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*Research Article*

# Changes in Liver and Splenic Stiffness after Direct-Acting Antiviral Therapy in Chronic Hepatitis C: A Single-Centre, Prospective, Observational Study

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*Background*. Liver and spleen stiffness measured by shear-wave elastography have been demonstrated to correlate well with liver fibrosis and hepatic venous pressure gradient, respectively. *Aim*. To investigate the long-term effect of direct-acting antivirals (DAA) on liver and splenic stiffness in patients with chronic hepatitis C. *Methods*. We conducted a single-centre prospective observational study including 129 chronic hepatitis C patients who achieved a sustained virological response (SVR) with DAA treatment. Liver and spleen stiffness were measured by point shear-wave elastography at pretreatment, end of treatment (EOT), and 48 and 96 weeks after EOT (SVR48 and SVR96, respectively). *Results*. Liver stiffness measurements (LSM) continued to decline to SVR96, whereas there was no change in spleen stiffness measurements (SSM). Stratified analysis at the SSM 3.2 m/s, which was estimated as the cut-off value of clinically significant portal hypertension, showed that SSM did not change in the low SSM group (SSM <3.2 m/s, n =81), whereas in the high SSM group (SSM ≥3.2 m/s, n =48), the SSM decreased significantly between pretreatment and EOT but did not change thereafter. Moreover, multivariate analysis of risk factors for the SSM remaining in the range of SSM ≥3.2 m/s at SVR96 in the high SSM group revealed that LSM ≥1.93 m/s was a significant factor (p =0.019). *Conclusion*. These results suggest that DAA treatment of chronic hepatitis C patients may improve liver fibrosis in the long term and some patients with advanced liver fibrosis may not expect an improvement of portal hypertension even if an SVR is achieved.

## 1. Introduction

The treatment of chronic hepatitis C virus (HCV) infection has shifted from interferon therapy to direct-acting antiviral (DAA) therapy. International guidelines now recommend DAA therapy for almost all patients with chronic hepatitis C, except those with a short life expectancy [1]. Di Marco et al. reported that even if a sustained virological response (SVR) was achieved with peg-interferon and ribavirin therapy in patients with type C compensated cirrhosis, there were no changes in the rate of oesophageal varices progression or that of conversion to uncompensated cirrhosis [2]. Nagaoki et al. also reported that the risk of exacerbation of oesophageal varices was still high in type C compensated cirrhosis with a radial portosystemic collateral vessel after the achievement of SVR with peg-interferon therapy [3]. However, there have been few studies of the effect of DAA therapy on portal hypertension in chronic hepatitis C. Lens et al. reported a significant decrease in liver stiffness and the hepatic venous pressure gradient (HVPG) at 24 and 96 weeks after SVR in patients with HCV-related cirrhosis associated with portal hypertension defined as HVPG ≥10 mmHg, whereas portal hypertension remained in 78% and 53% of patients, respectively, [4, 5].

The gold standard for the assessment of hepatic fibrosis is liver biopsy, although sampling errors may exist and its invasiveness and expensiveness make repeated biopsy difficult. Sporea et al. found a significant correlation between

liver stiffness and liver biopsy evaluated by the METAVIR score with shear-wave elastography (SWE) [6]. Similar reports have been presented by Lupsor et al. and confirmed by several meta-analyses [7–10]. Accordingly, liver stiffness is now considered a non-invasive indicator to assess liver fibrosis.

However, the gold standard for assessing the presence and severity of portal hypertension is HVPG. As for liver biopsy procedures, HVPG measurement is invasive and expensive. Colecchia et al. reported a strong correlation between HVPG and spleen stiffness when measured by transient elastography, suggesting its usefulness for the assessment and monitoring of portal pressure [11]. Several studies also showed that spleen stiffness measured by SWE correlated strongly with HVPG [12–14]. Spleen stiffness as assessed by SWE might be a non-invasive method for the estimation of portal hypertension.

To clarify the long-term effects of DAA therapy on liver fibrosis and portal pressure, we investigated the changes in liver stiffness as an index of liver fibrosis and spleen stiffness as an index of portal pressure assessed by SWE after treatment for 2 years.

