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Post-Treatment Course of Indices Predicting Liver Fibrosis in Adult Chronic Hepatitis C Patients Treated with Direct-Acting Antivirals

Doğrudan Etkili Antivirallerle Tedavi Edilen Yetişkin Kronik Hepatit C Hastalarında Karaciğer Fibrozunu Öngören Endekslerin Tedavi Sonrası Seyri

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ABSTRACT

Objectives: Hepatitis C virus (HCV) infection is a chronic infection that can lead to liver failure, cirrhosis, and hepatocellular carcinoma over time. In recent years, direct-acting antivirals (DAAs) have mostly eliminated the virus. Studies on their effect on the improvement of liver fibrosis are ongoing. Indices such as the aspartate transaminase platelet ratio index (APRI), fibrosis-4 index (FIB-4), aspartate transaminase to alanine transaminase ratio (AAR), fibrosis index, and gamma glutamyl transferase to platelet ratio (GPR) are suggested to predict liver fibrosis. The aim of this study was to evaluate the course of these indices before and after DAA treatment.

Materials and Methods: The data of patients aged 18 years and older who were treated with DAAs for HCV infection in certain outpatient clinics of infectious diseases and clinical microbiology of a reference center between February 19, 2019 and May 31, 2023 were collected from the electronic record system. Demographic information, comorbidities, information about HCV infection, hemogram, and biochemical tests required for calculating the indices were obtained.

Results: The study included 131 patients. The median age of the patients was 31 [interquartile range (IQR): 27] years. At the end of the treatment, the patients were followed up for a median of 183 days for hemogram (n=81) and 185 days for biochemical tests (n=82). Among the indices, APRI (p<0.001), FIB-4 (p<0.001), fibrosis index (p=0.004) and GPR (p<0.001) increased significantly after DAA compared with before, while AAR decreased.

Conclusion: In this study, it was determined that fibrosis predictive indices indicated a significant regression after treatment.

Keywords: APRI, FIB-4, direct-acting antivirals, fibrosis index, hepatitis C

ÖZ

Amaç: Hepatit C virüsü (HCV) enfeksiyonu, zamanla karaciğer yetmezliğine, siroza ve hepatoselüler karsinoma yol açabilen kronik bir enfeksiyondur. Son yıllarda doğrudan etkili antiviraller (DAA'lar) virüsü büyük ölçüde ortadan kaldırdı. Karaciğer fibrozisinin iyileştirilmesine etkileri üzerine çalışmalar devam etmektedir. Aspartat transaminaz trombosit oranı indeksi (APRI), fibrozis-4 indeksi (FIB-4), aspartat transaminaz/alanin transaminaz oranı (AAR), fibrozis indeksi ve gama glutamil transferaz/trombosit oranı (GPR) gibi indekslerin karaciğer fibrozisini öngördüğü ileri sürülmektedir. Bu çalışmanın amacı bu indekslerin DAA tedavisi öncesi ve sonrası seyrini değerlendirmektir.

Gereç ve Yöntemler: 19 Şubat 2019 ile 31 Mayıs 2023 tarihleri arasında bir referans merkezinin bazı enfeksiyon hastalıkları ve klinik mikrobiyoloji polikliniklerinde HCV enfeksiyonu nedeniyle DAA tedavisi gören 18 yaş ve üzeri hastaların verileri elektronik kayıt sisteminden toplandı. İndekslerin hesaplanması için gerekli olan demografik bilgiler, komorbiditeler, HCV enfeksiyonuna ilişkin bilgiler, hemogram ve biyokimyasal testler elde edildi.

Bulgular: Çalışmaya 131 hasta dahil edildi. Hastaların ortanca yaşı 31 [çeyrekler arası aralık (IQR): 27] yıldı. Tedavi sonunda hastalar ortalama 183 gün hemogram (n=81) ve 185 gün biyokimyasal tetkikler (n=82) için takip edildi. İndekslerden APRI (p<0,001), FIB-4 (p<0,001), fibrozis indeksi (p=0,004) ve GPR (p<0,001) DAA sonrası öncesine göre anlamlı derecede artarken, AAR azaldı.

Sonuç: Bu çalışmada fibrozis prediktif indekslerinin tedavi sonrasında anlamlı gerileme gösterdiği belirlendi.

