Influence of Sustained Virological Response on APRI in Chronic Hepatitis C: is APRI a Marker of Only the Stage of Fibrosis?

Kronik Hepatit C'de Sürekli Virolojik Yanıtın APRI Üzerindeki Etkisi: APRI Sadece Fibrozis Evresinin Bir Belirteci mi?

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ABSTRACT

Objectives: Aspartate transaminase (AST) to platelet ratio index (APRI) is widely used to predict the stage of liver fibrosis in patients with chronic hepatit C virus (HCV) infection. In this study, we aimed to evaluate changes in APRI scores in patients with chronic HCV infection who received pegylated interferon (PEG IFN) + ribavirin or direct acting antiviral (DAA) ± ribavirin.

Materials and Methods: We retrospectively reviewed our data of patients with chronic HCV infection who received PEG IFN + ribavirin or DAA ± ribavirin. Patients were classified into 3 groups according to sustained virological response (SVR) by treatment regimens: a) SVR with PEG IFN + ribavirin (PEG IFN-SVR), b) non SVR with PEG IFN + ribavirin (PEG IFN-non SVR), c) SVR with DAA ± ribavirin (DAA-SVR).

Results: The study included 156 patients. APRI scores decreased significantly in PEG IFN-SVR (1.17±1.37 vs 0.38±0.35) and DAA-SVR groups (0.99±0.88 vs 0.31±0.16) (both p=0.001), whereas it did not change in PEG IFN-non SVR group (1.26±1.07 vs 1.33±1.36) (p=0.810) after treatment. In PEG IFN-SVR and DAA-SVR groups, proportions of patients who had APRI scores ≤0.5 and ≤1 increased, while proportions of patients who had APRI scores >1.5 and >2 decreased significantly after treatment (all p<0.05).

Conclusion: APRI score is not indicator of only the stage of fibrosis. Hepatic necroinflammation also influences APRI score by increasing AST levels and decreasing platelet levels.

Keywords: HCV, APRI, fibrosis, necroinflammation

ÖZ

Amaç: Aspartat transaminaz (AST)/trombosit oranı indeksi (APRI), kronik hepatit C virüsü (HCV) enfeksiyonu olan hastalarda karaciğer fibrozisinin evresini tahmin etmek için yaygın olarak kullanılmaktadır. Bu çalışmada, pegile interferon (PEG IFN) + ribavirin veya direkt antiviral ajan (DAA) ± ribavirin tedavisi alan kronik HCV enfeksiyonlu hastalarda APRI skorlarındaki değişiklikleri araştırmayı amaçladık.

Gereç ve Yöntemler: PEG IFN + ribavirin veya DAA + ribavirin tedavisi görmüş kronik HCV enfeksiyonlu hastaların verilerini retrospektif olarak gözden geçirdik. Hastalar tedavi rejimleri ve kalıcı virolojik yanıta (KVY) göre 3 gruba ayrıldı a) PEG IFN + ribavirin ile KVY (PEG IFN-SVR), b) PEG IFN + ribavirin ile KVY elde edemeyen (PEG IFN-non SVR), c) DAA ± ribavirin ile KVY elde edilen (DAA-SVR).

Bulgular: Çalışmaya 156 hasta dahil edildi. APRI skorlarının, PEG IFN-SVR (1,17±1,37'ye karşı 0,38±0,35) ve DAA-SVR gruplarında (0,99±0,88'e karşı 0,31±0,16) önemli ölçüde azaldığı görüldü (her ikisi p=0,001). Buna karşın PEG IFN-non SVR grubunda (1,26±1,07 vs 1,33±1,36) ise tedavi sonrası anlamlı değişim görülmedi (p=0,810). PEG IFN-SVR ve DAA-SVR gruplarında, APRI skorları ≤0,5 ve ≤1 olan hastaların oranı artarken, APRI skorları >1,5 ve >2 olan hastaların oranı tedaviden sonra anlamlı olarak azaldı (tümü p<0,05). PEG IFN-non SVR grubunda ise APRI skorları ≤0,5, >1,5, ≤1 ve >2 olan hastaların oranı değişmedi (p>0,05).

