

# Liver stiffness improvement in hepatitis C patients after successful treatment

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## ABSTRACT

**Background:** Successful treatment of chronic hepatitis C with direct-acting antiviral agents (DAAs) is expected to lead to improvement in liver fibrosis in most of the patients. However, limited data are available on the improvement of advanced liver fibrosis and cirrhosis, measured by transient elastography after treatment. This study assessed the change in liver stiffness measurements after successful treatment with DAAs in patients with pre-treatment advanced fibrosis or cirrhosis.

**Methods:** This observational retrospective cohort study included 514 mono-infected chronic hepatitis C patients, treated with all possible DAA-regimes in the Amsterdam region, the Netherlands. Liver stiffness was measured using FibroScan® at baseline and during follow-up. Cut-off values for staging liver fibrosis were  $\geq 9.5$  kPa for advanced fibrosis (F3) and  $\geq 14.6$  kPa for cirrhosis (F4).

**Results:** Liver stiffness decreased significantly from a median of 15.6 kPa (IQR 11.4-25.4) to 9.4 kPa (IQR 6.2-17.0) in 197 patients with pre-treated advanced fibrosis or cirrhosis. In 50.3% of these patients, liver stiffness improved to a value fitting with mild to moderate fibrosis ( $< 9.5$  kPa, F0-F2) after successful treatment. Multivariate analysis demonstrated that a pre-treatment FibroScan® value of  $\geq 20.0$  kPa was associated with persisting advanced fibrosis or cirrhosis after treatment (OR 29.07,  $p < 0.001$ ).

**Conclusion:** Liver stiffness improves significantly after successful direct-acting antiviral agent treatment in chronic hepatitis C patients with advanced fibrosis or cirrhosis prior to DAA treatment. Long-term outcomes regarding occurrence of hepatocellular carcinoma (HCC)

in these patients are required to determine whether they can be safely discharged from HCC surveillance.

## KEYWORDS

Chronic hepatitis C, direct-acting antiviral agents, improvement of liver stiffness, liver stiffness measurement, transient elastography.

## INTRODUCTION

An acute infection with the hepatitis C virus (HCV) results in a chronic infection in 70-85% of all cases. Worldwide, approximately 71 million individuals are chronically infected.<sup>1</sup> Chronic inflammation can cause liver fibrosis and may ultimately progress into liver cirrhosis with significant morbidity and mortality, which may lead to complications such as hepatic decompensation, liver failure, and hepatocellular carcinoma (HCC).<sup>1,3</sup> The rate of fibrosis progression is associated with various co-factors such as increasing age, high body mass index (BMI), elevated serum alanine aminotransferase (ALT) levels, HCV genotype, concomitant alcohol abuse, and co-infection with hepatitis B virus (HBV), or human immunodeficiency virus (HIV).<sup>4-6</sup>

Transient elastography (FibroScan®) provides a non-invasive measure for liver stiffness which is used to quantitatively assess liver fibrosis. Although FibroScan® is not very accurate for the differentiation between moderate

(F2) and advanced liver fibrosis (F3),<sup>7</sup> it is well-validated to establish patients with no signs of liver fibrosis (F0-F1) and those with cirrhosis (F4).<sup>3,8,9</sup>

To prevent further progression of liver fibrosis in chronic hepatitis C (CHC) patients, eradication of the virus is important. Direct-acting antiviral agents (DAAs) have become widely available with little side effects, a relatively short treatment duration and cure rates above 95%.<sup>10,11</sup> Achieving a sustained virological response (SVR) with DAAs is associated with a significant decrease in liver stiffness as measured by FibroScan®.<sup>12,13</sup> This absolute decrease seemed to be greater in patients with higher pre-treatment liver stiffness values.<sup>12</sup> However, most results are based on liver stiffness measurements (LSM) shortly after end of treatment. Limited data are available about the long-term effect of successful treatment with DAAs on LSM in patients with pre-treatment advanced liver fibrosis or cirrhosis.