## 2. Materials and Methods

*2.1. Patients.* This was a single-centre prospective observational cohort study conducted in accordance with the Declaration of Helsinki and approved by the institutional review board of Ikeda Municipal Hospital (clinical trial registration number: A22004). Informed consent was obtained from each patient at the start of treatment.

Between June 29, 2015 and January 9, 2020, 156 patients with chronic hepatitis C who started DAA treatment for 12 weeks were enrolled in this study. The enrolled patients underwent SWE for the measurement of liver and spleen stiffness at pretreatment, end of treatment (EOT), and 48 and 96 weeks after EOT (SVR48 and SVR96, respectively). Of these 156 patients, 20 patients were excluded because their liver stiffness or spleen stiffness measurements were judged to be "inadequate" as described below. Seven patients were excluded from the study for loss to follow-up. Finally, the remaining 129 patients achieved SVR and were included in this study analysis (Figure 1). DAA regimens were ledipasvir/sofosbuvir (n = 57), sofosbuvir/ribavirin (n = 34), glecaprevir/pibrentasvir (n = 31), elbasvir/grazoprevir (n = 6), and sofosbuvir/velpatasvir (n = 1).

*2.2. Measurements.* Liver stiffness and spleen stiffness were measured by the acoustic radiation force impulse (ARFI) point SWE (pSWE) (Acuson S2000, Virtual Touch Tissue Quantification mode). All patients were fasted for at least 6 hours before the examination. Liver stiffness was measured eight times in the supine position, with the right arm at maximum abduction, at the right lobe of the liver through the intercostal space, avoiding the area with the great vessels. Spleen stiffness was also measured eight times at the splenic hilum through the left intercostal space with the same technique as for liver stiffness. During the examination, the patient was instructed to avoid deep inhalation and exhalation and to stop breathing at a medium respiratory level to minimize respiratory motion, following recent ultrasound elastography guidelines [15, 16]. As an indicator of variability, the ratio of the interquartile range (IQR) of liver and spleen stiffness to the median (IQR/M) was calculated and an IQR/M > 30% was defined as "inadequate" [17]. Liver stiffness measurements (LSM) and spleen stiffness measurements (SSM) were expressed as the median of eight measurements, respectively. LSM and SSM were evaluated at pre-treatment, end of treatment (EOT), and 48 and 96 weeks after EOT (SVR48 and SVR96, respectively). Albumin, alanine aminotransferase (ALT), and platelet counts were measured by blood tests at the same time points.

In the ARFI point SWE measurements, 5 (0.8%) LSM and 18 (3.0%) SSM cases were judged inadequate. Finally, 20 patients with inadequate measurements were excluded.

*2.3. Statistical Analysis.* Continuous variables were expressed as the median (IQR). Categorical variables were expressed as frequencies (percentages). Differences in continuous variables at each measurement time point were evaluated for statistical significance by the Friedman test, and those that were significant were evaluated further for significance between groups by the Wilcoxon signed-rank sum test. All calculated P-values were two-sided, with P-values $<0.05$ being considered statistically significant, and Bonferroni correction was used for comparisons between groups. Patient-related factors before DAA treatment were evaluated to assess explainable risk factors for residual portal hypertension. Patient-related factors included age, sex, LSM, albumin, ALT, and platelet count. For continuous variables, receiver operating characteristic (ROC) curve analysis was performed to determine the cut-off value (COV) for risk prediction, and continuous variables were divided into two groups by COV. The univariate logistic regression model was used to determine the odds ratio (OR) between two groups with 95% confidence intervals (CI), and significance was assessed by the likelihood-ratio test. Furthermore, a multivariate logistic regression analysis was conducted by selecting variables to minimize Akaike's Information Criterion (AIC) using a stepwise method for factors that were significant in the univariate analysis. All statistical analyses were performed using JMP statistical software (ver. 15.2.1, SAS Institute Inc.).

## 3. Results

Baseline characteristics are shown in Table 1. The median age at baseline was 73 years (IQR: 66, 78), and there were 50 males in the study (38.7%), of which 58 (45.0%) had liver cirrhosis (Fib4-Index ≥3.25).

