Medical Journal of Bakırköy

Med J Bakirkoy 2023;19:15-21
DOI: 10.4274/BMJ.galenos.2023.2022.9-9

Research

# Fibrosis Regression Post Direct-acting Antiviral Treatment in Hepatitis C Virus Patients

## Hepatit C Virüslü Hastalarında Direkt Etkili Antiviral Tedavi Sonrası Fibrozisin Gerilemesi

Nurhan Demir[1], Alper Güllüoğlu[2]

[1]University of Health Sciences Türkiye, İstanbul Haseki Training and Research Hospital, Clinic of Gastroenterology, İstanbul, Türkiye
[2]University of Health Sciences Türkiye, İstanbul Haseki Training and Research Hospital, Clinic of Emergency Medicine, İstanbul, Türkiye

## ABSTRACT

**Objective:** We studied long-term serial changes in aspartate aminotransferase/platelet ratio index (APRI) and fibrosis-4 (FIB-4) scores in hepatitis C virus patients with a sustained virologic response after direct-acting antiviral (DAA) therapy.

**Methods:** Seventy-five patients treated with DAA were included in this study. APRI and FIB-4 scores were calculated at the beginning of DAA treatment, at the end of treatment (EOT), one and two years after treatment.

**Results:** Twenty-eight patients had cirrhosis. APRI and FIB-4 scores (1.38 vs. 0.49, p<0.001; 4.25 vs. 2.79, p<0.001) Improved in all patients at the EOT. There was also a trend toward decreased scores for APRI and FIB-4 at follow-up based on EOT of 2nd-year results (APRI, 0.49 vs. 0.41, p=0.87; FIB-4, 2.79 vs. 2.50, p=0.44). There were significant improvements in cirrhotic patients' two-year APRI and FIB-4 scores (0.86 vs. 0.58, p<0.001; 4.74 vs. 3.59, p<0.001). Similarly, in the 1st and second years, APRI and FIB-4 scores were compared after EOT in cirrhotic patients (0.84 vs. 0.58, p=0.007; 4.74 vs. 3.59, p=0.004) and showed remarkable improvement.

**Conclusion:** Improvements in liver fibrosis markers were prominent in patients with advanced fibrosis. The regression in liver fibrosis based on non-invasive tests has persisted even two years after the treatment.

**Keywords:** Fibrosis regression, HCV, APRI, FIB-4

## ÖZ

**Amaç:** Çalışmamızda doğrudan etkili antiviral (DAA) sonrası sürekli virolojik yanıt elde eden hepatit C virüsü hastalarında aspartat aminotransferaz/trombosit oran indeksi (APRI) ve fibrozis-4 (FIB-4) skorlarındaki uzun süreli seri değişiklikleri araştırmayı amaçladık.

**Gereç ve Yöntem:** Bu çalışmaya DAA tedavisi uygulanan 75 hasta dahil edildi. APRI ve FIB-4 skorları, DAA tedavisinin başında, tedavi sonunda (EOT), tedaviden bir ve iki yıl sonra hesaplandı.

**Bulgular:** Yirmi sekiz hastada siroz vardı. APRI ve FIB-4 skorları [1,38 vs. 0,49, p<0,001; 4,25 vs. 2,79, p<0,001] EOT'deki tüm hastalarda düzeldi. İkinci yıl sonuçlarına göre EOT'ye dayalı takipte APRI ve FIB-4 puanlarında azalma yönünde bir eğilim de vardı (APRI, 0,49 vs. 0,41, p=0,87; FIB-4, 2,79 vs. 2,50, p=0,44). Sirotik hastaların iki yıllık APRI ve FIB-4 skorlarında anlamlı iyileşmeler vardı [0,86 vs. 0,58, p<0,001; 4,74-3,59, p<0,001]. Benzer şekilde 1. ve 2. yıllarda sirotik hastalarda EOT sonrası APRI ve FIB-4 skorları karşılaştırıldığında [0,84 vs.0,58, p=0,007; 4,74 vs. 3,59, p=0,004] hastalarda anlamlı düzelme görüldü.

**Sonuç:** İlerlemiş fibrozisi olan hastalarda karaciğer fibrozis belirteçlerindeki belirgin iyileşmeler görüldü. İnvaziv olmayan testlere dayanan karaciğer fibrozundaki gerileme, tedaviden iki yıl sonra bile devam etmiştir.

