

# Hepatic fibrosis changes in patients with chronic hepatitis C infection who respond to direct-acting antivirals

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**BACKGROUND:** Clearance of hepatitis C virus (HCV) can potentially slow or reverse liver fibrosis and cirrhosis. Studies of fibrosis changes after treatment with direct-acting antivirals (DAAs) are limited.

**OBJECTIVES:** We aimed to assess the impact of DAAs on fibrosis in HCV treatment responders.

**DESIGN:** Retrospective cohort study.

**SETTING:** Tertiary care centers.

**PATIENTS AND METHODS:** This study included adult patients who received DAA treatment for HCV (naïve and experienced) from June 2015 to January 2019 who were treatment responders. Biochemical and hematological data and noninvasive fibrosis markers were recorded at baseline and follow-up.

**MAIN OUTCOME MEASURES:** Aspartate aminotransferase/platelet ratio index (APRI), fibrosis-4 score (FIB-4) and liver stiffness measurements (LSM) at baseline and follow-up.

**SAMPLE SIZE AND CHARACTERISTICS:** 172 HCV treatment responders, mean (SD) age 54.1 (14.1) and body mass index 28.8 (6.5) kg/m<sup>2</sup> at baseline; 96 (55.8%) were females.

**RESULTS:** Fifty-eight (33.7%) patients were HCV treatment-experienced. Most patients were genotype 4 (n=125, 73%) and the mean follow-up was 141 (57.9) weeks. Compared with baseline, changes in alanine aminotransferase ( $P<.001$ ), aspartate aminotransferase ( $P<.001$ ), and albumin ( $P=.01$ ) were statistically significant. Changes in LSM (15.09 kPa [11.4] vs. 10.19 kPa [7.4],  $P<.001$ ), APRI (0.81 [0.7] vs. 0.34 [0.2],  $P<.001$ ), and FIB-4 (1.99 [1.4] vs. 1.35 [0.9],  $P<.001$ ), and AST/ALT ratio (0.86 [0.32] vs. 0.95 [0.41],  $P=.015$ ) were statistically significant. Differences in many of the same parameters were statistically significant between patients with low fibrosis (F0-F1) (n=59, 34.3%) and significant fibrosis ( $\geq$ F2) (n=113, 65.7%).

**CONCLUSIONS:** Our findings confirm that clearance of HCV with DAAs is associated with significant improvement in fibrosis as assessed by noninvasive liver fibrosis measures, which supports the concept of post-treatment fibrosis regression. Long follow-up studies are needed to assess the impact on morbidity and mortality.

**LIMITATIONS:** Absence of histological correlation with these noninvasive scores. No assessment of fibrosis changes based on HCV genotype or treatment regimen.

**CONFLICT OF INTEREST:** None.

Chronic hepatitis C virus (HCV) infection is a global health burden and a challenge for practitioners. HCV infection is the leading cause of liver cirrhosis and its consequences, such as liver decompensation and hepatocellular carcinoma.<sup>1</sup> The HCV treatment goal is to eradicate the virus and ultimately slow fibrosis progression and cirrhosis complications. Growing evidence has shown that viral eradication can improve clinical, histologic, and biochemical outcomes and ultimately reduce mortality.<sup>1-3</sup> Sustained virologic response (SVR) is defined as undetectable HCV RNA at 12–24 weeks after cessation of HCV therapy. It is considered the best available indicator of viral eradication and cure from this infection.<sup>4</sup>