LSM showed a long-term decline to SVR96 (Figure 2(a)). Stratified analysis at LSM 1.43 m/s at pre-treatment, which was estimated to be consistent with F3 [6], showed the low LSM group (LSM < 1.43 m/s, n = 69) had no change up to EOT, followed by a gradual decline (Figure 3(a)), whereas the high LSM group (LSM ≥ 1.43 m/s, n = 60) showed a sustained decline up to SVR96 (Figure 3(b)).

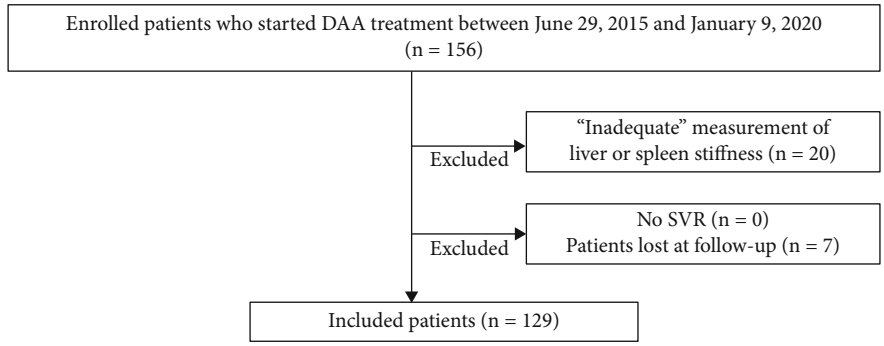


Figure 1: Flowchart of the study design. Abbreviations: DAA, direct-acting antiviral; SVR, sustained virological response; "inadequate" measurement, the ratio of the interquartile range (IQR) to the median was more than 30% in 8 measurements of liver and spleen stiffness.

Table 1: Baseline characteristics of 129 patients with chronic hepatitis C who achieved a sustained virological response with DAA treatment (n =129).

| | |
|---|---|
| Age, years | 73(66-78) |
| Sex, male/female, n (%) | 50/79 (38.8/61.2) |
| CH/LC, n (%) | 71/58 (55.0/45.0) |
| ALB, g/dL | 3.8(3.5-4.0) |
| ALT, IU/L | 28(20-55) |
| PLT, $\times 10^4/\mu$L | 1.59(1.20-1.89) |
| FIB-4 index | 3.06(2.01-4.78) |
| Liver stiffness (m/s)† | 1.40(1.20-1.77) |
| Spleen stiffness (m/s)† | 2.97(2.62-3.34) |

†Liver and spleen stiffness were measure by point shear-wave elastography. Abbreviations: DAA, direct acting antivirals; CH, Chronic hepatitis; LC, liver cirrhosis; ALB, albumin; ALT, alanine aminotransferase; PLT, platelet count. Continuous variables were expressed as the median and first-third quartiles. Categorical variables were summarized as frequencies (percentages).

In contrast, there was no change in the SSM (Figure 2(b)). Stratified analysis at SSM 3.2 m/s at pre-treatment, which was estimated as a cut-off value for clinically significant portal hypertension (CSPH) [12], showed no SSM change in the low SSM group (SSM <3.2 m/s, n =81) (Figure 4(a)). In the high SSM group (SSM ≥3.2 m/s, n =48), the SSM decreased significantly between pretreatment and EOT, but did not change thereafter (Figure 4(b)).