Sonuç: APRI skoru, sadece fibrozisin evresinin göstergesi değildir. Hepatik nekroinflamasyon, AST seviyelerini artırarak ve trombosit seviyelerini düşürerek APRI skorunu da etkiler.

Anahtar Kelimeler: HCV, APRI, fibrozis, nekroinflamasyon

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Introduction

Chronic hepatitis C virus (HCV) infection is one of the most common causes of chronic hepatitis, cirrhosis, liver failure, hepatocellular carcinoma (HCC) and death from liver disease (1). Chronic hepatitis C (CHC) related decompansated cirrhosis and HCC are the leading indications for liver transplantation in developed countries (2). In CHC, the aim of therapy is to achieve sustained virological response (SVR) (3). SVR is associated with regression of liver fibrosis and cirrhosis, and reduction in the risk of HCC development at long term follow-up (4). With the use of direct acting antiviral agents (DAA), >95% of patients achieve SVR (5). In CHC, the stage of liver fibrosis is important for deciding to start antiviral treatment and estimating prognosis. The antiviral therapy may be delayed in patients with no or mild fibrosis, while it should be started in patients with significant fibrosis and cirrhosis (6). Those patients with significant fibrosis and cirrhosis must also be under HCC surveillance.

Although liver biopsy is the gold standard method to define the stage of fibrosis, it has several limitations. The biopsy specimen represents 1/50,000 of the liver which leads to under- or overestimation of the stage of fibrosis (7). Moreover, it is invasive and has serious complications including pain, bleeding and even death. It is also costly (8). In order to overcome these limitations, several non-invasive tests have been developed to predict significant fibrosis and cirrhosis. Since APRI score is based on readily available blood tests and thus is costless, it is the most widely used of these tests (9).

However, APRI may be elevated not only due to advanced stage of fibrosis but also due to high degree of hepatic necroinflammation. APRI score is based on aspartate aminotransferase (AST) and platelet levels. In CHC, hepatic necroinflamation leads to increase in not only alanine aminotransferase (ALT) but also AST levels. This in turn may lead to elevated APRI score and thus overestimation of the stage of fibrosis. On the other hand, AST and ALT levels decrease after SVR due to the resolution of hepatic necroinflammation. However, the same is not true for fibrosis (10). So, increased APRI score may reflect high histological activity index in conjunction the stage of fibrosis.

The aim of the present study is to evaluate changes in APRI score in patients with chronic HCV infection who received pegylated interferon (PEG IFN) + ribavirin and DAA ± ribavirin treatment.

Materials and Methods

We retrospectively reviewed our data of patients with chronic HCV infection who admitted to gastroenterology clinic between 2003 and 2018. The patients were included in the study if they 1) were ≥18 years-old, 2) had anti HCV and HCV RNA positivity for at least 6 months, 3) had liver biopsy result before antiviral treatment, 4) had laboratory test results allowing calculation of APRI score, and serum HCV RNA levels prior to and 24 weeks after treatment, 5) received PEG IFN + ribavirin or DAA ± ribavirin including either sofosbuvir/ledipasvir or ombitasvir/paritaprevir/ritonavir + dasabuvir. Patients were excluded if they 1) were <18 years-old, 2) had coinfection with hepatitis B virus and/or human immunodeficiency

virus, 3) had other etiology for chronic liver diseases, 4) had history of liver transplantation and HCC. One hundred and fifty six patients who met the inclusion criteria were included in the study.

The laboratory test results including AST, ALT, alkaline phosphatase (ALP), gamma-glutamyl transferase (GGT) and upper limit of normal (ULN) values of each test, and platelet values prior to and 24 weeks after treatment were recorded. We calculated APRI scores at corresponding time points according to the following formula: (AST/ULN)/platelet ×100. The thresholds of APRI were ≤0.5 and >1.5 for the exclusion and prediction of significant fibrosis, and ≤1 and >2 for the exclusion and prediction of cirrhosis (11).