Anahtar Kelimeler: APRI, FIB-4, doğrudan etkili antiviraller, fibrozis indeksi, hepatit C

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Introduction

Hepatitis C virus (HCV) is a hepatotropic virus that can lead to chronic infection, liver failure, cirrhosis, and hepatocellular carcinoma over time. Although therapeutic interventions were initiated before 1989 when the virus was identified, interferon, regulated interferon, and ribavirin were prescribed after the virus was identified. Because of long treatment durations and high probability of failure in sustained viral suppression, hepatitis C-directed therapies have been targeted. After the approval of the first direct-acting antivirals (DAAs) in 2011, many antivirals rapidly entered the market (1). In Türkiye, telaprevir and boceprevir were first introduced; however, they are not used in practice due to side effects and difficulty of use. In time, ombitasvir-paritapravir-ritonavir-dasabuvir (3D regimen) with/without ribavirin, sofosbuvir-ledipasvir, glecaprevir-pibrentasvir, sofosbuvir-velpatasvir, and voxilaprevir became available. DAAs are highly successful in achieving viral elimination and providing a sustained viral response (SVR) (2). However, studies on their effect on the improvement of liver fibrosis are ongoing.

Although liver biopsy is the gold standard in the evaluation of liver fibrosis, it is rarely performed today because it is an interventional procedure (3). There are indices such as the aspartate aminotransferase (AST) to platelet ratio index (APRI) (4), fibrosis-4 index (FIB-4) (5), aspartate aminotransferase to alanine aminotransferase (ALT) ratio (AAR)[6], fibrosis index (7), and gamma-glutamyl-transpeptidase (GGT) to platelet ratio (GPR) (8) recommended in the literature for the prediction of liver fibrosis.

This study aimed to evaluate the course of fibrosis predictive indices before and after treatment in adult patients treated with DAAs for chronic hepatitis C infection.

Materials and Methods

This cross-sectional study was conducted in the Department of Infectious Diseases and Clinical Microbiology at Ankara Bilkent City Hospital. The hospital where the study was conducted is a reference hospital with approximately 3,800 beds. This hospital was put into service in February 2019. The hospitals that make up this hospital have many years of experience in treating patients with viral hepatitis. However, to obtain more complete data, recruitment was conducted between February 19, 2019 and May 31, 2023.

Patients aged 18 years who were initiated on DAA therapy for chronic hepatitis C by certain outpatient clinics of the infectious diseases and clinical microbiology were included in the study. Patients were not excluded from any reason.

Data were obtained only through the hospital's electronic record system. No data were imputed for missing data. In the standardized data collection form prepared electronically for the study, demographic information, comorbid conditions, possible hepatitis C acquisition routes, HCV genotype, treatment experience, treatment regimen and dates, pre-treatment and post-treatment hemogram, biochemical tests, international normalized ratio and HCV-RNA results and dates, and liver biopsy findings, if any, were recorded. The patients' age at the time of treatment initiation was taken as the basis.

Within the scope of the study, the five indices predicting liver fibrosis for the pre- and post-treatment periods were calculated using the following formulas.

APRI (4) = AST(IU/L)/upper limit of normal (35 IU/L) (IU/L) x 100/platelet (109/L),

FIB-4 (5) = Age (years) x AST (IU/L)/platelet (10^9/L) √ ALT (IU/L),

AAR (6) = AST (IU/L)/ALT (IU/L),

Fibrozis index (7) = 8 - 0.01 x platelet (10^9/L) - serum albumin (g/dL),

GPR (8) = GGT (IU/l)/platelet (10^9/L).

SVR12 was accepted to be an undetectable HCV-RNA at 12 weeks post-treatment and SVR24 at 24 weeks post-treatment.

Ethical Considerations

The protocol of the study was ethically approved by the Ankara Bilkent City Hospital Clinical Research Ethics Committee on June 21, 2023 (approval number: E1-23-3715). The study was conducted according to the ethical principles of the Declaration of Helsinki. Identity information of the individuals was not collected. Because the data were collected retrospectively, informed consent was not obtained from the patients. The findings of the study will be presented as an oral presentation at the 16th National Viral Hepatitis Congress to be held in Antalya on October 12-15, 2023.

Statistical Analysis

Qualitative variables are presented as numbers and percentages, and quantitative variables are presented as medians [interquartile range = (IQR)]. The fit of quantitative variables to normal distribution was evaluated by normality tests (Shapiro-Wilk and Kolmogorov Smirnov) and visually (histogram, defended Q-Q plots). Because of non-normal distribution, pre- and post-treatment comparisons were made using the Wilcoxon signed-rank test. The correlation of the indices with each other was evaluated by Spearman's correlation for both pre- and post-treatment periods. Statistical significance was set as $p<0.05$ (two-sided). Analyses were performed using Statistical Packages for the Social Sciences (IBM Corp., Armonk, New York, U.S.A) version 23 software.

