwent PEG and ribavirin (RBV) combination therapy (PEG/RBV) for 24 weeks. In addition, patients with serotype 1 and ≥ 5 log IU/ml HCV-RNA underwent PEG/RBV therapy for 48 weeks or combination therapy with telaprevir (TVR), PEG, and RBV (TVR/PEG/RBV) for 24 weeks.

The IFN formulation was PEG 2a (Pegasys; Chugai Pharmaceutical Co., Ltd., Tokyo, Japan) in PEG monotherapy, and PEG 2a and RBV (Copegus; Chugai Pharmaceutical Co., Ltd.) or PEG 2b (Peg-Intron; Merck & Co., Inc., Whitehouse Station, N.J., USA) and RBV (Rebetol; Merck & Co., Inc.) in PEG/RBV therapy. In TVR/PEG/RBV therapy, TVR (Telavic; Mitsubishi Tanabe Pharma, Osaka, Japan), PEG, and RBV were used.

In each regimen, the initial dose of PEG 2a was 180 μ g once a week. PEG 2b was administered at a dose of 1.5 μ g/kg once a week. RBV was orally administered after meals twice daily, as follows: when the hemoglobin level was ≥ 13 g/dl, 600, 800, and 1,000 mg were administered to those weighing <60 , 60–80, and >80 kg, respectively;

when the hemoglobin level was <13 g/dl, 400, 600, and 800 mg were administered to those weighing <60 , 60–80, and >80 kg, respectively.

TVR was administered at a dose of 2,250 mg/day after meals 3 times a day with doses separated by 8-hour intervals, but the dose was reduced to 1,500 mg/day when the subject was female, aged ≥ 70 years, or weighed <50 kg.

Chronic hepatitis C patients who had achieved SVR after completion of 24 weeks of therapy formed the SVR group ($n = 21$, 80.8%), while patients who did not achieve SVR were classified as the non-SVR group ($n = 5$, 19.2%).

Liver Fibrosis Index

RTE was performed before and after IFN therapy using US EUS-8500 and the linear probe EUP-L52 (3–7 MHz; Hitachi Aloka Medical, Ltd., Tokyo, Japan) to estimate the LFI. The probe was pressed against the right intercostal region of the patient in a supine position, and the strain of the liver caused by heartbeats was displayed on the screen in real time. An examiner who was unaware of the patients' background selected 10 high-quality images to estimate the median LFI value using a method that has been reported previously [21–23].

Liver Stiffness

FibroScan was used to perform abdominal US in patients in a supine position for the measurement of pre- and posttreatment LS. The convex probe was used to examine liver parenchyma at the right intercostal region, and after verifying the absence of a tumor, cyst or any lesion in the measurement area of the liver that might interfere with the examination, the measurement of the same area was repeated 10 times to calculate the median LS value and interquartile range. The measurements were normalized to the median values of 10 acquisitions with a success rate of $\geq 60\%$ and an interquartile range of $<30\%$ of the median stiffness.

Statistical Analysis

Groups were compared using Wilcoxon's signed rank test and confirmed by the nonparametric Mann-Whitney U test. Correlation between data was tested using the Pearson correlation coefficient and the nonparametric Spearman rank correlation analysis. Differences were considered statistically significant if $p < 0.05$. Analysis was performed using SPSS Statistics 20 (IBM, Armonk, N.Y., USA).

Results

Demographics and Baseline Features

The number of patients who received PEG, PEG/RBV, and TVR/PEG/RBV therapy was 1, 12, and 13, respectively. The proportion of patients who achieved SVR with PEG, PEG/RBV, and TVR/PEG/RBV therapy was 100, 78, and 84.6%, respectively.

Relationship between Treatment Efficacy and LS or LFI before and after IFN Therapy

A significant positive correlation was observed both between pre- and posttreatment LS and LFI ($r = 0.567$, $p = 0.003$ and $r = 0.576$, $p = 0.002$, respectively).