The goal of our study was to assess the change in liver stiffness using FibroScan® after successful DAA treatment in patients with CHC mono-infection and pre-treatment signs of advanced liver fibrosis or cirrhosis (FibroScan®  $\geq 9.5$  kPa).

## MATERIALS AND METHODS

### Study design and population

In this observational retrospective cohort study, we included mono-infected CHC patients who were successfully treated with DAAs from January 2014 to August 2018 at the Amsterdam University Medical Center (UMC), location Academic Medical Centre (AMC), and Onze Lieve Vrouwe Gasthuis (OLVG), location Oost, both in Amsterdam, the Netherlands. All adult patients who were successfully treated (i.e., achieved SVR) with DAAs for their chronic Hepatitis C Virus (HCV) infection with an available FibroScan® result prior to treatment and during follow-up were included. Exclusion criteria were co-infection with human immunodeficiency virus (HIV) or hepatitis B virus (positive Hepatitis B surface Antigen), concomitant liver diseases (such as primary sclerosing cholangitis, haemochromatosis, or auto-immune hepatitis), and a medical history of hepatocellular carcinoma (HCC).

### Data collection

Medical record data were retrospectively collected. The following baseline characteristics were collected: age at onset of DAA treatment, gender, ethnicity, HCV genotype, body mass index (BMI), excessive alcohol use (defined as  $\geq 4$  alcohol units (50 gram) per day), and comorbidities such as diabetes mellitus. Laboratory values at baseline and 12 to 24 weeks after end of treatment (EOT) were collected, including HCV-RNA, liver enzymes, and platelet count.

Alanine aminotransferase test (ALT) levels were quantified by automated techniques at each participating centre. The upper limit of normal (ULN) for ALT were  $\geq 34$  U/ml for female and  $\geq 45$  U/ml for male. SVR was defined as an undetectable HCV-RNA 12 to 24 weeks after EOT.

### Assessment of liver stiffness

Liver stiffness was evaluated using transient elastography, FibroScan® (Echosens, France). Liver stiffness measurements at baseline and at one or more time points during follow-up were collected. Staging of liver fibrosis was based on the following cut-off values:  $\leq 7.0$  kPa for F0-F1 (no or mild fibrosis), 7.1 to 9.4 kPa for F2 (moderate fibrosis), 9.5 to 14.5 kPa for F3 (advanced fibrosis), and  $\geq 14.6$  kPa for F4 (cirrhosis).<sup>9</sup> In clinical practice, FibroScan® was not repeated after successful treatment in patients with no signs of fibrosis using FibroScan® prior to treatment. Therefore, only patients with baseline FibroScan®  $\geq 9.5$  kPa were included and categorised according to the baseline value into three groups: FibroScan® 9.5-14.5 kPa; FibroScan® 14.6-19.9 kPa; and FibroScan®  $\geq 20.0$  kPa. Patients without available FibroScan® measurements during follow-up were excluded from the analysis. Follow-up measurements after SVR were categorised from 0 to 24 weeks (FS0-24) after EOT, 24 to 100 weeks (FS24-100) after EOT and  $> 100$  weeks after EOT (FS  $> 100$ ).

For quantification of hepatic steatosis, CAP (controlled attenuated parameter; dB/m) measurements were obtained at baseline and during follow-up.

### Primary outcome

Change in liver stiffness measure (LSM) using FibroScan®, expressed as value in kPa and its corresponding fibrosis grade (F0-F4), after achieving SVR in patients with baseline FibroScan® value  $\geq 9.5$  kPa (F3-F4).

### Secondary outcome

To define characteristics of patients with an improved LSM from  $\geq 9.5$  kPa pre-treatment to  $< 9.5$  kPa after successful DAA treatment.