Results

The median age of the 131 patients included in the study was 31 [minimum (min)-maximum (max): 19-83, IQR=27] years. Of the patients 30.5% were female and 82.4% were treatment-naive. All patients were non-sirotic. All 45 patients who were followed up for 12 weeks or longer and 33 patients who were followed up for 24

weeks or longer were negative for HCV-RNA after treatment. The characteristics of the study group are presented in Table 1.

Table 1. Features of chronic hepatitis C patients treated with direct-acting antivirals

	n	%
Male gender	91	69.5
Co-morbidity*		
Substance abuse	52	39.7
Hypertension	18	13.7
Diabetes mellitus	11	8.4
Malignancy	10	7.6
Hepatitis B co-infection	5	3.8
Congestive heart failure	5	3.8
Coronary heart disease	4	3.1
Chronic renal disease	3	2.3
Chronic obstructive pulmonary disease	3	2.3
Human immunodeficiency virus co-infection	2	1.5
Asthma	2	1.5
Hypothyroidism	2	1.5
Hemophilia	2	1.5
Allergic rhinitis	2	1.5
Gastritis	2	1.5
Transmission route of hepatitis C		
Unknown	73	55.7
Intravenous drug use	56	42.7
Hemodialysis	1	0.8
Dental intervention	1	0.8
Genotype of the hepatitis C virus**		
1a	16	12.2
1b	52	39.7
2	15	11.5
3	29	22.1
4	12	9.2
Hepatitis C treatment		
3D regimen	13	9.9
3D regimen + ribavirin	6	4.6
Glecaprevir + pibrentasvir	80	61.1
Sofosbuvir + velpatasvir + voxilaprevir	32	24.4
Experience with hepatitis C treatment		
Treatment-naive	108	87.8
Treatment-experienced***	15	12.2

*There was one patient each with scoliosis, vasculitis, venous insufficiency, seizures, syphilis, and bone tuberculosis. A patient can have more than one disease. **Patients are infected with more than one genotype. ***Two patients had experience with interferon, five patients with pegylated interferon-ribavirin, three patients with 3D regimen, one patient each with sofosbuvir-ledipasvir, glecaprevir-pibrentasvir, and sofosbuvir-velpatasvir- voxilaprevir. The treatment regimens of the two treatment-experienced patients were unknown. Eight patients had missing data

Among the laboratory parameters used in the calculation of the indices, leucocytes, neutrophils, hemoglobin, and thrombocytes increased statistically significantly, whereas ALT, AST, and GGT decreased (Table 2).

Patients were followed up for a median of 183 (min-max: 1-1,396, IQR: 308) days for the hemogram (n=81) and 185 (min-max: 1-1,396, IQR: 329) days for the biochemical tests (n=82) after the end of treatment. The distribution of the indices and HCV-RNA values before and after DAAs is given in Table 3.

Among the indices examined in the pre- and post-treatment periods, AAR had a negative and statistically significant correlation only with FIB-4 in both periods and with GPR in the post-treatment period. There was a moderate positive correlation between the other indices (Table 4).

In the SVR12 confirmed subgroup, there was a statistically significant decrease in all indices except AAR and an increase in AAR before and after DAAs (Table 5).

Discussion

Hepatitis C infections, which are known to cause chronic liver disease, liver fibrosis, cirrhosis, and HCC in their natural course, are now successfully treated virologically (1). In hepatitis B infection, which was successfully suppressed by treatment earlier than hepatitis C, regression of fibrosis, which is believed to be irreversible over time, has been promising. As the number of patients treated with DAAs and the duration of follow-up increases, regression of liver fibrosis will be observed similar to that in hepatitis B (1). Currently, histopathologic examination of the liver, which is the gold standard for the evaluation of liver fibrosis, is not frequently preferred because it requires an interventional procedure. Indices calculated on the imaging and laboratory basis can be used in the evaluation of liver fibrosis (3). According to the results of this study, there was a significant regression in APRI, FIB-4, fibrosis index, and GPR values, indicating regression of liver fibrosis after treatment compared with pretreatment and an increase in AAR.

All patients who could be followed up for SVR were negative. In patients who reached SVR12, there was a significant regression in indices other than AAR, as in the whole group, and a significant increase in AAR. The fact that the results were similar to the overall group in the subgroup where the SVR status was known with certainty suggests that a high viral success was also achieved in the subgroup where the SVR status was not known with certainty.