All biopsy specimens were analyzed by a single pathologist experienced in hepatopathology. The stage of fibrosis was scored according to the ISHAK system (12). Significant fibrosis was defined as F3-6 and cirhosis as F5-6.

SVR was defined as negative HCV RNA at 24th week after the end of treatment in patients who received PEG IFN + ribavirin or DAA ± ribavirin. Non SVR was defined as any treatment outcome other than SVR. Patients were classified into 3 groups according to SVR by treatment regimens: a) SVR with PEG IFN + ribavirin (PEG IFN-SVR), b) non-SVR with PEG IFN + ribavirin (PEG IFN-non SVR), c) SVR with DAA (DAA-SVR).

Local Ethic Committee approval was taken from the University of Health Sciences Turkey, Haydarpaşa Numune Training and Research Hospaital (approval number: 771/12/2018-14).

Statistical Analysis

We compared APRI scores at baseline and at the 24th week after treatment in each group. We also compared proportions of patients who had APRI scores ≤0.5, >1.5, ≤1 and >2 at baseline and at week 24 after treatment in each group.

Continuous variables were presented as means ± standard deviation, and categorical variables as number (%). Means of metric variables were assessed by using paired Sample test. McNemar's test was used for two groups with paired data. ANOVA test was applied for all group comparisons. Level of significance was defined as p<0.05. Statistical analyses were performed by using SPSS v.23.0 (SPSS, Inc, Chicago, IL, USA) for Windows.

Results

In total, 156 patients were included in the study. All patients were Caucasian. Of them, 108 received PEG IFN + ribavirin and 48 received DAA ± ribavirin treatment. Of the patients who received PEG IFN + ribavirin, 59 achieved SVR and 49 did not achieve SVR. All patients who received DAA ± ribavirin achieved SVR.

The mean ages of patients in groups PEG IFN-SVR, PEG IFN-non SVR and DAA-SVR were 52.64±9.89, 56.29±9.06 and 58.65±10.92 years, respectively (p=0.008). The groups were similar in terms of gender (p=0.170). The proportions of patients with significant fibrosis and cirrhosis in each group were 25.4%, 59.2% and 81.2% (p=0.001), and 11.9%, 42.9% and 22.9% (p=0.002), respectively. Baseline characteristics of patients are shown in (Table 1).

There were significant decreases in AST/ULN and ALT/ULN at the 24th week after treatment in comparison to pretreatment values in all 3 groups (all p<0.05). The platelet levels did not change in PEG

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IFN-SVR group (p=0.800), decreased in PEG IFN-non SVR group (p=0.010) and increased in DAA-SVR group (p=0.005) at the 24th week after treatment in comparison to baseline. APRI decreased significantly in PEG IFN-SVR and DAA-SVR groups (both p=0.001), while it did not change in PEG IFN-non SVR group (p=0.810) at the 24th week after treatment in comparison to baseline (Table 2).

In group PEG IFN-SVR, proportions of patients who had APRI scores ≤0.5 (from 35.6% to 84.7%) and ≤1 (from 69.5% to 96.6%) increased, while proportions of patients who had APRI scores >1.5 (from 22.0% to 3.4%) and >2 (from 13.6% to 1.7%) decreased significantly at the 24th after treatment in comparison to baseline (all p<0.05). In group DAA-SVR, proportions of patients who had APRI scores ≤0.5 (from 35.4% to 87.5%) and ≤1 (from 66.7% to 100.0%) increased, while proportions of patients who had APRI scores >1.5 (from 18.7% to 0.0%) and >2 (from 12.5% to 0.0%) decreased significantly at week 24 after treatment in comparison to baseline (all p<0.05). In group PEG IFN-non SVR, proportions of patients who had APRI scores ≤0.5, >1.5, ≤1 and >2 did not change (all p>0.05) (Table 3).