### Statistical analysis

Graphic representation of the results was performed using Graph Pad Prism version 7 for Windows (GraphPad Software, San Diego, California, USA). Statistical analysis was performed using IBM SPSS for Windows version 24.0 (SPSS Inc., Chicago, Illinois, USA). Data was analysed using chi-squared test, Fisher's exact test, Mann-Whitney U test, Wilcoxon signed-rank test, and student's t-test where appropriate. Univariate and multivariate logistic regression was used to estimate odds ratios (ORs) for persisting advanced fibrosis, defined as a liver stiffness value  $\geq 9.5$  kPa at follow-up. The risk factors

included were thrombocytopenia at baseline, baseline LSM values, baseline LSM value  $\geq 20.0$  kPa, diabetes mellitus, ethnicity, and HCV genotype. Pearson's or Spearman's correlation were used to test the presence of correlation. Differences were considered statistically significant when  $p < 0.05$ .

## RESULTS

### Baseline characteristics

A total of 514 patients with CHC were treated with DAAs in our hospitals between January 2014 to August 2018, of whom 197 (38.3%) had an LSM value  $\geq 9.5$  kPa at baseline and at least one available LSM during follow-up. In these 197 patients, the median LSM value prior to treatment was 15.6 kPa (IQR 11.4-25.4). At baseline, 90 patients had a LSM of 9.5 to 14.5 kPa; 36 patients had a score of 14.6 to 19.9 kPa; and 71 patients had a LSM of  $\geq 20.0$  kPa. Median follow-up time after EOT was 36 months (IQR 29-42). The baseline characteristics are shown in table 1. Follow-up measurements were available in 96 patients at FS0-24, in 127 patients at FS25-100, and in 60 patients at FS > 100. In 42 patients, the value at FS > 100 was the second or third FibroScan® measurement during follow-up.

### Change in LSM

A statistically significant decrease in LSM was observed both in the whole group as well as in different subgroups (figure 1 and table 2) after successful treatment. Compared with baseline LSM, a median decrease of 5.7 kPa was observed at FS0-24, of 5.9 kPa at FS 25-100, and a decrease of 6.3 kPa at FS > 100. The median difference in all

**Table 1.** Baseline characteristics of all patients with pre-treatment LSM  $\geq 9.5$  kPa (advanced liver fibrosis or cirrhosis, F3 or F4)

Baseline characteristics (n = 197)		
Gender (male)	n (%)	148 (75.1%)
Age at start treatment (years)	mean $\pm$ SD	56 $\pm$ 9
BMI (kg/m <sup>2</sup> )	mean $\pm$ SD	26.1 $\pm$ 4.2
Diabetes mellitus	n (%)	37 (18.8%)
Ethnicity	n (%)	
Caucasian		107 (54.3%)
Middle Eastern/Northern African		38 (19.3%)
Other/unknown		52 (26.4%)
HCV genotype	n (%)	
Genotype 1		101 (51.3%)
Genotype 2		17 (8.6%)
Genotype 3		47 (23.9%)
Genotype 4		32 (16.2%)
LSM by FibroScan® (kPa)	median (IQR) n (%)	15.6 (11.4-25.4)
F3		90 (45.7%)
F4		107 (54.3%)
Excessive alcohol use†	n (%)	
Current		16 (8.1%)
Former		38 (19.3%)

BMI = body mass index; HCV = hepatitis C virus; IQR = interquartile range; LSM = liver stiffness measurements; n = number; SD = standard deviation.

† Excessive alcohol use is defined as  $\geq 4$  alcohol units (50 gram) per day. Former use is defined as a known history of excessive alcohol use but current use < 4 units per day.