Then, we analysed the risk factors for remaining portal hypertension, namely SSM values ≥3.2 m/s at SVR96 as an outcome in the high SSM group. COVs for age, LSM, albumin, ALT, and platelet count established by ROC curve analysis are shown in Table 2. Univariate logistic regression analysis was performed for sex, age, LSM, albumin, ALT, and platelet count in the two groups by COV: sex (female, OR =4.04, 95% CI: 1.05–15.58, p =0.034), LSM (≥1.93 m/s: OR =9.69, 95% CI: 1.86–50.42, p =0.0018), ALT (≥35 IU/L: OR =4.06, 95% CI: 1.22–13.58, p =0.019), and platelet counts (<1.26 × 10 [4]/$\mu$L: OR =6.05, 95% CI: 1.59–23.01 p =0.0048) were significant factors (Table 2). The multivariate analysis using a stepwise method revealed that LSM (≥1.93 m/s: OR =7.61, 95% CI: 1.40–41.30, p =0.019) was a significant factor for remaining portal hypertension at SVR 96 (Table 3). Figure 5 shows a change in the SSM in the high SSM group stratified by an LSM value of 1.93 m/s. In patients with an LSM <1.93 m/s in the high SSM group (n =34), the SSM was significantly decreased below 3.2 m/s between pretreatment and EOT, but it did not change thereafter (Figure 5(a)). In those with an LSM of 1.93 m/s in the high SSM group (n =14), the SSM remained above 3.2 m/s thorough SVR96 (Figure 5(b)).

Serum albumin levels increased to SVR48 and then remained almost unchanged. The ALT declined quickly to EOT and slowly to SVR 48. Platelet counts slightly increased to EOT (Figure 6).

## 4. Discussion

In this study, we used LSM and SSM measured by SWE as indicators of liver fibrosis [6–10, 17] and portal hypertension [11–14, 17], respectively, and investigated the long-term effect of DAA on LSM and SSM in patients with chronic hepatitis C. We found that DAA treatment resulted in an early decrease in the LSM, which was sustained thereafter. This trend was particularly strong in the high LSM group. LSM reduction was also observed in the low LSM group, although to a smaller degree. These changes in the LSM by DAA treatment may reflect a long-term improvement in liver fibrosis. We also observed that ALT declined quickly to EOT and slowly to SVR 48. LSM was reported to be affected by liver inflammation [18, 19]. The early rapid improvement in LSM in this study might be associated with an improvement in liver inflammation by DAA.

Similar results were reported by Hsu et al., who retrospectively analysed 395 patients with chronic hepatitis C treated with DAA [20]. The authors measured liver stiffness at baseline and 12 weeks after DAA treatment using ARFI in 199 patients who achieved SVR and found that there was a decrease in the median LSM from 1.78 m/s to 1.38 m/s. Attia et al. prospectively observed 275 consecutive patients with chronic hepatitis C treated with DAA. LSM was conducted by ARFI at baseline, and SVR24 and SVR48 by transient elastography at baseline and SVR24 [21]. They reported that ARFI and transient elastography detected a decrease in the LSM at SVR24. They also reported that ARFI measurements showed a continuous decrease in LSM in patients with cirrhosis up to 48 weeks after DAA treatment, but there was no LSM change in patients without cirrhosis. These reports

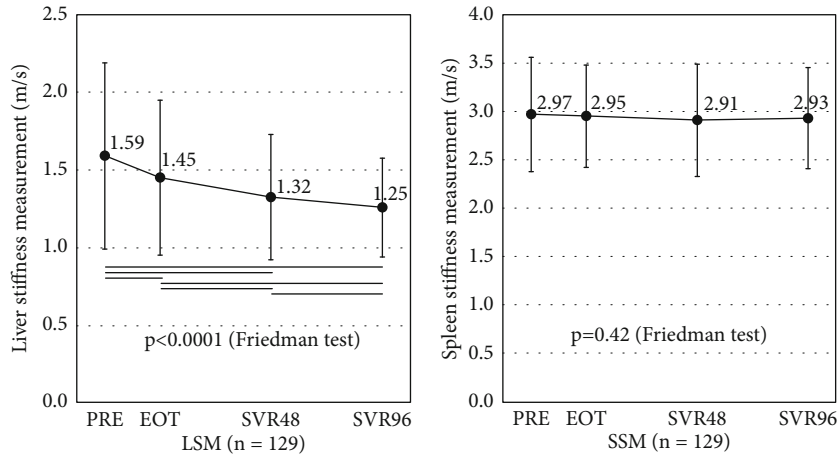


Figure 2: Changes in liver stiffness measurements (LSM) and spleen stiffness measurements (SSM) in patients with chronic hepatitis C treated with direct acting antivirals. (a) LSM. (b) SSM. Bars indicate Bonferroni-corrected p-values <0.05. Abbreviations: LSM, liver stiffness measurement; SSM, spleen stiffness measurement; PRE, pre-treatment; EOT, end of treatment; SVR48, 48 weeks after EOT; SVR96, 96 weeks after EOT.