Discussion

In the present study, we evaluated changes in APRI scores in CHC patients after treatment. In the patients who achieved SVR with either PEG IFN + ribavirin or DAA ± ribavirin, APRI scores decreased significantly at the 24th week after treatment. On the other hand, APRI scores did not change in those patients who did not achieve SVR. Moreover, proportions of those who had APRI scores ≤0.5 and ≤1 increased, while proportion of patients who had APRI scores >1.5 and >2 decreased significantly after achieving SVR with either PEG IFN + ribavirin or DAA ± ribavirin. In contrast, they did not change in patients who did not achieve SVR. Our findings were consistent with the existing literature which evaluated changes in several noninvasive tests in CHC patients after treatment.

Bachofner et al. (13) assessed changes in APRI scores in 392 patients with chronic HCV infection who received DAA treatment. They reported that APRI scores decreased significantly from 1.07 to 0.41 in patients with SVR. Moreover, all the patients with SVR had APRI scores below the cut off values for the prediction of significant fibrosis. Similar to our study, APRI scores in SVR

Table 1. Baseline characteristics of patients

	PEG IFN-SVR (n=59)	PEG IFN-non-SVR (n=49)	DAA-SVR (n=48)	p
Age (mean ± SD)	52.64±9.89	56.29±9.06	58.65±10.92	0.008
Gender (male, %)	34 (57.6)	23 (46.9)	19 (39.6)	0.170
HCV RNA (mean ± SD, IU/mL)	4.865.062±10.450.502	3.406.105±4.769.597	7.672.239±7.503.896	0.030
Genotype, n (%)				
G1	44 (74.6)	47 (95.9)	41 (85.4)	0.001
Non-G1	3 (5.1)	0 (0)	7 (14.6)	0.001
Unknown	12 (20.3)	2 (4.1)	0 (0)	0.001
Fibrosis, n (%)				
F0-2	44 (74.6)	20 (40.8)	9 (18.8)	0.001
F3-6	15 (25.4)	29 (59.2)	39 (81.2)	0.001
F0-4	52(88.1)	28 (57.1)	37 (77.1)	0.030
F5-6	7(11.9)	21 (42.9)	11 (22.9)	0.002
SD: Standard deviation, PEG IFN: Pegylated interferon, SVR: Sustained virological response, DAA: Direct acting antivirals				

Table 2. Changes in laboratory parameters and APRI scores at week 24 after treatment in comparison to baseline

	PEG IFN-SVR (n=59)			PEG IFN-non SVR (n=49)			DAA-SVR (n=48)		
	Baseline Mean ± SD	Post-Tx Mean ± SD	p	Baseline Mean ± SD	Post-Tx Mean ± SD	p	Baseline Mean ± SD	Post-Tx Mean ± SD	p
AST/ULN	1.91±1.53	0.69±0.41	0.001	1.79±1.20	1.61±0.80	0.010	1.59±1.04	0.59±0.17	0.001
ALT/ULN	2.03±1.66	0.53±0.48	0.001	1.56±0.86	1.46±0.73	0.010	1.82±1.54	0.48±0.26	0.001
ALP/ULN	0.63±0.24	0.56±0.24	0.001	0.62±0.21	0.58±0.26	0.300	0.62±0.29	0.56±0.26	0.080
GGT/ULN	1.01±1.04	0.50±0.45	0.001	1.65±1.36	1.14±0.97	0.520	1.57±1.77	0.67±0.83	0.001
Platelet (x10⁹/L)	207.75±70.18	210.81±63.42	0.800	170.59±57.51	164.88±63.17	0.010	194.90±63.08	215.23±76.07	0.005
APRI	1.17±1.37	0.38±0.35	0.001	1.26±1.07	1.33±1.36	0.810	0.99±0.88	0.31±0.16	0.001
PEG IFN: Pegylated interferon, SVR: Sustained virological response, DAA: Direct acting antivirals, Post-Tx: Post-treatment, ULN: Upper limit of normal, AST: Aspartate transferase, ALT: Alanine transferase, ALP: Alkaline phosphatase, GGT: Gamma-glutamyl transferase, APRI: AST to platelet ratio index, SD: Standard deviation									

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Table 3. Changes in APRI scores at week 24 after treatment in comparison to baseline according to cut off values