In a study conducted by Bachofner et al. (9) in three centers and followed 549 patients between November 2013 and December 2015, a significant decrease in APRI and FIB-4 indices was reported in the post-treatment period. In a cohort study of 143 chronic hepatitis C patients receiving DAAs in Hannover, Germany, between 2014 and 2017, a rapid decrease in APRI and FIB-4 indices was observed in the first 24 weeks. It was reported to be more stable after the first 24 weeks, and there was no statistically significant difference. In the transient elastographic examination, a slower but significant decline was recorded between weeks 24 and 96. The group in this study had different characteristics from the group in the present study, as 48% of the participants were cirrhotic and the mean age was 58 years. In particular, the median

Table 2. Distribution of laboratory findings before and after the treatment

	Pretreatment		Posttreatment		
	n	**Median (IQR)**	**n**	**Median (IQR)**	**p-value**
Leucocyte (/µL)	119	7050 (2580)	107	7520 (3390)	**0.015**
Neutrophil (/µL)	119	3970 (2170)	107	4160 (2540)	**0.006**
Lymphocyte (/µL)	119	2150 (840)	107	2220 (1100)	0.22
Hemoglobin (g/dL)	119	14.6 (2.1)	107	14.8 (2.5)	**0.043**
Thrombocyte (x1000/µL)	119	233 (83)	107	235 (81)	**0.047**
Alanine aminotransferase (IU/L)	119	50.0 (72.0)	109	19.0 (11.0)	**<0.001**
Aspartate aminotransferase (IU/L)	118	37.5 (29.0)	109	17.0 (11.0)	**<0.001**
Alkaline phosphatase (IU/L)	98	82.5 (29.0)	90	78.0 (40.0)	0.39
Gamma-glutamyl-transpeptidase (IU/L)	95	30.0 (30.0)	84	19.0 (12.0)	**<0.001**
Total bilirubin (mg/dL)	101	0.60 (0.55)	89	0.60 (0.30)	0.67
Direct bilirubin (mg/dL)	102	0.20 (0.20)	88	0.20 (0.20)	0.44
Albumin (g/L)	104	46 (4)	83	46 (5)	**0.001**
INR	81	1.0 (0.1)	61	1.0 (0.1)	0.33

IQR: Interquartile range, INR: International normalized ratio

Table 3. Distribution of indices for predicting liver fibrosis before and after treatment

	Pre-treatment		**Post-treatment**		
	(n)	**Median (IQR)**	**(n)**	**Median (IQR)**	**p-value**
APRI	117	0.46 (0.55)	107	0.22 (0.17)	<0.001
FIB-4	116	0.78 (0.83)	107	0.67 (0.56)	<0.001
AAR	117	0.68 (0.40)	109	0.93 (0.58)	<0.001
Fibrosis index	103	1.06 (0.98)	82	1.02 (0.86)	0.004
GPR	94	0.15 (0.14)	83	0.08 (0.06)	<0.001
	Pre-treatment		**Post-treatment ≥ 12 weeks**		
	(n)	**Median (IQR)**	**(n)**	**Median (IQR)**	**p-value**
HCV-RNA	45	721443 (2446578)	45	0 (0)	<0.001
	Pre-treatment		**Post-treatment ≥ 24 weeks**		
	(n)	**Median (IQR)**	**(n)**	**Median (IQR)**	**p-value**
HCV-RNA	33	626519 (3400742)	33	0 (0)	<0.001

IQR: Interquartile range, APRI: Aspartate aminotransferase to platelet ratio index, FIB-4: Fibrosis-4 index, AAR: Aspartate aminotransferase to alanine aminotransferase ratio, GPR: Gamma-glutamyl-transpeptidase to platelet ratio, HCV: Hepatitis C virus, RNA: Ribonucleic acid

Table 4. Correlations between the indices predicting liver fibrosis

Pretreatment	**APRI**	**FIB-4**	**AAR**	**Fibrosis index**	**GPR**
APRI	1.000	0.593*	-0.158	0.404*	0.509*
FIB-4		1.000	0.437*	0.526*	0.306*
AAR			1.000	0.066	-0.065
Fibrosis index				1.000	0.236*
GPR					1.000
Posttreatment	**APRI**	**FIB-4**	**AAR**	**Fibrosis index**	**GPR**
APRI	1.000	0.533*	0.179	0.382*	0.591*
FIB-4		1.000	0.541*	0.475*	0.254*
AAR			1.000	0.128	-0.285*
Fibrosis index				1.000	0.422*
GPR					1.000