**Anahtar Kelimeler:** Fibrozis gerilemesi, HCV, APRI, FIB-4

**Address for Correspondence:** Nurhan Demir, University of Health Sciences Türkiye, İstanbul Haseki Training and Research Hospital, Clinic of Gastroenterology, İstanbul, Türkiye
Phone: +90 505 260 84 11 E-mail: nolandemir@gmail.com ORCID ID: orcid.org/0000-0003-0037-7775

**Cite as:** Demir N, Güllüoğlu A. Fibrosis Regression Post Direct-acting Antiviral Treatment in Hepatitis C Virus Patients. Med J Bakirkoy 2023;19:15-21

**Received:** 21.10.2022
**Accepted:** 16.01.2023

©Copyright 2023 by Medical Journal of Bakırköy published by Galenos Yayınevi.

## INTRODUCTION

Hepatitis C virus (HCV) is one of the leading causes of liver-related morbidity and mortality worldwide (1,2). Continued fibrogenesis in the liver often leads to cirrhosis. The risk of hepatocellular carcinomas (HCC) increases with progressive fibrosis, with most cases occurring in patients with advanced fibrosis and/or or cirrhosis (3). Recently, excellent responses have been obtained with the new direct antiviral agents (DAA) used in treating chronic hepatitis C. Thanks to these drugs that directly target the HCV, over 90% sustained virological response (SVR) has been achieved (4). Because of DAA-based treatments, it has been shown that HCV eradication is achieved, the course of the disease improves, cirrhosis and related complications, and the development of HCC is reduced (5). This result is probably attributed to fibrosis regression after viral eradication (6). The best method for evaluating fibrosis regression is to examine it with liver biopsy. However, it is impractical to perform a liver biopsy to assess the fibrosis stage in all patients. Many non-invasive methods are widely used, including imaging technologies and serum biomarkers. Several laboratory indices, including the aspartate aminotransferase/platelet ratio index (APRI) and fibrosis-4 (FIB-4), are good indicators for using liver fibrosis in patients with chronic HCV infection. The sensitivity and specificity of the FIB-4 and APRI scores have been validated, particularly for chronic hepatitis C (CHC) patients with advanced fibrosis and cirrhosis (7).

It has numerous advantages, such as ease of procedure, reproducibility, patient acceptance, cost-effectiveness, and absence of biopsy-related risks. The aim of this study was to evaluate the dynamics of APRI and FIB-4 (NIT's).

Scores of HCV patients who achieved SVR after receiving DAA and follow-up the course of NIT's screened fibrosis regression in patients with cirrhosis who achieved SVR in the years after treatment.

## METHODS

### Study Design

The study was planned as a single-centre, retrospective study. Data were analyzed according to changes in FIB-4 and APRI fibrosis scores in patients with CHC treated with DAA therapy.

### Ethics Statement

The study was approved by the Ethics and Clinical Research Committee of the University of Health Sciences Türkiye, İstanbul Haseki Training and Research Hospital (decision no: 27-2022, date: 16.02.2022) and conducted following the Declaration of Helsinki.

### Study Population

Patients who had DAA therapy for CHC between December 2016 and December 2019 by University of Health Sciences Türkiye, İstanbul Haseki Training and Research Hospital Gastroenterology Polyclinic and who achieved a persistent viral response SVR were retrospectively analyzed. We explained SVR as the serum HCV ribonucleic acid (RNA) level that was undetected after discontinuation of treatment in our study. We analyzed laboratory data at the start of DAA treatment, at the end of treatment (EOT), one and two years after treatment. Excluded are the chronic liver disease of a non-HCV aetiology (e.g., autoimmune hepatitis, Wilson's disease, hemochromatosis, diabetes mellitus), viral hepatitis B infection or immunodeficiency virus infections (e.g., human immunodeficiency virus), malignancy and organ transplantation. Additionally, patients with incomplete clinical laboratory data required for non-invasive measurements of liver fibrosis were excluded. Demographic information for each patient, laboratory data, HCV treatment regimen, and SVR history were obtained from medical records.

### Non-invasive Measurements of Liver Fibrosis

Two non-invasive biomarkers for fibrosis, APRI, and FIB-4, were calculated before and after SVR based on the following formulas (8).

APRI was calculated with the following formula: [Aspartat aminotransferase (AST) (IU/L)/AST (high limit of normal range-IU/L)/platelet count ($10^9$/L)] x100, and the patients were sub-grouped due to determined cut-offs from previous studies (<1, 1-2, >2). The used APRI cut-off score was 2 in the detection of cirrhosis (9).