Fig. 1. LS and LFI before and after IFN therapy. Pre- and posttreatment LS (**a**) and LFI (**b**) are represented by solid and dotted lines for the SVR and non-SVR patients, respectively. Nos. 1–5 are the 5 patients in the non-SVR group.

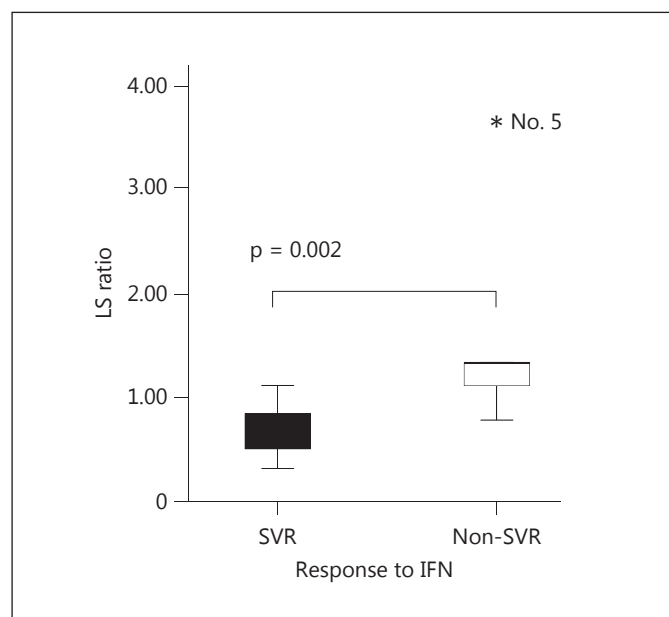
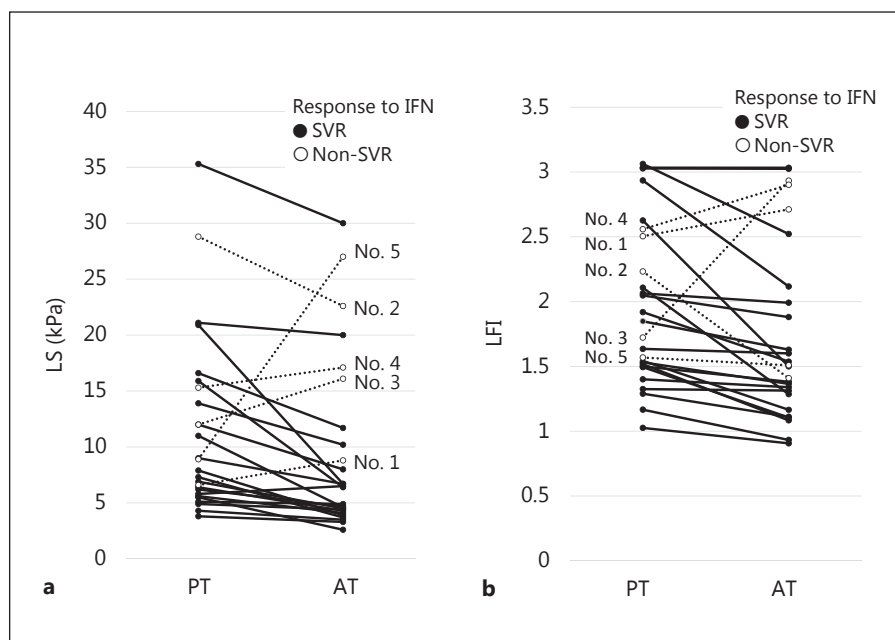


Fig. 2. Relationship between treatment efficacy and the LS ratio. The LS ratio was significantly lower in the SVR group than in the non-SVR group ($p = 0.002$). The asterisk is the extreme outlier with values more than 3 times the height of the boxes. No. 5 is a patient in the non-SVR group, numbered identical to figure 1.