Patients who achieve SVR with interferon-based therapy have demonstrated histologic improvements in follow-up biopsies compared to baseline biopsies.<sup>5-8</sup> In a study using transient elastography and the FibroTest to assess changes in fibrosis after a mean follow-up of 10 years of interferon-based therapy, regression of fibrosis was seen in 56% of patients with cirrhosis.<sup>9</sup> However, new cirrhosis was observed in 11% of cases without cirrhosis at baseline, yielding a net reduction in cirrhosis of only 5.3%. In recent years, treatment with new direct-acting antivirals (DAAs) has been associated with very high cure rates and excellent overall safety and tolerability. This success has led to the global ambition to eradicate HCV infection by 2030.<sup>10</sup> Furthermore, the impact of DAA on patient outcomes still needs to be assessed in the long term.<sup>11</sup> A study of several noninvasive indices in patients who achieved SVR after DAAs demonstrated a rapid decline in liver enzymes, aspartate aminotransferase/platelet ratio index (APRI), and fibrosis-4 score (FIB-4); however, the authors found a slower improvement in the platelet count, and a rapid decline in the former was attributed to the possibility of a reduction in necroinflammation.<sup>12</sup> Overall, the clearance of HCV can slow or reverse liver fibrosis and cirrhosis. However, limited studies exist assessing fibrosis changes post-treatment with DAAs with long-term follow-up. Therefore, this study aimed to assess the long-term effect of virus clearance on the liver fibrosis stage in chronic hepatitis C responders to DAAs using multiple noninvasive methods.

## PATIENTS AND METHODS

This retrospective cohort study used prospectively collected data in the Systematic Observatory Liver Disease registry (SOLID).<sup>13</sup> This study included adult patients at King Saud University Medical City and King Faisal Specialist Hospital in Riyadh who received DAA treatment for HCV (naïve and experienced) from June 2015

to January 2019 and achieved SVR. Inclusion criteria were age between 18 and 80 years, SVR (negative HCV RNA 12 weeks after treatment) achieved after DAA, and adequate data before treatment and within 6 months of treatment, including liver stiffness measurement (LSM) by FibroScan. Patients provided consent to participate in the study. Exclusion criteria were baseline LSM more than 6 months before treatment initiation and the presence of other liver diseases, including HBV, metabolic disease, autoimmune disease, alcoholic liver disease, a diagnosis of hepatocellular carcinoma, the presence of portal vein thrombosis, and liver decompensation. Patients were followed every six months in the outpatient clinics. The study was conducted following the Declaration of Helsinki and was approved by the institutional review board of the two participating institutions, King Saud University Medical City (number: E-194159) and King Faisal Specialist Hospital (RAC number: 2161184).

### *Clinical and laboratory assessments*

Before treatment and at the follow-up visit, all patients had detailed clinical assessments (medical history and physical examination) and anthropometric measurements, including height, weight, and body mass index (BMI). Laboratory evaluations included complete blood count, liver function tests, international normalized ratio, and HCV PCR (Cobas Amplicor, HCV Roche, Branchburg, NJ, USA, v 2.0, detection limit  $\leq 15$  IU/mL) baseline and follow-up.

### *Noninvasive fibrosis assessment*

For all patients, the noninvasive scores for the APRI were calculated as  $\text{AST}/\text{upper limit of the normal AST range} \times 100/\text{platelet count}$ . FIB-4 was  $\text{age (years)} \times \text{AST (U/L)}/\text{platelet count (10}^9/\text{L)} \times \text{ALT}/2$  (U/L), and the alanine aminotransferase/aspartate aminotransferase (AST/ALT) ratio was calculated at baseline and at follow-up based on the previously published methodology.<sup>14,15</sup>

The LSM was performed for all patients at baseline and compared with post-treatment follow-up using the FibroScan device (ECHOSENS FibroScan 502 Touch) and a standard M probe or an XL probe (for obese patients with BMI  $>30$  kg/m<sup>2</sup>). As advised by the manufacturer, the FibroScan assessment was applied through the intercostal spaces on fasting patients lying in the dorsal decubitus position with the right arm maximally abducted. An exam was considered reliable with  $\geq 10$  compelling readings, a success rate  $>60\%$ , and the ratio of the interquartile range (IQR) to the median of 10 readings  $\leq 0.3$ . FibroScan was performed by experienced and certified operators in both centers. Patients

were classified based on LSM into low fibrosis (F0-F1), significant fibrosis ( $\geq$ F2), and advanced fibrosis ( $\geq$ F3) groups, and cirrhosis was F4 based on LSM.<sup>16,17</sup> In this analysis, we included only the latest laboratory tests and noninvasive measurements of liver fibrosis; hence, the duration of follow-up in this study was calculated as the time between baseline and the latest follow-up.