The formula for the calculation of the FIB-4 index was as follows: age (years) x AST (IU/L)/[platelet count ($10^9$/L)/√ alanine aminotransferase (ALT) (IU/L)]. The previously identified cut-off levels were used to classify patients (<1.45, 1.45-3.25, >3.25). Advanced fibrosis was defined as FIB-4>3.25 (10).

### Antiviral Therapy

The patient's presence and degree of cirrhosis, whether the previous treatment is experienced, and the virus genotype, play a role in selecting direct-acting antiviral therapy. The period of treatment was given a duration ranging from 8 to 24 weeks. DAA protocols comprised sofosbuvir (SOF, 400 mg once daily) with ribavirin (RBV, 500 mg /600 mg twice a day); SOF/ledipasvir (LDV) (400 mg/90 mg once daily) ± RBV; The PrOD regimen (paritaprevir 75 mg once daily, ombitasvir 12.5 mg, and ritonavir 50 mg plus dasabuvir

250 mg twice daily) ± RBV; glecaprevir (GLE, 300 mg once daily) plus pibrentasvir (PIB, 120 mg once daily). Treatment duration was 8, 12, or 24 weeks, determined due to baseline genetic and fibrosis grade. The treatment last point was identified as the failure to detect HCV RNA in serum by a sensitive test (less than ≤15 (IU/mL) after the EOT.

### Statistical Analysis

Data of the study were analyzed with the inclusion body myositis statistical package for the social sciences statistical 22.0 program. Descriptive analyses are given as percentages and numbers. Because the percentage and frequencies of the study data did not fit the normal distribution in the dependent group analysis, the Wilcoxon test was used in the comparison. A p-value of less than 0.05 was accepted as significant in statistical analysis. If the p-value was very low in the computation, the value is expressed as p<0.001.

## RESULTS

### Demographic and Clinical Findings

This study included seventy-six patients who had received treatment. Patient demographics and baseline characteristics are shown in Table 1. Of the patients, 32 (42.1%) were male, and 44 (57.9%) were female. The mean age of the patients was 61±13 years. Twenty-eight patients (36.8%) had cirrhosis. Twenty patients (25.9%) were previously treated for HCV infection (treatment-experienced). SVR could not be obtained in one patient who did not complete the treatment. Other than this, 75 patients were determined to have SVR (98.7%). Sixty-three (82.9%) patients were genotype 1 (75% genotype 1b, 7.9% genotype 1a). Additionally, 9 (11.8%) patients were genotype 2, 4 (3.9%) genotype 3, 1 (1.3%) genotype 5. In the TURHEP study published in 2015, in our country most of the CHC patients were genotype 1b (92.1%) (2). 40.8% PrOD, 18.4% LDV/SOF, 11.7% PrOD+RBV, 10.5% SOF+RBV, 9.2% LDV/SOF+RBV and 9.2% used GLE+PIB. The baseline median AST and ALT levels were 55 (36-89) U/L and 52 (40-103) U/L, respectively. The median platelet count was 172 (119-259)×10$^9$/L. The median HCV RNA level was 9.82 (9.72-14.67) log10 IU/mL, the median APRI value was 1.19 (0.62-2.45), and the median FIB-4 value was 2.93 (1.57-5.80). After EOT, 98% of patients had a SVR (Table 1). The data of 75 patients with SVR, 72 patients with follow-up at one year, and 63 patients with follow-up at two years were evaluated. During the first year, one cirrhotic patient died from cardiac failure, and one non-cirrhotic patient died from a lung abscess. In the second year, two cirrhotic patients died, one due to newly detected HCC secondary hepatic decompensation and the other due to endometrial cancer.

### Platelet Count, ALT, and AST Levels at the End of Treatment in Patients with SVR

In patients who received DAA therapy with SVR (n=75), the median platelet count increased at the EOT (p<0.001). The median AST (p=0.002) and ALT (p=0.036) values decreased (Table 2).