While posttreatment LS was significantly lower in the SVR group ($p = 0.003$), no significant correlation was observed between posttreatment LFI and treatment efficacy ($p = 0.079$). After IFN therapy, LS mostly decreased in the SVR group, but increased in 4 (80%) of the 5 patients in the non-SVR group (fig. 1a, No. 1, 3–5). Overall, LFI decreased after therapy in the SVR group, but increased in 3 (60%) of the 5 patients in the non-SVR group (fig. 1b, No. 1, 3, 4).

Relationship between Treatment Efficacy and LS or LFI Ratios

LS (LFI at AT/LFI at PT) and LFI (LS at AT/LS at PT) ratios were calculated using the pre- and posttreatment values. While the LS ratio in the SVR group was significantly lower than in the non-SVR group ($p = 0.002$; fig. 2), the LFI ratio was slightly lower in the SVR group than in the non-SVR group ($p = 0.067$; fig. 3).

Investigation of the relationship between treatment efficacy and the LS or LFI ratios revealed that in the SVR group, the LS ratio was >1 in 1 patient, but other LFI ratios were all ≤ 1 (fig. 4). Both LS and LFI ratios were ≤ 1 in the majority of SVR patients (fig. 4).

In the non-SVR group, 4 of the 5 patients had a LS ratio >1 . Patients with both LS and LFI ratios >1 all belonged to the non-SVR group (3/3, 100%). In addition, all patients but 1 with an LS ratio >1 belonged to the non-SVR group (4/5, 80%). On the other hand, all patients but 1 with both LS and LFI ratios <1 belonged to the SVR group (18/19, 94.7%).

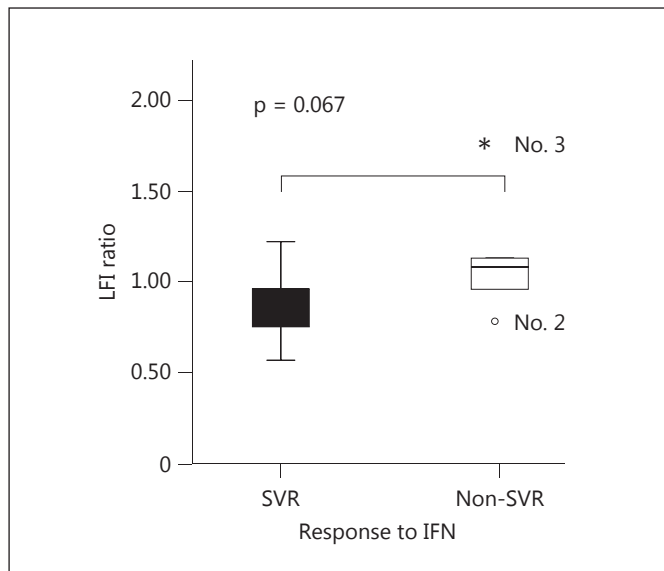


Fig. 3. Relationship between treatment efficacy and the LFI ratio. The LFI ratio tended to be low in the SVR group compared with the non-SVR group ($p = 0.067$). The open circle is the outlier, which is defined as values that do not fall in the inner fences. The asterisk is the extreme outlier with values more than 3 times the height of the boxes. Nos. 2 and 3 are the patients in the non-SVR group, numbered identical to figure 1.