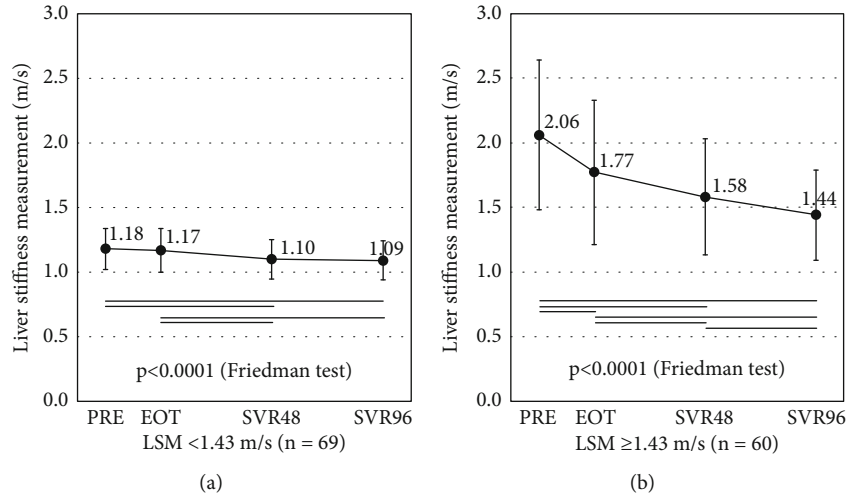


Figure 3: Changes in liver stiffness measurements (LSM) stratified by an LSM value of 1.43 m/s in patients with chronic hepatitis C treated with direct acting antivirals. (a) LSM <1.43 m/s (n =69). (b) LSM ≥1.43 m/s (n =60). Bars indicate Bonferroni-corrected p-values <0.05. Abbreviations: LSM, liver stiffness measurement; PRE, pre-treatment; EOT, end of treatment; SVR48, 48 weeks after EOT; SVR96, 96 weeks after EOT.

were consistent with our results, and this is the first study to show that an improvement in the LSM continued for 2 years after DAA treatment.

However, the SSM did not improve with DAA treatment. We investigated the effect of DAAs on the SSM of patients with or without CSPH by dividing the patients into low and high SSM groups. We used 3.2 m/s as a cut-off value for high SSM, which was reported by Jansen et al. as the predicted cut-off value for CSPH using ARFI pSWE in a multicentre study [12]. Takuma et al. [22], Rizzo et al. [ 23] and Kim et al. [ 24] reported cut-off values of spleen stiffness to estimate oesophageal varices using pSWE, which were similar to the report of Jansen et al. [12].

The normal value of SSM was reported to be 2.6–2.85 m/s [17], and the value of SSM in the low SSM group (SSM <3.2 m/s) before treatment was close to this value. As expected, there was no change in the SSM in the low SSM group during the observation period. However, an early improvement in SSM was observed in the high SSM group suggesting a certain effect of DAA treatment on portal hypertension. Ravaioli et al. retrospectively analysed 146 patients with advanced chronic liver disease treated with DAAs for whom SSM was measured by transient elastography was available at baseline and SVR24 [25]. They reported a significant decrease in the SSM from 58.8 kPa to 38.2 kPa. These results are consistent with the early phase improvement of the SSM in the high SSM group of our study.