**Table 1.** Patient's demographics and baseline characteristics

| Patient's demographics and baseline characteristics | Total cohort (n=76) |
|---|---|
| | n (%) or median IQR |
| **Sex** | |
| Male | 32 (42.1) |
| Female | 44 (57.9) |
| Age (years) [mean, SD] | 61±13 |
| AST (U/L) | 55 (33-92) |
| ALT (U/L) | 52 (31-82) |
| Platelet count (×10$^9$/L) | 172 (119-259) |
| APRI | 0.79 (0.38-1.68) |
| FIB-4 | 2.95 (1.54-5.81) |
| HCV viral load (IU/mL) | 9,829,414 (972,19-14,678,475) |
| **HCV genotype** | **n (%)** |
| 1A | 6 (7.9) |
| 1B | 57 (75) |
| 2 | 9 (11.8) |
| 3 | 3 (3.9) |
| 5 | 1 (1.3) |
| Liver cirrhosis, n (%) | 28 (36.8) |
| HCV treatment-experienced (%) | 20 (25.9) |
| SVR, n (%) | 75 (97.4) |
| **DAA treatment regimen [n (%)]** | |
| Ombitasvir-paritaprevir-ritonavir + dasabuvir | 31 (40.8) |
| Ombitasvir-paritaprevir-ritonavir + dasabuvir + ribavirin | 9 (11.8) |
| Sofosbuvir + ledipasvir | 14 (18.4) |
| Sofosbuvir + ledipasvir + ribavirin | 7 (9.2) |
| Sofosbuvir + ribavirin | 8 (10.5) |
| Glecaprevir + pibrentasvir | 7 (9.2) |

Results are expressed as median (IQR). The frequencies are expressed as number and percentage (%). SD: Standard deviation, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, APRI: Aspartate aminotransferase to platelet ratio index, FIB-4: Fibrosis 4 score, HCV: Hepatitis C virus, IQR: Interquartile range, DAA: Direct-acting antiviral, SVR: Sustained virologic response

Baseline Mean Values Detected in APRI and FIB-4 Scores in Patients with Cirrhosis and Non-cirrhosisThe APRI and FIB-4 index exhibited significant statistical differences between patients with and without cirrhosis (7). Baseline APRI and FIB-4 scores of the patients with cirrhosis and non-cirrhosis are presented in Table 3.

### At Baseline and EOT, the Scores of Non-invasive Tests (APRI, FIB-4)

At the end of the therapy, we observed significant decreases in APRI scores and and scores of FIB-4 [0.56 (0.30-1.06) vs. 0.24 (0.16-0.34), p<0.001; 2.20 (1.24-3.28) vs. 1.60 (0.85-2.15), p<0.001 respectively] significant decreases were observed.

### End of Treatment, 1st Year, and 2nd Year After Treatment, Non-invasive Test Scores

At the EOT, 1st year after treatment, and 2nd year after treatment, we calculated the scores of APRI and FIB-4 in both groups, and the results are presented in Figures 1 and 2 by boxplot charts. Data is presented for cirrhotic patients in Table 4 and Figure 3. Data presented for non-cirrhotic patients on and Table 5 and Figure 4.We found a tendency to decline in the median scores of APRI and FIB-4 at follow-up based on EOT results (APRI, 0.49 vs. 0.41, p=0.87; FIB-4, 2.79 vs. 2.50, p=0.44), but there were no significant differences. However, cirrhotic patients had striking results after two years of follow-up. Both EOT 1& 2nd year APRI and FIB-4 in the cirrhotic patient [0.86 vs. 0.58, p<0.001; 4.74 vs. 3.59, p<0.001], as well as 1st and 2nd year APRI and FIB-4 [0.84 vs. 0.58, p=0.007; 4.74 vs. 3.59, p=0.004] had significant improvement. There was no statistically significant difference in non-cirrhotic patients at the two-year follow-up after EOT.

**Table 2.** Paired samples correlations all patients

| | | n | Correlation | p-value |
|---|---|---|---|---|
| ALT | Pre-treatment ALT & EOT ALT | 75 | 0.243 | 0.036 |
| AST | Pre-treatment AST & EOT AST | 75 | 0.351 | 0.002 |
| PLT | Pre-treatment PLT & EOT PLT | 75 | 0.804 | 0.000 |

ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, EOT: End of treatment, PLT: Platelet

**Table 3.** Baseline mean APRI and FIB-4 scores in cirhosis vs. non-cirhosis groups

| Variables | Cirrhosis (28 patients) | Non-cirrhosis (48 patients) | p-value |
|---|---|---|---|
| APRI mean | 2.39 | 0.81 | <0.0001 |
| FIB-4 mean | 7.22 | 2.50 | <0.0001 |

APRI: Aspartate aminotransferase to platelet ratio index, FIB-4: Fibrosis-4 score. Results are expressed as mean value. Statistical significance of the differences between the cirrhotic patientsand non-cirrhotic patients was determined by p<0.05 using the independent samples t-test