### Statistical analysis

We entered data into an excel spreadsheet, and used IBM SPSS package version 20 (Armonk, New York, United States: IBM Corp) to analyze the sociodemographic, biochemical, and noninvasive parameters. We present descriptive statistics using the number and percent for categorical variables, whereas the mean and standard deviation (or median and interquartile range) was calculated for continuous data. We used the paired t-test for the comparison between baseline and follow-up parameters. A multivariate logistic regression analysis was done to explore any relationships between fibrosis and demographic or clinical factors.

## RESULTS

We included 172 HCV responders to DAAs, including 96 (55.8%) females (**Table 1, Figure 1**). The mean baseline age was 54.1 (14.1) years, BMI was 28.8 (6.5) kg/m<sup>2</sup>, and 58 (33.7%) were HCV treatment-experienced. The mean follow-up of 141(57.9) weeks (median 138 weeks, IQR 96.4) with no losses to follow up. Sixty-two patients (36.2%) had baseline cirrhosis; the mean baseline LSM fibrosis score for the cohort was 15.09 (11.4) kPa, and 125 (73%) had HCV genotype 4. From baseline to follow-up, significant improvements were observed in the laboratory parameters ALT, AST, albumin, and platelets, as well in multiple noninvasive fibrosis measures (LSM, APRI, FIB-4, and the AST/ALT ratio (**Table 2**). At follow-up and among 62 patients with baseline cirrhosis, fibrosis improved by one stage in 24.6%, two stages in 23.1%, three stages in 4.6%, and four stages in 6.2% of cases. No change was observed in 38.4% of cases (baseline and follow-up fibrosis scores were the same), and fibrosis increased in only 3.1% of the 62 cases.

Fifty-nine patients (34.3%) had low fibrosis (F0-F1) and 113 (65.7%) had significant fibrosis ( $\geq$ F2). Our analysis showed consistent and significant improvements in ALT, AST, APRI, and FIB-4 in both groups; however, LSM levels decreased significantly after treatment only in patients with significant and advanced fibrosis (**Table 3**). The changes in FIB-4 were more substantial in patients with significant and advanced fibrosis, while the changes in APRI score levels were consistent irrespective of the degree of fibrosis. In the additional analysis to as-

sess changes in patients with advanced fibrosis stage (F3 and F4) (**Figure 2**), the results were similar to the changes in patients with significant fibrosis; however, albumin changes (improvement) showed slight but statistically significant improvement for changes albumin from baseline to follow up in low, significant and advanced fibrosis. Since greater fibrosis is associated with advanced age in many studies, our finding in the multivariate analysis of a borderline statistical significance with age but not other factors, was not unexpected.

## DISCUSSION

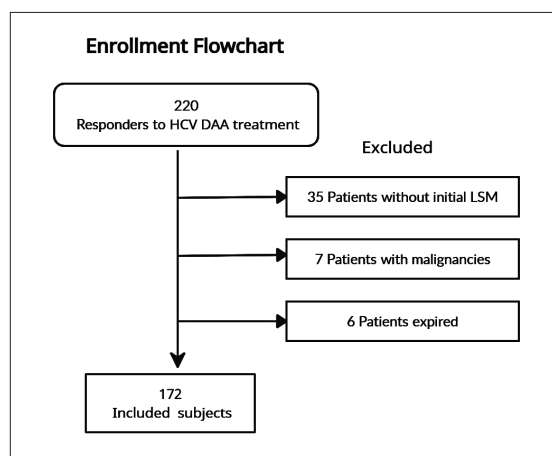
The key findings of our study include the significant improvement in vital hepatic biochemical and noninvasive fibrosis parameters in post-treatment follow-up

**Table 1.** Baseline characteristics of study patients (n=172).

Variable	Result
Male/Female	76 (44.2)/96 (55.8)
Age (years)	54.1 (14.1) <sup>a</sup>
Body mass index (kg/m <sup>2</sup> )	28.81 (6.5) <sup>a</sup>
Treatment-Naïve/Experienced	114 (66.3)/58 (33.7)
Hepatitis C virus genotype 4	125 (73.0)
Cirrhosis	62 (36.2)
Diabetes mellitus	47 (34.8)
Hypertension	56 (41.5)
Hyperlipidemia	16 (11.9)
Duration of follow-up (weeks)	138 (47.4-273) <sup>b</sup>

Values are <sup>a</sup>mean and standard deviation or number and percentage.