**Table 2.** Change in LSM during follow-up

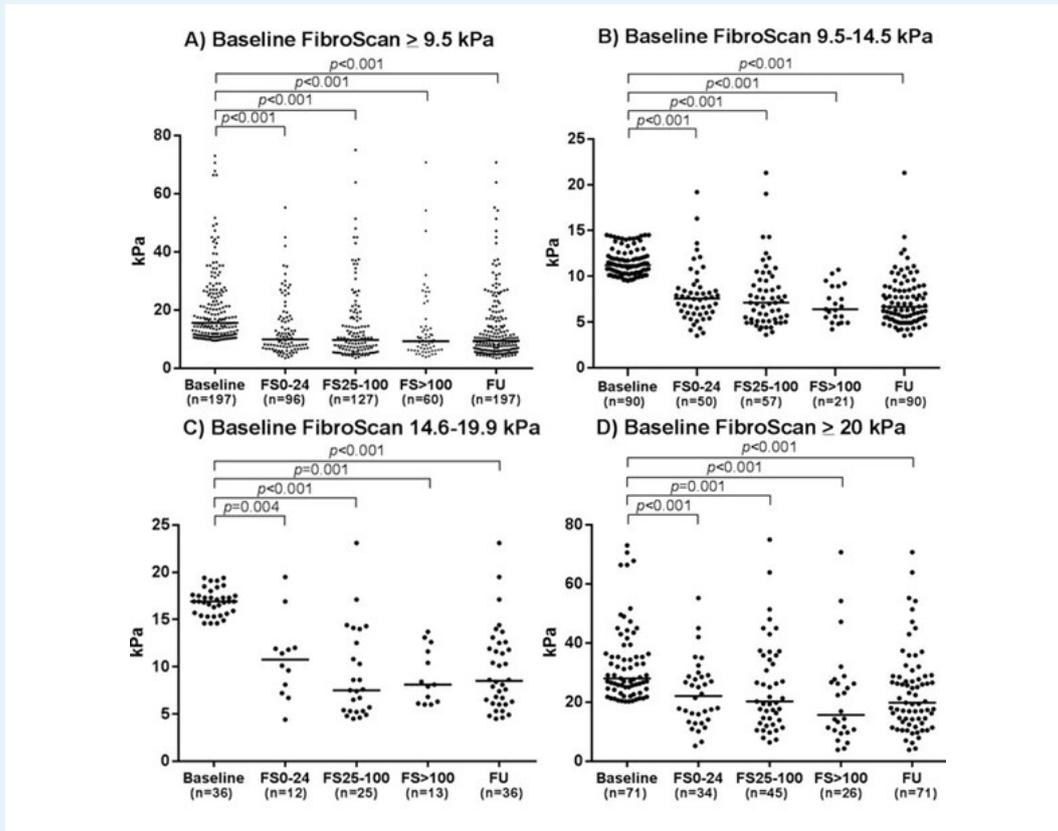
	N	Baseline	FS0-24	FS25-100	FS > 100	Last available†
FibroScan® baseline $\geq 9.5$ kPa (kPa) (median, IQR)	197	15.6 (11.4-25.4)	9.9 (6.7-17.1)* (n = 96/197)	9.7 (6.2-17.3)* (n = 127/197)	9.3 (6.2-14.1)* (n = 60/197)	9.4 (6.2-17.0)*
FibroScan® baseline 9.5-14.5 kPa (kPa) (median, IQR)	90	11.2 (10.3-12.5)	7.6 (6.0-8.7)* (n = 50/90)	7.1 (5.1-9.6)* (n = 57/90)	6.4 (5.2-8.9)* (n = 21/90)	6.6 (5.3-8.7)*
FibroScan® baseline 14.6-19.9 kPa (kPa) (median, IQR)	36	16.9 (15.6-17.6)	10.8 (7.4-12.0)* (n = 12/36)	7.5 (5.3-13.3)* (n = 25/36)	8.1 (6.2-12.1)* (n = 13/36)	8.5 (6.2-12.4)*
FibroScan® baseline $\geq 20.0$ kPa (kPa) (median, IQR)	71	28.0 (24.2-36.4)	22.1 (13.9-28.8)* (n = 34/71)	20.2 (13.4-35.8)* (n = 45/71)	15.7 (10.3-27.0)* (n = 26/71)	20.2 (13.3-29.1)*

FS0-24 = FibroScan® measurement between 0 and 24 weeks after end of treatment; FS25-100 = FibroScan® measurement between 25 and 100 weeks after end of treatment; FS > 100 = FibroScan® measurement more than 100 weeks after end of treatment; IQR = interquartile range; LSM = liver stiffness measurements; n = number.