*P<0.05 in Spearman's correlation, APRI: Aspartate aminotransferase to platelet ratio index, FIB-4: Fibrosis-4 index, AAR: Aspartate aminotransferase to alanine aminotransferase ratio, GPR: Gamma-glutamyl-transpeptidase to platelet ratio

Table 5. Distribution of indices predicting liver fibrosis before and after treatment in patients with sustained viral suppression at week 12 (SVR12)

	Pre-treatment		Post-treatment		
	n	Median (IQR)	n	Median (IQR)	p-value
APRI	43	0.46 (0.34)	44	0.23 (0.15)	<0.001
FIB-4	43	0.87 (0.83)	44	0.75 (0.78)	<0.001
AAR	43	0.81 (0.38)	44	0.91 (0.61)	0.005
Fibrosis index	37	1.20 (0.86)	36	0.99 (0.76)	0.034
GPR	35	0.15 (0.14)	37	0.09 (0.06)	<0.001

IQR: Interquartile range, APRI: Aspartate aminotransferase to platelet ratio index, FIB-4: Fibrosis-4 index, AAR: Aspartate aminotransferase to alanine aminotransferase ratio, GPR: Gamma-glutamyl-transpeptidase to platelet ratio

of the first APRI (2.9) and FIB-4 (1.4) scores were higher compared with our younger group without cirrhotic patients (10).

In a prospective cohort study of 102 chronic hepatitis C patients in Beijing between 2017 and 2019, patients were evaluated at the end of DAA treatment and at 12, 24, and 48 weeks after completion. Significant regression was observed in the APRI and FIB-4 values at the end of treatment. Although there was a regression in subsequent follow-up periods, it was reported to be statistically insignificant. A more significant decrease was found in the metavir 3-4 subgroup (11). The more significant decrease in indices in the cohort in Hannover, which has a high proportion of elderly and cirrhotic patients, and in the subgroup with advanced fibrosis in the cohort in Beijing compared with our group is explained by the fact that the patients in our group were younger and had lower baseline index scores.

In a study involving 50 patients who received treatment between 2016 and 2017, which aimed to evaluate the efficacy of DAAs in chronic hepatitis C patients from Turkey, it was reported that there was a significant regression in APRI and FIB-4 scores until the 12th week compared with baseline, followed by a stable course to the 12th week at weeks 24 and 36 (12).

In a study conducted by Aydın and Köksal (2) in 95 patients who received DAA in a center and who were followed up for at least 12 weeks after treatment, it was found that the APRI and FIB-4 scores of the patients showed a significant decrease in the 4th week of treatment compared with pretreatment, and there was no difference at the end of treatment, i.e., the 12th week. Similar to our group, it was reported that AAR increased significantly at week 4 compared with pretreatment, and there was no significant difference afterwards (2).

APRI, FIB-4, GPR, and the fibrosis index were found to have significant, positive, and moderate correlations with each other before and after treatment. The fact that AAR does not significantly correlate with most of the other indices makes it more disadvantageous than other indices. However, its ease of calculation is an advantage.

Study Limitations

Because this study is a single-center study, the generalizability of the results is limited. In terms of the number of patients evaluated, it has a larger sample size than our country and many single-center studies. However, the retrospective collection of the data and the short follow-up period due to the young age of most patients and possibly reluctance and difficulty in accessing health care services are negatives. A limitation of this study is that the findings related to the indices studied cannot be correlated with liver histopathology as the gold standard.

Conclusion

In conclusion, it is recommended that APRI, FIB-4, GPR, and fibrosis indices, which are used in the prediction of liver fibrosis, should be calculated and followed up at the patient's admission and at the initiation of treatment.

Ethics

Ethics Committee Approval: The protocol of the study was ethically approved by the Ankara Bilkent City Hospital Clinical Research Ethics Committee on June 21, 2023 (approval number: E1-23-3715).

Informed Consent: Because the data were collected retrospectively, informed consent was not obtained from the patients.

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Authorship Contributions

Surgical and Medical Practices: İ.H., A.K.K., R.G., Concept: İ.H., A.K.K., R.G., Design: A.S., R.G., Data Collection and Processing: A.S., Analysis or Interpretation: A.S., İ.H., A.K.K., R.G., Literature Search: A.S., İ.H., A.K.K., R.G.,Writing: A.S., İ.H., A.K.K., R.G.

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