<sup>b</sup>Median (range).



**Figure 1.** Flow diagram of patient disposition.

**Table 2.** Changes from baseline to follow-up in laboratory parameters and noninvasive fibrosis markers (n=172).

Variable	Baseline	Follow-up	Change from baseline (%)	P value
Laboratory parameters				
Platelets ( $\times 10^9/L$ )	208.55 (76.9)	224.57 (82.4)	7.7	<b>.003</b>
Hemoglobin (g/L)	137.39 (20.3)	135.51 (22.0)	-1.4	.415
ALT (IU/L)	71.25 (60.6)	26.02 (14.5)	-63.5	<b>&lt;.001</b>
AST (IU/L)	55.77 (41.7)	22.43 (11.0)	-59.8	<b>&lt;.001</b>
ALP (IU/L)	109.73 (48.5)	92.39 (38.7)	-15.8	<b>&lt;.001</b>
Albumin (g/L)	37.05 (9.1)	38.88 (4.7)	4.9	<b>.010</b>
Bilirubin ( $\mu\text{mol/L}$ )	11.29 (5.6)	10.66 (7.6)	-5.6	.393
Noninvasive fibrosis markers				
LSM (kPa)	15.09 (11.4)	10.19 (7.4)	-32.5	<b>&lt;.001</b>
CAP (dB/m)	234.11 (59.6)	241.70 (64.7)	3.2	.274
AST/ALT	0.86 (0.32)	0.95 (0.41)	10.5	<b>.015</b>
FIB-4	1.99 (1.4)	1.35 (0.9)	-32.2	<b>&lt;.001</b>
APRI	0.81 (0.7)	0.34 (0.2)	-58.0	<b>&lt;.001</b>

Data are mean and standard deviation. ALT: alanine aminotransferase; AST: aspartate aminotransferase; ALP: alkaline phosphatase; LSM: liver stiffness measurement; CAP: controlled attenuation parameter; FIB-4: fibrosis-4; APRI: AST to platelet ratio index.

**Table 3.** Changes from baseline to follow up in laboratory and noninvasive fibrosis markers in patients with low fibrosis, significant fibrosis and advanced fibrosis (n=172).

	Low fibrosis (F0, F1) (n=59)			Significant fibrosis (F2, F3, F4) (n=113)			Advanced fibrosis (F3, F4) (n=102)		
	Baseline	Follow-up	P value	Baseline	Follow-up	P value	Baseline	Follow-up	P value
ALT (IU/L)	50.0 (28.8)	24.2 (14.9)	<b>&lt;.001</b>	82.3 (69.4)	27.0 (14.2)	<b>&lt;.001</b>	78.7 (64.1)	27.0 (14.6)	<b>&lt;.001</b>
AST (IU/L)	35.4 (19.1)	19.7 (8.3)	<b>&lt;.001</b>	66.4 (46.3)	23.8 (11.9)	<b>&lt;.001</b>	64.5 (42.7)	24.1 (12.1)	<b>&lt;.001</b>
Bilirubin ( $\mu\text{mol/L}$ )	10.7 (5.3)	9.07 (6.21)	.141	11.62 (5.7)	11.47 (8.1)	.877	11.54 (5.6)	11.7 (8.4)	.206
Albumin (g/L)	37.68 (4.03)	39.15 (3.74)	<b>&lt;.001</b>	36.71 (10.83)	38.73 (5.08)	<b>.048</b>	35.92 (5.91)	38.76 (5.32)	<b>&lt;.001</b>
Platelets ( $\times 10^9/L$ )	220.8 (66.2)	254.7 (77.4)	<b>.013</b>	202.1 (81.5)	209 (81.0)	.511	199.1 (79.88)	206.5 (79.59)	.277
LSM (kPa)	5.73 (1.51)	5.20 (1.60)	.070	19.97 (11.30)	12.84 (8.32)	<b>&lt;.001</b>	21.10 (11.35)	13.84 (8.47)	<b>&lt;.001</b>
AST/ALT	0.73 (0.22)	0.91 (0.38)	<b>.003</b>	0.92 (0.34)	0.98 (0.42)	.281	0.94 (0.35)	0.99 (0.43)	.091
FIB-4	1.29 (1.01)	0.95 (0.57)	<b>.027</b>	2.36 (1.43)	1.56 (0.96)	<b>&lt;.001</b>	2.37 (1.41)	1.61 (0.98)	<b>&lt;.001</b>
APRI	0.49 (0.40)	0.28 (0.19)	<b>&lt;.001</b>	0.98 (0.80)	0.37 (0.24)	<b>&lt;.001</b>	0.96 (0.77)	0.37 (0.25)	<b>&lt;.001</b>