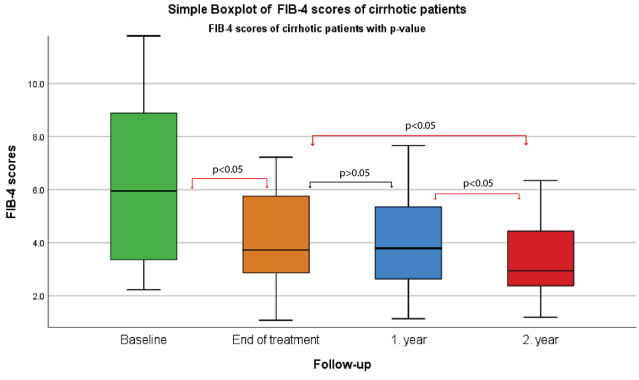


**Figure 1.** Follow-up plotbox diagrams of 1st year and 2nd year after treatment, FIB-4 scores of cirrotic patients

FIB-4: Fibrosis-4 score

## DISCUSSION

Since the prognosis after treatment is mainly determined by the fibrosis stage, it is essential to assess whether fibrosis regression can be achieved after the completion of DAA therapy.

It has been shown that more fewer undesired conditions like liver cirrhosis, hepatic decompensation, and HCC are observed in patients with CHC who gained SVR than in those without SVR (11). However, the elimination of hepatic adverse events could not be warranted with SVR because these patients should receive post-SVR surveillance. In patients who have SVR, the residual liver fibrosis stage can predict adverse events in the liver (12). This study adds valuable data to the available literature through data from extended follow-up periods and comparative results, which might lead to better clarification to interpret the changes in the liver after treatment. It is one of the few studies observing changes in liver fibrosis screened with non-invasive tests over two years at specified time points of APRI and FIB-4 computation and comparing derived data before and after DAA treatment. Study outcomes were interpreted as follows; an improvement in liver fibrosis screened with NIT's between baseline and EOT might be associated with the resolution of inflammation soon after starting DAA therapy, whereas improvement over two years after treatment completion is more likely to represent a regression in liver fibrosis.

### Our Pre-treatment and Post-treatment Results

In both cirrhotic and non-cirrhotic liver disease, significant regression was observed in screened fibrosis levels calculated using reliable non-invasive markers, regardless of the initial fibrosis stage after DAA therapy.

**Table 4.** Follow up APRI and FIB-4 scores for cirrhotic patients

| Variables | EOT vs. 1 year post-EOT (26 patients) | | | EOT vs. 2 year post-EOT (23 patients) | | | 1 year vs. 2 year post-EOT (23 patients) | | |
|---|---|---|---|---|---|---|---|---|---|
| | EOT | 1 year post-EOT | p-value | EOT | 2 year post-EOT | p-value | 1 year post-EOT | 2 year post-EOT | p-value |
| APRI | 0.86 | 0.84 | 0.905 | 0.86 | 0.58 | 0.000 | 0.84 | 0.58 | 0.007 |
| FIB-4 | 4.74 | 4.62 | 0.878 | 4.74 | 3.59 | 0.000 | 4.62 | 3.59 | 0.004 |

APRI: Aspartate aminotransferase to platelet ratio index, FI-4: Fibrosis-4 score, EOT: End of treatment

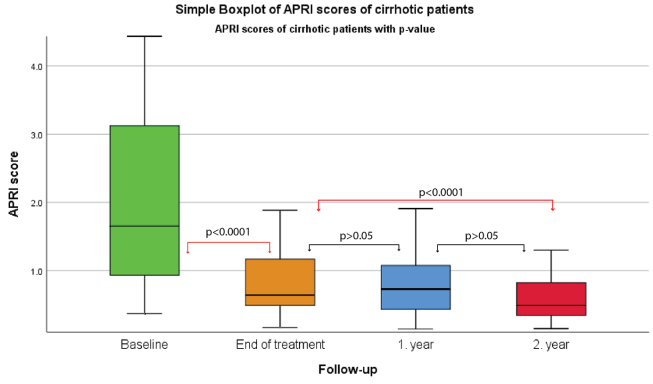


**Figure 2.** Follow-up plotbox diagrams of 1st year and 2nd year after treatment, APRI scores of cirrotic patients
APRI: Aspartate aminotransferase to platelet ratio index