In addition, we analysed risk factors for remaining portal hypertension, that is, SSM ≥3.2 m/s at SVR96 in the high SSM group and found that only an LSM value ≥1.93 m/s at

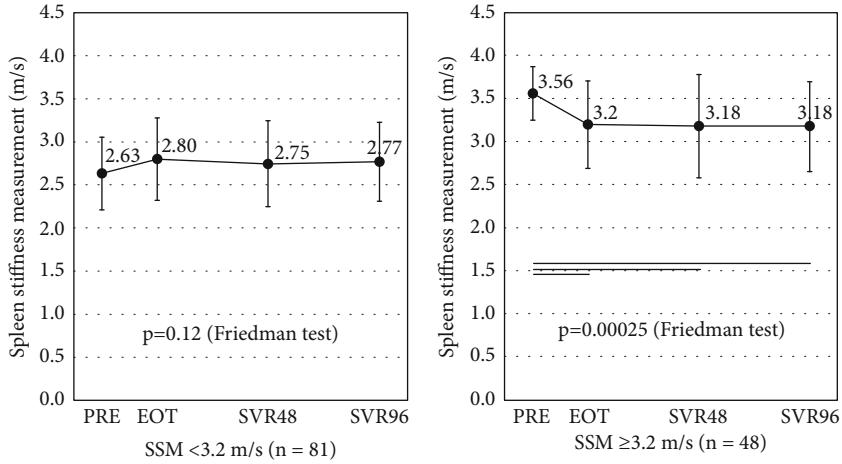


Figure 4: Changes in spleen stiffness measurements (SSM) stratified by an SSM value of 3.2 m/s in patients with chronic hepatitis C treated with direct acting antivirals. (a) SSM <3.2 m/s (n =81). (b) SSM ≥3.2 m/s (n =48). Bars indicate Bonferroni-corrected p-values <0.05. Abbreviations: SSM, spleen stiffness measurement; PRE, pre-treatment; EOT, end of treatment; SVR48, 48 weeks after EOT; SVR96, 96 weeks after EOT.

Table 2: Receiver operating characteristics (ROC) associated with remaining portal hypertension in patients with a spleen stiffness value of ≥3.4 m/s at pretreatment (high SSM group, n =48).

| Characteristics | COV | AUC | Sensitivity | Specificity |
|---|---|---|---|---|
| Age, years | 74 | 0.5435 | 0.52 | 0.65 |
| LSM, m/s | 1.93 | 0.6896 | 0.48 | 0.91 |
| ALB, g/dL | 3.8 | 0.5670 | 0.56 | 0.61 |
| ALT, IU/L | 35 | 0.6626 | 0.64 | 0.70 |
| PLT, $\times 10^4/\mu$L | 12.6 | 0.6165 | 0.60 | 0.83 |

Abbreviations: SSM, spleen stiffness measurement; LSM, liver stiffness measurement; ALB, albumin; ALT, alanine aminotransferase; PLT, platelet count; COV, cut-off value; AUC, area under the receiver operating characteristic curve.

Table 3: Univariate and multivallate analyses of factors associated with remaining portal hypertension in patients with a spleen stiffness value of ≥3.4 m/s at pretreatment (high SSM group, n =48).

| | Univariate | | | Multivariate | | |
|---|---|---|---|---|---|---|
| Factor | OR | 95% CI | p-value | OR | 95% CI | p-value |
| Age<74 years | 1.52 | 0.46-5.04 | 0.49 | | | |
| Sex (female) | 4.04 | 1.05-15.58 | 0.034 | | | |
| LSM ≥1.93 m/s | 9.69 | 1.86-50.42 | 0.0018 | 7.61 | 1.40-41.30 | 0.019 |
| ALB ≥3.8 g/dL | 1.98 | 0.63-6.26 | 0.24 | | | |
| ALT ≥35 IU/L | 4.06 | 1.22-13.58 | 0.019 | 2.93 | 0.79-10.83 | 0.11 |
| PLT<12.6 × $10^4/\mu$L | 6.05 | 1.59-23.01 | 0.0048 | | | |

Abbreviations: SSM, spleen stiffness measurement; LSM, liver stiffness measurement; ALB, albumin; ALT, alanine aminotransferase; PLT, platelet count; OR, odds ratio; 95% CI, 95% confidence interval. P-values were assessed by the likelihood-ratio test.

pre-treatment was a significant risk factor. In patients with LSM ≥1.93 m/s at pre-treatment in the high SSM group, the SSM did not improve and remained above 3.2 m/s during the observation period (Figure 5(b)). Knop et al. prospectively investigated LSM and SSM using ARFI point SWE at baseline and 24 weeks after SVR in 54 HCV-related cirrhosis patients with very high LSM levels treated by DAAs [26]. They reported that the LSM improved from 2.7 (1.2–4.1) m/s to 2.4 (1.2–3.9) m/s, whereas the SSM remained unchanged, which is consistent with our results observed in advanced hepatic fibrosis cases in the high SSM group. As previously reported, even after the successful treatment of chronic hepatitis C, attention should be paid to worsening portal hypertension, especially in cases of advanced hepatic fibrosis with a portosystemic shunt [ 2, 3].