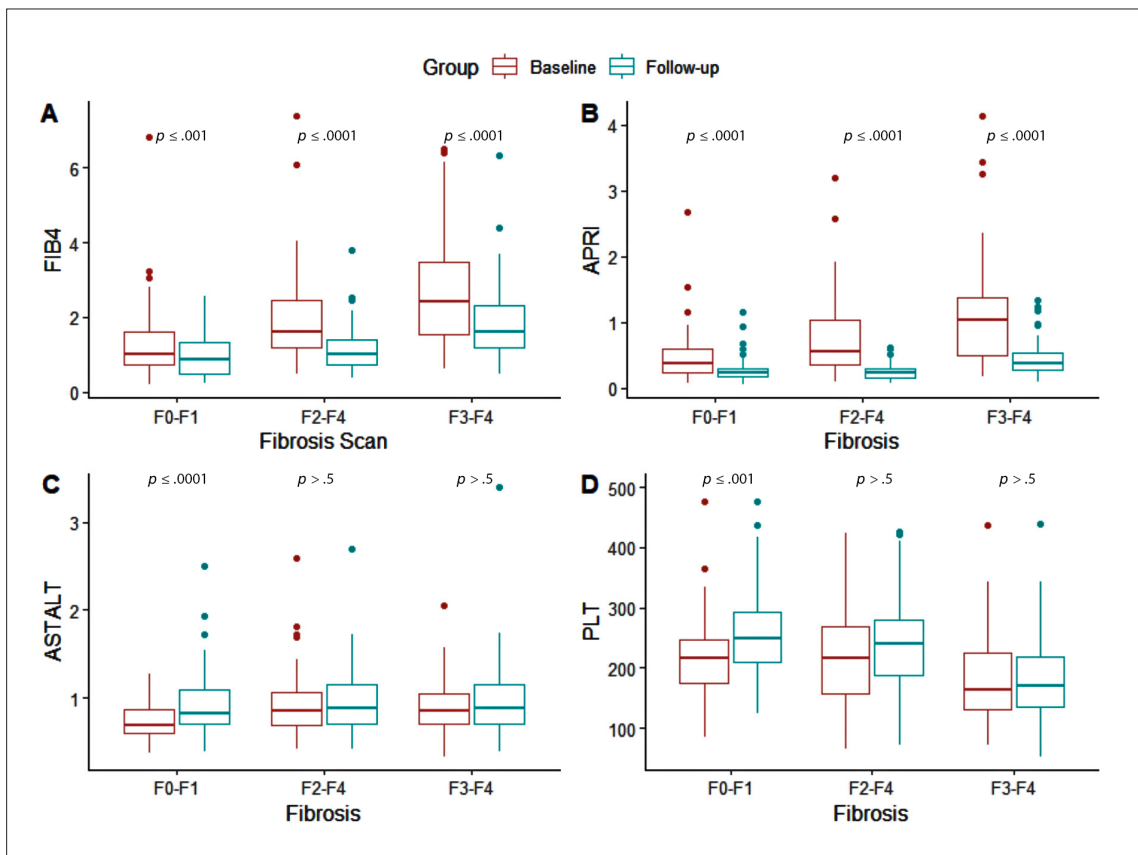
Data are mean and standard deviation. ALT: alanine aminotransferase; AST: aspartate aminotransferase; ALP: alkaline phosphatase; LSM: liver stiffness measurement; CAP: controlled attenuation parameter; FIB-4: fibrosis-4; APRI: AST to platelet ratio index.