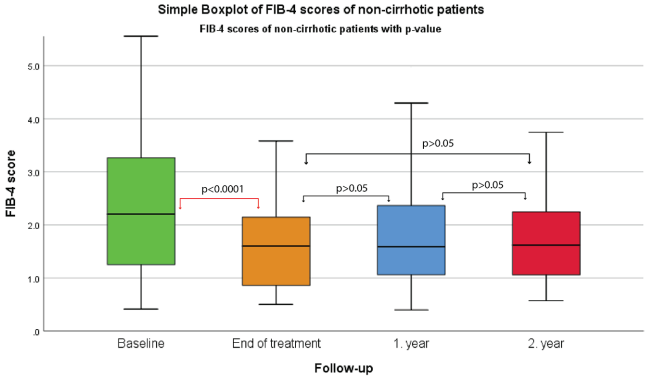


**Figure 3.** Follow-up plotbox diagrams of 1st year and 2nd year after treatment, FIB-4 scores of non-cirrotic patients
FIB-4: Fibrosis-4 score

Non-invasive tests (APRI, FIB-4 index) exhibited significant statistical differences between patients with and without cirrhosis (13). In recent studies, a remarkable decrease in hepatic enzymes and improvement in biochemical profile have been reported after DAA treatment (14,15). By Zhang et al. (16) comparing pre-treatment and EOT, ALT, AST, and platelet results, significant decreases were found (p=0.036, p=0.002, p=0.000, respectively). After SVR, a favorable improvement in hematological parameters (particularly platelets) has been reported. Changes in APRI and FIB-4 scores may be related to the rapid decline in hepatic

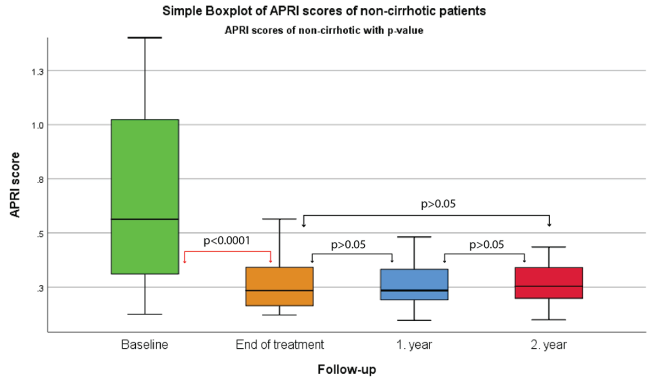


**Figure 4.** Follow-up plotbox diagrams of 1st year and 2nd year after treatment, APRI scores of non-cirrotic patients
APRI: Aspartate aminotransferase to platelet ratio index

transaminases (AST, ALT) and increase in platelets, mainly due to improvement in necroinflammation. However, this rapid regression achieved at the EOT may only reflect necroinflammatory resolution rather than actual fibrosis regression, leading to an overestimation of fibrosis regression.

### Our Results of the EOT and One-year Post-EOT

We analyzed the EOT results of patients with and without cirrhosis, the 1st and 2nd-year APRI and FIB-4 scores, to reduce the confounding effect of the improvement in fibrosis scores necroinflammatory healing on liver fibrosis measurements in ongoing follow-ups.

### Our Results of the EOT and Two-year Post-EOT

Impressive results were obtained in NIT's screening fibrosis regression at the 2nd-year follow-up in the cirrhotic patient group. In comparative computing of the EOT and two-year post-EOT scores of APRI (p=0.007) and FIB-4 (p=0.004), significant differences were found.

Most of the studies performed were performed shortly after the EOT (12 and 24 weeks) (17-19). The resolution of inflammation could be the primary reason of timely improvement; on the other hand, continued regression one year after EOT may be due to fibrosis reduction, as observed in liver biopsy studies paired with interferon-

**Table 5.** Follow-up APRI and FIB-4 scores for non-cirrhotic patients

| Variable | EOT vs. 1 year post-EOT (46 patients) | | | EOT vs. 2 year post-EOT (39 patients) | | | 1 year vs. 2 year post-EOT (39 patients) | | |
|---|---|---|---|---|---|---|---|---|---|
| | EOT | 1 year post-EOT | p-value | EOT (48 patients) | 2 year post-EOT | p-value | 1 year post-EOT | 2 year post-EOT | p-value |
| APRI | 0.28 | 0.29 | 0.909 | 0.28 | 0.26 | 0.313 | 0.29 | 0.26 | 0.312 |
| FIB-4 | 1.71 | 1.86 | 0.259 | 1.71 | 1.86 | 0.306 | 1.86 | 1.89 | 0.315 |

APRI: Aspartate aminotransferase to platelet ratio index, FIB-4: Fibrosis-4 score, EOT: End of treatment

based therapy (20,21). Prakash and Rockey (22) showed that 39% of cirrhotic patients had a reduction of <2.67 in the FIB-4 monitoring technique.