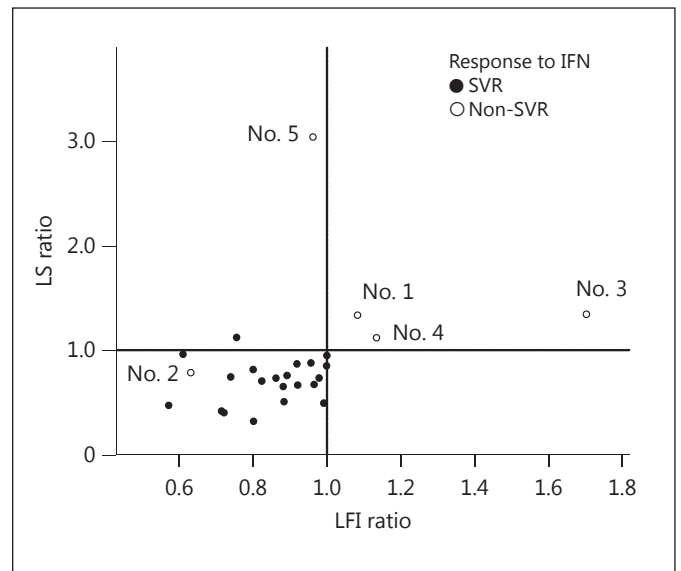


Fig. 4. Relationship between treatment efficacy and LS and LFI ratios. In the SVR group, all patients had a LFI ratio < 1 . Patients whose LS and LFI ratios were ≥ 1 all belonged to the non-SVR group. Nos. 1–5 are the 5 patients in the non-SVR group, numbered identical to figure 1.

Discussion

A previous study involving liver biopsies before and after antiviral therapy revealed that antiviral therapy improved fibrosis because of SVR [8]. Histological improvement also lowers the risk of liver cancer [7]. Therefore, even though the diagnosis of liver fibrosis is important and liver biopsy is the gold standard for its diagnosis, it is difficult to repeat liver biopsy because of its invasiveness and possible sampling errors [24]. A noninvasive diagnostic tool for liver fibrosis using hematological testing or ultrasonography is desirable. Shear wave elastography, using FibroScan for example, has become a popular method for the diagnosis of liver fibrosis and it measures LS or the propagation velocity of shear waves noninvasively [25]. However, shear wave elastography is also known to be affected by inflammation, jaundice, and congestion [12–16]. LS reportedly stays at low levels after antiviral therapy for HCV [20], but in addition to the improvement of liver fibrosis, the improvement of inflammation is thought to contribute greatly to the decline of LS values. However, because strain elastography represented by RTE visualizes slight deformations in the liver caused by heartbeats, this technology theoretically captures the changes in liver fi-

brosis without being affected by the presence of inflammation. Indeed, a study using an engineered model of liver fibrosis revealed that a blue area in RTE, which expands with the progression of liver fibrosis and represents an area with relatively low strain, was an area of collagen fibers that increases as the stage of liver fibrosis worsens [26]. This suggests that the influence of inflammation and fibrosis should be studied separately by concurrently performing and comparing the results of shear wave and strain elastography. In the present study, we therefore performed FibroScan and RTE concurrently before and after antiviral therapy (2 years after therapy initiation) and analyzed the correlation between the efficacy of antiviral therapy and changes in the measurement values.

A significant correlation was observed between treatment efficacy and LS or LFI. In particular, LFI was reduced in all SVR patients. Patients with a decrease in LS or LFI accounted for 96.2 and 100% of the patients who had achieved SVR, respectively. Patients with a decrease in both LS and LFI accounted for 100% of the SVR patients. Although LS increased in 1 of the SVR patients despite achieving SVR, it decreased quickly after alcohol cessation, indicating that the amount of alcohol consumption had increased greatly in this patient after viral clearance.

As reported previously, LS decreases in patients with successful antiviral therapy because of the improvement of liver fibrosis. However, LS is greatly affected by inflammation and tends to be higher in patients with alcoholic liver injury than in chronic hepatitis patients. Therefore, physicians should be aware that high LS values do not necessarily indicate ineffectiveness of antiviral therapy.

Theoretically, LFI is not affected by inflammation and simply reflects the severity of liver fibrosis. However, it was also reported that the levels of LFI vary between measurement sites or operators, suggesting that this might have been the cause of the decreased LFI in the non-SVR patients in this study. While the LFI decreased in some non-SVR patients, patients with an increased LFI all belonged to the non-SVR group. Therefore, an increased LFI may serve as a useful indicator of ineffective antiviral therapy. The LFI may also be useful for evaluating the efficacy of antiviral therapy in patients with an increase in LS despite achieving a SVR.

This study examined a small number of patients (21 SVR and 5 non-SVR patients), so further studies of a greater number of patients are needed to acquire more accurate results.

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Disclosure Statement

The authors declare that no financial or other conflicts of interest exist in relation to the content of this article.

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