† Last available FibroScan® value during follow-up per patient.

\* Significant decline ( $p < 0.05$ ) compared to baseline FibroScan® using Wilcoxon Signed Rank test.

**Figure 1.** Change in liver stiffness measurements (kPa) according to baseline LSM measurements during follow-up at different time points



LSM measurements at baseline and at one or more time points during follow-up. The dots represent the LSM of individual patients at each time point. The line represents the median value. Corresponding p-value (Wilcoxon Signed Rank test) represents change in LSM per time point compared to baseline.

A) Change in LSM in all patients with baseline LSM  $\geq 9.5$  kPa (n = 197).

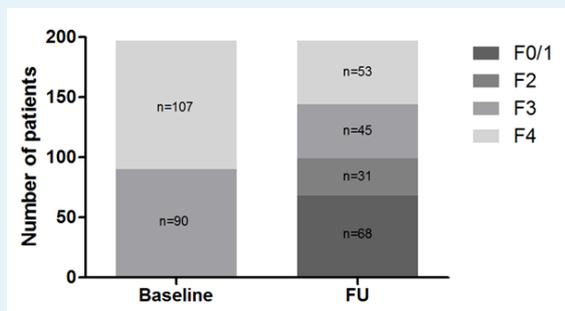
B) Change in LSM in patients with baseline LSM 9.5-14.5 kPa (n = 90).

C) Change in LSM in patients with baseline LSM 14.6-19.9 kPa (n = 36).

D) Change in LSM in patients with baseline LSM  $\geq 20.0$  kPa (n = 71).

FS0-24 = FibroScan® measurement between 0 and 24 weeks after end of treatment; FS25-100 = FibroScan® measurement between 25 and 100 weeks after end of treatment; FS > 100 = FibroScan® measurement more than 100 weeks after end of treatment; FU = Last available FibroScan® measurement during follow-up; n = number.

**Figure 2.** Change in fibrosis score according to baseline LSM values during follow-up



LSM, expressed as fibrosis score F0-F4, at baseline and at the last available FibroScan® value per patient during follow-up in patients with baseline LSM  $\geq 9.5$  kPa.

FU = Last available FibroScan® measurement during follow-up; n = number.

patients between baseline LSM and last available LSM during follow-up was 5.7 kPa (IQR 3.0-9.3). This led to an improvement to mild to moderate fibrosis (LSM < 9.5 kPa) in 50.3% (n = 99) of the 197 included patients (figure 2). Moreover, in 24.3% (n = 26) of the patients with LSM compatible with probable cirrhosis at baseline ( $\geq 14.6$  kPa, F4), LSM improved to values compatible with F0-F2 (< 9.5 kPa). In 15.9% (n = 17) of these patients, LSM even normalised ( $\leq 7.0$  kPa, F0-1). In patients with a pre-treatment LSM  $\geq 20.0$  kPa (n = 71), only 8.5% (n = 6) improved to LSM values compatible with mild to moderate fibrosis (F0-F2). Progression of LSM was observed in only 21 of the 197 patients (10.7%), with a median progression from 26.3 kPa (IQR 17.6-35.8) at baseline to 32.9 kPa (IQR 22.2-49.3) at the last available LSM during follow-up.

**Table 3.** Characteristics of patients (n = 197) with FibroScan® value compatible with advanced fibrosis or cirrhosis at baseline during follow-up: improvement versus no improvement