A recent systematic review of 24 observational studies with another invasive fibrosis assessment method that is vibration- controlled transient elastography, showed a significant early reduction in liver stiffness followed by a milder decrease one year later in patients with HCV infection (who acquired SVR), by Singh et al. (23).

Our post-EOT 2-year follow-up results; although the 1st year NIT's screened fibrosis regression was insignificant in cirrhotic patients with a high fibrosis score, in the second year, fibrosis reduction continued and became significant in this group.

Limitations of the study. First, we had no histological examination was to observe correlations with transitory variance in non-invasive fibrosis parameters of patients while taking and after DAA treatment. Second, there was a scarce number of patients since it was a single-center study. Since it was a small cohort, we could not statistically determine additional patient factors independently associated with significant improvement in fibrosis scores.

## CONCLUSION

The study adds important and detailed data to the literature by revealing a continuous improvement in NIT's screened for liver fibrosis two years after EOT. Although long-term fibrosis regression was more limited than observed rapid decreases at EOT, this finding is significant when considering cirrhosis and advanced fibrosis regression, which is a slow process requiring long-term follow-up.

Multi-centre clinical studies with a larger dataset will allow more detailed and robust statistical and clinical data to reveal long-term treatment responses.

### ETHICS

**Ethics Committee Approval:** The study was approved by the Ethics and Clinical Research Committee of the University of Health Sciences Türkiye, Haseki Training and Research Hospital (decision no: 27-2022, date: 16.02.2022). The research conforms to the provisions of the Declaration of Helsinki in 1995.

**Informed Consent:** Retrospective study.

### Authorship Contributions

Surgical and Medical Practices: N.D., A.G., Concept: N.D., Design: N.D., Data Collection or Processing: N.D., A.G., Analysis or Interpretation: N.D., A.G., Literature Search: N.D., A.G., Writing: N.D.

**Conflict of Interest:** No conflict of interest was declared by the authors.

**Financial Disclosure:** The authors declared that this study received no financial support.

## REFERENCES

1. Polaris Observatory HCV Collaborators. Global prevalence and genotype distribution of hepatitis C virus infection in 2015: a modelling study. Lancet Gastroenterol Hepatol 2017;2:161-76.
2. Tozun N, Ozdogan O, Cakaloglu Y, Idilman R, Karasu Z, Akarca U, et al. Seroprevalence of hepatitis B and C virus infections and risk factors in Turkey: a fieldwork TURHEP study. Clin Microbiol Infect 2015;21:1020-6.
3. Haydon GH, Jarvis LM, Simmonds P, Harrison DJ, Garden OJ, Hayes PC. Association between chronic hepatitis C infection and hepatocellular carcinoma in a Scottish population. Gut 1997;40:128-32.
4. Kaymakoğlu S, Köksal İ, Kaymakoğlu S, Tabak F, Akarca US, Akbulut A, et al. Recommendation for treatment of hepatitis C virus infection. Turk J Gastroenterol 2017;28(Suppl 2):94-100.
5. Backus LI, Belperio PS, Shahoumian TA, Mole LA. Impact of Sustained Virologic Response with Direct-Acting Antiviral Treatment on Mortality in Patients with Advanced Liver Disease. Hepatology 2019;69:487-97.
6. Sperl J, Horvath G, Halota W, Ruiz-Tapiador JA, Streinu-Cercel A, Jancoriene L, et al. Efficacy and safety of elbasvir/grazoprevir and sofosbuvir/pegylated interferon/ribavirin: A phase III randomized controlled trial. J Hepatol 2016;65:1112-9.

7. Wai CT, Greenson JK, Fontana RJ, Kalbfleisch JD, Marrero JA, Conjeevaram HS, et al. A simple noninvasive index can predict both significant fibrosis and cirrhosis in patients with chronic hepatitis C. Hepatology 2003;38:518-26.