In our study, the LSM of 5 (0.8%) cases were inadequate with an IQR/M >30%, and the SSM was inadequate in 18 (3.0%) cases. Procopet et al. reported success rates of 99%

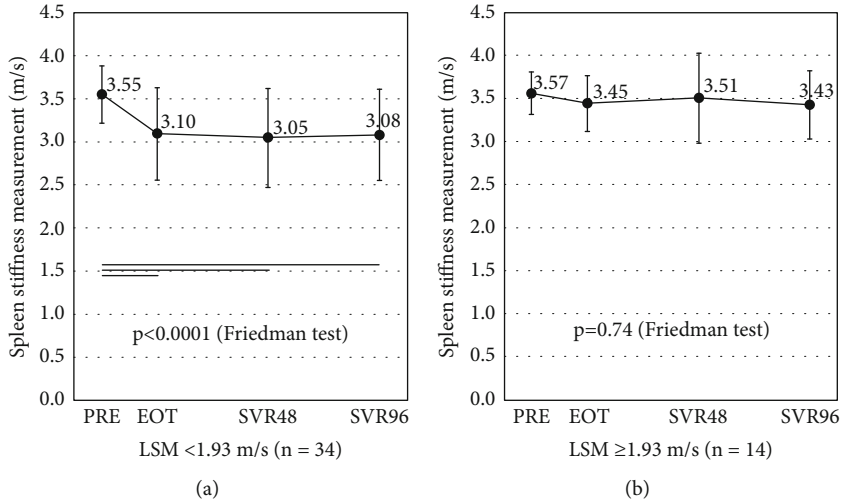


Figure 5: Changes in spleen stiffness measurements (SSM) in the high SSM group stratified by a liver stiffness measurement (LSM) value of 1.93 m/s in patients with chronic hepatitis C treated with direct acting antivirals. (a) LSM <1.93 m/s (n =34). (b) LSM ≥1.93 m/s (n =14). Bars indicate Bonferroni-corrected p-values <0.05. Abbreviations: LSM, liver stiffness measurement; SSM, spleen stiffness measurement; PRE, pre-treatment; EOT, end of treatment; SVR48, 48 weeks after EOT; SVR96, 96 weeks after EOT.