		F0-F2 after treatment (n = 99)	F3-F4 after treatment (n = 98)	p-value†
<b>Gender (male)</b>	n (%)	67 (67.7%)	81 (82.7%)	0.015
<b>Age at start treatment (years)</b>	mean ± SD	54 ± 9	57 ± 8	NS
<b>BMI (kg/m<sup>2</sup>)</b>	mean ± SD	25.5 ± 4.0	26.6 ± 4.3	NS
<b>Diabetes mellitus</b>	n (%)	12 (12.1%)	25 (25.5%)	0.016
<b>Ethnicity</b>	n (%)			
Caucasian		63 (63.6%)	44 (44.9%)	0.006
Middle Eastern/ Northern African		11 (11.1%)	27 (27.6%)	0.008
Other/unknown		25 (25.3%)	27 (27.6%)	NS
<b>HCV genotype</b>	n (%)			
Genotype 1		58 (58.6%)	43 (43.8%)	0.039
Genotype 2		11 (11.1%)	6 (6.1%)	NS
Genotype 3		21 (21.2%)	26 (26.5%)	NS
Genotype 4		9 (9.1%)	23 (23.5%)	0.006
<b>Baseline LSM (kPa)</b>	median (IQR)	11.9 (10.4-14.6)	24.4 (17.2-33.3)	< 0.001
9.5-14.5 kPa	n (%)	73 (73.7%)	17 (17.3%)	< 0.001
> 14.6 kPa	n (%)	26 (26.3%)	81 (82.7%)	< 0.001
> 20.0 kPa	n (%)	6 (6.1%)	65 (66.3%)	< 0.001
<b>Excessive alcohol use ‡</b>	n (%)			
Current		6 (6.1%)	10 (10.2%)	NS
Former		15 (15.2%)	23 (23.5%)	NS
<b>Laboratory values at baseline</b>				
ALT (U/l)	median (IQR)	81 (51-132)	82 (49-126)	NS
Bilirubin (µmol/l)	median (IQR)	8 (6-11)	10 (8-14)	0.002
Platelet count (x10 <sup>9</sup> /l)	median (IQR)	209 (157-250)	137 (95-205)	< 0.001
Thrombocytopenia§	n (%)	19 (19.2%)	55 (56.1%)	< 0.001
<b>Laboratory values 12-24 weeks after EOT</b>				
ALT (U/l)	median (IQR)	22 (17-31)	27 (21-37)	0.002
Bilirubin (µmol/l)	median (IQR)	7 (6-10)	9 (6-13)	0.008
Platelet count (x10 <sup>9</sup> /l)	median (IQR)	201 (164-245)	145 (95-204)	< 0.001
Thrombocytopenia§	n (%)	12/89 (13.5%)	45/84 (53.6%)	< 0.001

ALT = alanine aminotransferase; EOT = end of treatment; HCV = hepatitis C virus; IQR = interquartile range; n = number; NS = not significant; SD = standard deviation  
 † Chi square, Fisher's exact or Mann Whitney U test.  
 ‡ Excessive alcohol use was defined as ≥ 4 alcohol units (50 gram) per day. Former use was defined as a known history of excessive alcohol use but current use < 4 units per day.  
 § Thrombocytopenia was defined as platelet count < 150x10<sup>9</sup>/l.

Table 3 shows the characteristics of patients whose advanced fibrosis or cirrhosis persisted during follow-up (n = 98), compared to the patients who showed an improvement to fibrosis score F0-F2 (n = 99) after successful treatment. Patients whose LSM values remained in a range fitting with fibrosis scores F3 or F4 were more often male, HCV genotype 4, and from Middle Eastern or Northern African descent.

Baseline CAP measurements were available in 121 individuals with a mean CAP of 249.0 dB/m (SD ± 54.5).

No significant change was observed during follow-up after treatment. Compared with baseline values, a mean difference of -14.5 dB/m was observed at FS0-24 (SD ± 66.5; n = 49; p = 0.135), of +4.8 dB/m at FS25-100 (SD ± 58.5; n = 81; p = 0.465), and +7.2 dB/m at FS > 100 (SD ± 57.9; n = 35; p = 0.469).

**Correlation in LSM and ALT**

The median baseline ALT level in all patients was 81 U/ml (IQR 51-126). ALT at 12-24 weeks after EOT was measured in 193 patients and decreased to a median of 24 U/ml (IQR

18-35). When using Spearman's correlation coefficient, there was a significant correlation between change in LSM (between baseline and last available LSM) and change in ALT (between ALT at baseline and 12-24 weeks after EOT) ( $p = 0.000$ ).