8. European Association for Study of Liver; Asociacion Latinoamericana para el Estudio del Higado. EASL-ALEH Clinical Practice Guidelines: Non-invasive tests for evaluation of liver disease severity and prognosis. J Hepatol 2015;63:237-64.

9. Chou R, Wasson N. Blood tests to diagnose fibrosis or cirrhosis in patients with chronic hepatitis C virus infection: a systematic review. Ann Intern Med 2013;158:807-20.

10. Ghany MG, Morgan TR; AASLD-IDSA Hepatitis C Guidance Panel. Hepatitis C Guidance 2019 Update: American Association for the Study of Liver Diseases-Infectious Diseases Society of America Recommendations for Testing, Managing, and Treating Hepatitis C Virus Infection. Hepatology 2020;71:686-721.

11. Gonzalez HC, Duarte-Rojo A. Virologic Cure of Hepatitis C: Impact on Hepatic Fibrosis and Patient Outcomes. Curr Gastroenterol Rep 2016;18:32.

12. Makiyama A, Itoh Y, Kasahara A, Imai Y, Kawata S, Yoshioka K, et al. Characteristics of patients with chronic hepatitis C who develop hepatocellular carcinoma after a sustained response to interferon therapy. Cancer 2004;101:1616-22.

13. Köksal İ, Yılmaz G, Parlak M, Demirdal T, Kınıklı S, Candan M, et al. Diagnostic value of combined serum biomarkers for the evaluation of liver fibrosis in chronic hepatitis C infection: A multicenter, noninterventional, observational study. Turk J Gastroenterol 2018;29:464-72.

14. Elsharkawy A, Eletreby R, Fouad R, Soliman Z, Abdallah M, Negm M, et al. Impact of different sofosbuvir based treatment regimens on the biochemical profile of chronic hepatitis C genotype 4 patients. Expert Rev Gastroenterol Hepatol 2017;11:773-8.

15. Köklü S, Köksal I, Akarca US, Balkan A, Güner R, Demirezen A, et al. Daclatasvir plus asunaprevir dual therapy for chronic HCV genotype 1b infection: results of Turkish early access program. Ann Hepatol 2017;16:71-6.

16. Zhang C, Wu J, Xu J, Xu J, Xian J, Xue S, et al. Association between Aspartate Aminotransferase-to-Platelet Ratio Index and Hepatocellular Carcinoma Risk in Patients with Chronic Hepatitis: A Meta-Analysis of Cohort Study. Dis Markers 2019;13:2019:2046825.

17. Huang R, Rao H, Yang M, Gao Y, Wang J, Jin Q, et al. Noninvasive Measurements Predict Liver Fibrosis Well in Hepatitis C Virus Patients After Direct-Acting Antiviral Therapy. Dig Dis Sci 2020;65:1491-500.

18. Öztürk-Çerik H, Esen Ş, Altıntaş-Öner B, Çelik M, Özdemir T, Tanyel E. Evaluation of the Effectiveness of Direct-Acting Antiviral Agents in Patients With Hepatitis C. Klimik Derg 2020;33:297-306.

19. Abdelkader NAA, Ahmed OA, Sherief AF, Kandil DM, Gado MS, Al Balakosy AM. Evaluation of long-term changes of aspartate—platelet ratio index, FIB4, and liver stiffness in chronic hepatitis C patients successfully treated by direct-acting antivirals. Egypt Liver Journal 2021;11:1-8.

20. Huang R, Rao HY, Yang M, Gao YH, Wang J, Jin Q, et al. Histopathology and the predominantly progressive, indeterminate and predominately regressive score in hepatitis C virus patients after direct-acting antivirals therapy. World J Gastroenterol 2021;27:404-15.

21. Cammà C, Di Bona D, Schepis F, Heathcote EJ, Zeuzem S, Pockros PJ, et al. Effect of Peginterferon Alfa-2a on Liver Histology in Chronic Hepatitis C: a meta-analysis of individual patient data. Hepatology 2004;39:333-42.

22. Prakash S, Rockey DC. 1006 predictors of poor fibrosis regression after direct acting antiviral therapy in patients with chronic hepatitis C and cirrhosis. Gastroenterology 158: S-1302-S-1303.

23. Singh S, Facciorusso A, Loomba R, Falck-Ytter YT. Magnitude and Kinetics of Decrease in Liver Stiffness After Antiviral Therapy in Patients With Chronic Hepatitis C: A Systematic Review and Meta-analysis. Clin Gastroenterol Hepatol 2018;16:27-38.e4.