in the whole cohort and in the subgroups with low, significant, and advanced fibrosis. These outcomes after DAAs in our study were favorable and similar to the previous follow-up studies on post-DAA therapy. These studies have shown the possibility of fibrosis regression using various noninvasive methods studies.<sup>11</sup> Therefore, post-SVR fibrosis assessment using noninvasive methods, such as LSM, has been suggested on an individual patient basis to assess fibrosis regression or progression; however, until there is more evidence available, this should not alter surveillance for hepatocellular carcinoma in patients with advanced fibrosis.<sup>18</sup>

In our study, most of our patients (85%) showed biochemical improvement in liver injury parameters, such as ALT and AST. Improvements in these traditional biochemical surrogates of liver injury in the current study reflect improvements in inflammation.<sup>12</sup> We demonstrated significant improvement in LSM in the whole cohort at the follow-up assessment compared to baseline levels; this is consistent with other studies evaluating LSM post-SVR.<sup>19-21</sup> However, in our cohort subgroups analysis, the significant improvement in LSM

was limited to patients with significant fibrosis. The lack of significant changes in the low fibrosis patients could be explained by the narrow range of fibrosis staging in this group (F0-F1), in addition to the relatively small number of patients in this group.

Noninvasive scores, such as APRI and FIB-4, strongly correlated with the liver fibrosis stage before antiviral therapy.<sup>22</sup> In our study, improvement of these parameters has been observed; however, an argument regarding the actual changes in these liver enzyme-dependent scores is that changes could reflect improvement in necroinflammation rather than actual fibrosis regression. Previous studies have found a rapid decline in APRI and FIB-4 in the early weeks post-treatment linked to a reduction in necroinflammation.<sup>12,23</sup> However, the significant change (increase) in mean platelet count indicates the possibility of an actual reduction in portal hypertension and fibrosis in our patients. This has been shown by Sayyar et al in a study of 212 patients post-DAA at one-year follow-up.<sup>24</sup> In this study, a significant increase in PLT was observed up to 1 year after HCV antiviral treatment completion. This



**Figure 2.** Changes in noninvasive scores from baseline to follow-up.

finding is supported as well with other studies, which showed significant improvements in platelet counts, splenic stiffness, and portal hypertension after HCV treatment with DAAs.<sup>25,26</sup>

The possibility of attributing the reduction in non-invasive score values to the necroinflammation improvement can also be expanded to LSM. The LSM changes are more significant in the early course of treatment with further slower improvement in several studies.<sup>20,21,27</sup> However, these studies with extended follow-up post-SVR showed consistent and progressive improvement in LSM one year after treatment. Laursen et al showed that LSM decreased by 20% at the end of treatment, suggesting rapid resolution of liver inflammation; however, a further decrease by 15% was observed at the one-year follow-up after treatment while ALT was normalized.<sup>28</sup> Similarly, Chan et al found that further improvement in LSM at one year was observed with no correlation with ALT, suggesting that ALT did not linearly correlate with the change in liver stiffness across time points.<sup>29</sup> Taken together, an early rapid

decline in noninvasive markers early during treatment likely relates to necroinflammation improvement; however, further improvement in the long term is possible, as shown in these studies, albeit slower.

The strengths of our study include the longer follow-up time and the use of several noninvasive methods; however, our study has some limitations. First, there is no histological correlation with these noninvasive scores; however, many patients do not accept liver biopsy, and most guidelines do not recommend it as a follow-up. Second, most of the study patients were genotype 4, and we assess differences in fibrosis changes based on genotype. Third, the follow-up period was not equal for each case. Fourth, we did not assess changes based on the treatment regimen.

In conclusion, we have shown in this study that clearance of HCV with DAAs is associated in the long term with significant improvement in fibrosis as assessed by several noninvasive liver fibrosis tools. This was observed in all fibrosis categories, including advanced fibrosis stages.

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