**Univariate and multivariate analysis**

Univariate analysis (table 4) showed a statistically significant association between persistent LSM values fitting with F3 and F4 fibrosis scores after successful treatment and: male gender, thrombocytopenia at baseline, baseline LSM value (especially  $\geq 20$  kPa), diabetes mellitus, HCV genotype 1 and 4, and Middle Eastern or Northern African ethnicity. Thrombocytopenia (at baseline and at 12-24 weeks after end of treatment), LSM value at baseline, and baseline LSM  $\geq 20$  kPa were inter-related. In multivariate analysis, we tested for association between persistent LSM values fitting with advanced liver fibrosis or cirrhosis and: gender, diabetes mellitus, HCV genotype 1 and 4, ethnicity, and baseline LSM  $\geq 20.0$  kPa. Only baseline LSM value  $\geq 20.0$  kPa was significantly associated with persisting LSM values fitting with advanced liver fibrosis or cirrhosis (OR 29.07, 95% CI 11.02-76.67,  $p < 0.001$ ).

**Occurrence of HCC**

Two patients developed an HCC during follow up (112 and 85 weeks after EOT, respectively). Both patients had pre- and post-treatment LSM values of  $\geq 20$  kPa.

**DISCUSSION**

A significant change in LSM from a median of 15.6 to 9.4 kPa was observed in our cohort of 197 patients with

pre-treatment signs of advanced liver fibrosis or cirrhosis during a median follow-up of 36 months. In half of these patients, LSM improved to values compatible with mild to moderate fibrosis ( $< 9.5$  kPa). Moreover, in 24.3% of the patients with signs of cirrhosis ( $\geq 14.6$  kPa, F4) at baseline, LSM values improved to values fitting with F0-F2 ( $< 9.5$  kPa). There was no significant change in hepatic steatosis as measured by CAP in our cohort. With a median follow-up of 36 months, our study also shows the long-term effect of successful treatment with DAAs on LSM.

The observed decrease in LSM after successful treatment is in line with previous studies, showing that the largest improvement in LSM is to be expected within the first year of follow-up.<sup>12,14</sup> Rapid decline in LSM possibly correlates with resolution of hepatic inflammation.<sup>15,16</sup> In our cohort, we did find a significant correlation between decline in LSM during follow-up and decline in ALT 12-24 weeks after EOT. Improvement in LSM may also be explained by liver regeneration after viral eradication.<sup>12,17</sup> In our study, we did not have post-treatment histology results to investigate this assumption. Recently, two small retrospective studies compared the results of LSM as measured by FibroScan® with liver biopsy results after SVR in DAA-treated patients.<sup>18,19</sup> One study concluded improvement in LSM is overstated when compared to histologic staging but is confirmed with morphometric analysis (i.e., 46% reduction in fibrosis after SVR),<sup>18</sup> whereas in the other study LSM did not correlate with post-SVR liver biopsy results-although no morphometry was performed.<sup>19</sup> Hence, the presumed beneficial effect of DAA-treatment is mostly based on FibroScan® measurements and not histology-based.<sup>12,13,20,21</sup>

**Table 4.** Univariate analysis factors associated with persistent advanced fibrosis or cirrhosis after treatment ( $\geq 9.5$  kPa)

	P-value†	OR‡	95% CI
Gender (male)	0.016	2.28	1.16-4.45
Thrombocytopenia at baseline§	< 0.001	5.32	2.80-10.09
Baseline LSM (kPa)	< 0.001	1.26	1.18-1.36
LSM baseline $\geq 20$ kPa	< 0.001	30.53	12.10-77.05
Diabetes mellitus	0.018	2.48	1.17-5.28
Ethnicity (Middle Eastern/ Northern African)	0.005	3.04	1.41-6.56
HCV genotype 1	0.040	0.55	0.31-0.97
HCV genotype 4	0.008	3.07	1.34-7.03

EOT = end of treatment; HCV = hepatitis C virus; LSM = liver stiffness measurements; OR = Odds Ratio; 95% CI = 95% Confidence interval.  
 † Logistic regression.  
 ‡ Odds Ratio. Represents the change remaining FibroScan® value of  $\geq 9.5$  kPa.  
 § Thrombocytopenia was defined as platelet count  $< 150 \times 10^9/l$ .