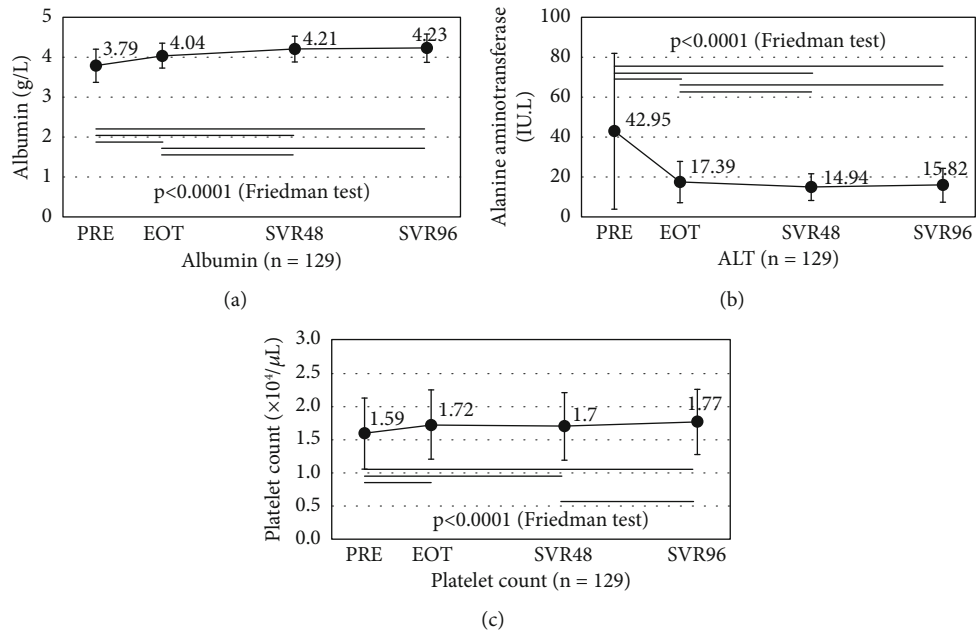


Figure 6: Changes in albumin, ALT, and platelet count in patients with chronic hepatitis C treated with direct acting antivirals. (a) Albumin. (b) ALT. (c) Platelet counts. Bars indicate Bonferroni-corrected p-values <0.05. Abbreviations: ALT, alanine aminotransferase; PRE, pre-treatment; EOT, end of treatment; SVR48, 48 weeks after EOT; SVR96, 96 weeks after EOT.

and 66% when measuring liver stiffness and spleen stiffness by RT-SWE, respectively, in 88 patients with clinically significant portal hypertension [27]. Lucchina et al. reported success rates of 90.7% and 77.8% when measuring liver stiffness and spleen stiffness by pSWE, respectively, in 54 patients with portal hypertension [28]. Cho et al. reported success in measuring spleen stiffness by two-dimensional SWE in 52.9% of 313 patients [29]. They reported that the success rate of SSM was lower than that of LSM and that SSM was sensitive to the abdominal wall thickness and spleen size. Accordingly, measurements of liver and spleen stiffness in our study were accurate and comparable with those of previous reports.

Limitations of this study included its single-centre design and the small number of patients. In addition, we were unable to perform prospective studies with other modalities for portal hypertension such as upper gastrointestinal endoscopy and contrast-enhanced computed tomography scanning. Guidelines recommend 10 measurements when measuring liver stiffness and spleen stiffness, but we performed measurements 8 times. However, there are reports that if the IQR/M ≤30% criteria are met, even five

measurements are sufficient for reliability [30–32]; therefore, we think eight measurements did not affect the reliability of our study.

In conclusion, DAA treatment showed a long-term improvement in liver stiffness, suggesting an improvement in liver fibrosis, whereas spleen stiffness decreased from pre-treatment to EOT in the high SSM group, suggesting an early effect of DAA on portal hypertension. However, portal hypertension persisted in many cases, and thus, the follow-up of portal hypertension is necessary even after successful DAA treatment, and special attention should be paid to cases of advanced hepatic fibrosis.

## Data Availability

The data presented in this study are available on request from the corresponding author.

## Conflicts of Interest

The author(s) declare(s) that they have no conflicts of interest.

## Authors' Contributions

Ryo Sugio: Conceptualization (Equal); Data curation (Lead); Formal analysis (Lead); Investigation (Equal); Methodology (Equal); Project administration (Equal); Resources (Equal); Visualization (Lead); Writing – original draft (Lead); Writing – review & editing (Equal). Yoshiyuki Sawai: Conceptualization (Equal); Data curation (Supporting); Formal analysis (Supporting); Investigation (Equal); Methodology (Equal); Project administration (Equal); Resources (Equal); Supervision (Equal); Visualization (Supporting); Writing – original draft (Supporting); Writing – review & editing (Equal). Kazuto Fukuda: Resources (Equal); Supervision (Equal). Takumi Igura: Resources (Equal). Sachiyo Kogita: Resources (Equal). Masahiro Ichihi: Investigation (Equal); Resources (Equal). Yasushi Seki: Investigation (Equal); Resources (Equal). Norihiro Fujita: Investigation (Equal); Resources (Equal). Masahide Oshita: Supervision (Equal); Yasuharu Imai: Conceptualization (Equal); Methodology (Equal); Project administration (Equal); Resources (Equal); Supervision (Equal); Writing – original draft (Supporting); Writing – review & editing (Equal). All authors were involved in the data acquisition as well as the review and approval of the manuscript, and all contributed to and agreed on the content of the manuscript.

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