Achieving SVR with DAAs is associated with a decrease in all-cause mortality and hepatocellular carcinoma.<sup>22</sup> In our cohort of 197 patients, only two patients developed an HCC during follow-up. Both patients had a post-treatment LSM > 20.0 kPa. Despite these positive outcomes after successful treatment of CHC, an important unanswered question is whether patients with a baseline LSM of  $\geq 9.5$  kPa can be safely discharged if their LSM improves to < 9.5 kPa after successful treatment. The current European guideline (2018) for management of CHC states that patients with LSM < 9.5 kPa prior to treatment initiation can be discharged after viral eradication. HCC surveillance should be continued in all patients with a baseline LSM of  $\geq 9.5$  kPa, despite successful treatment, although no consensus has been reached on the duration of follow-up.<sup>23</sup> In our study, with a median follow-up duration of 36 months, multivariate analysis indicated that an LSM value  $\geq 20$  kPa at baseline (OR 29.07,  $p < 0.001$ ) is associated with persisting high LSM values, and that patients with a baseline LSM < 20 kPa are more likely to improve in LSM to values < 9.5 kPa after successful treatment. However, studies investigating the long-term outcomes regarding occurrence of HCC in these patients are needed to assess whether they can be safely discharged from surveillance.

One of the strengths of our study is the large sample size of CHC patients with signs of advanced liver fibrosis or cirrhosis who underwent follow-up FibroScan® measurements after successful treatment of their CHC. However, this study also has its limitations. A limitation is the retrospective design, resulting in a heterogeneous group regarding follow-up time and the fact that we used FibroScan® and did not have histology from patients. As the influence of fasting on FibroScan® outcome is only recently recognised,<sup>24</sup> it is possible that some baseline FibroScan® values were non-fasting values. This could have caused an overestimation of the decline in LSM during follow-up.

## CONCLUSION

We show that LSM decreases in CHC patients successfully treated with DAAs with pre-treatment signs of advanced liver fibrosis or cirrhosis ( $\geq 9.5$  kPa). Moreover, in 50.3% of the patients with a baseline LSM value  $\geq 9.5$  kPa

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(F3-F4), liver stiffness improved to < 9.5 kPa (Fo-F2), and in 15.9% of patients with pre-treatment signs of cirrhosis (F4), LSM normalised ( $\leq 7.0$  kPa, Fo-F1). A baseline LSM value  $\geq 20.0$  kPa was associated with persisting signs of cirrhosis or advanced liver fibrosis. Furthermore, the consequences of the observed change in LSM regarding occurrence of HCC and liver-related death needs to be further investigated in long-term follow-up studies. Only with such data a reliable advice can be given upon the indication and duration of follow-up and surveillance after successful treatment of CHC with DAAs.

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## CONFLICT OF INTEREST STATEMENT

SW has served as a speaker, a consultant, or an advisory board member for AbbVie, Bristol-Myers-Squibb, and Gilead Sciences, and received unrestricted research support from AbbVie, Gilead, ENYO Pharma, and Roche, all outside of the submitted work. LB has served as a speaker, a consultant, and an advisory board member for AbbVie, Bristol-Myers-Squibb, Gilead Sciences, Janssen Therapeutics, Merck/MSD, and Roche. MvdV received consultancy fees paid to his institution from Abbvie, Gilead Sciences, ViiV Healthcare, MSD, and Janssen and received unrestricted research support from Abbvie, Gilead, MSD, and ViiV all outside the submitted work. All other authors: no conflicts declared.

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