APRI	PEG IFN-SVR (n=59)			PEG IFN-non-SVR (n=49)			DAA-SVR (n=48)		
	Pre tx	Post tx	p	Pre tx	Post tx	p	Pre tx	Post tx	p
≤0.5	21 (35.6)	50 (84.7)		11 (22.4)	12 (24.5)		17 (35.4)	42 (87.5)	
>0,5	28 (64.4)	9 (15.3)	0.010	38 (77.6)	37 (75.5)	0.890	31 (64.6)	6 (12.5)	0.001
≤1,5	46 (78.0)	57 (96.6)		37 (75.5)	36 (73.5)		39 (81.3)	48 (100.0)	
>1.5	13 (22.0)	2 (3.4)	0.003	12 (24.5)	13 (26.5)	0.310	9 (18.7)	0 (0)	0.004
≤1	41 (69.5)	57 (96.6)		28 (57.1)	28 (57.1)		32 (66.7)	48 (100.0)	
>1	18 (30.5)	2 (3.4)	0.001	21 (42.9)	21 (42.9)	0.920	16 (33.3)	0 (0)	0.001
≤2	51 (86.4)	58 (98.3)		42 (85.7)	41 (83.7)		42 (87.5)	48 (100.0)	
>2	8 (13.6)	1 (1.7)	0.040	7 (14.3)	8 (16.3)	0.170	6 (12.5)	0 (0)	0.030

PEG IFN: Pegylated interferon, SVR: Sustained viral response, DAA: Direct acting antivirals, Post-Tx: Post-treatment, APRI: AST to platelet ratio index

patients were significantly decreased, while they remained high in non SVR patients. They evaluated changes in transient elastograpy (TE) and FIB-4 scores as well. Not only APRI scores, but also TE and FIB-4 scores decreased in SVR patients. They concluded that suppression of viral replication might cause decreases in non-invasive tests without fibrosis regression. Similarly, Chekuri et al. (14) assessed changes in TE in patients who achieved SVR with either IFN-containing and IFN-free regimens. In both groups, liver stiffness decreased significantly 24 weeks after treatment. Decrease in LS was more significant in patients with cirrhosis than non-cirrhotics. However, 60% of LS-proven cirrhotic patients still had cirrhosis after therapy and LS remained unchanged beyond 24 weeks.

It is known that stage of fibrosis regresses after achieving SVR. However, it does not regress as rapidly as hepatic necroinflammation after successful treatment. Petrenkiene et al. (15) performed liver biopsy before and 24 weeks after treatment in patients who received IFN and ribavirin. In that study, histological activity index decreased significantly in both SVR and non-SVR groups after treatment. However, the stage of fibrosis remained unchanged even in patients who achieved SVR. Huang et al. (16) assessed changes in several non-invasive fibrosis scores in 40 CHC patients who achieved SVR with DAA. They assessed changes in histological changes in paired liver biopsy specimens 24 weeks after treatment as well. In that study, the degree inflammation improved and the stage fibrosis regressed in 83% and 38% of patients, respectively after achieving SVR. Decrease in APRI scores were similar in both patients with or without fibrosis regression (16). Briefly, 24 weeks after treatment is too short for fibrosis scores to improve and it occurs several years after treatment (17). So, rapid decrease in APRI and other non-invasive scores can not be the result of fibrosis regression. Rather, it can be due to rapid resolution of hepatic necroinflammation after SVR.

The effect of hepatic necroinflammation on non-invasive fibrosis scores was shown in several studies. Fujita et al. evaluated the effect of hepatic necroinflammation on various noninvasive scores including APRI in 122 patients with CHC (18). In that study, non-invasive scores were shown to be influenced by the grade of histological activity. This is also true for serum ALT levels, since ALT levels were higher in patients with high grade of histological activity than those with low grade of histological activity in the same stage of fibrosis. The depending on histopathological examination, they indicated that ALT level might be a significant predictor for necroinflammatory activity. Huang et al. (16) showed that APRI scores were higher in patients with more severe inflamation and advanced fibrosis.

Similarly, liver stiffness was shown to be increased significantly in patients with more severe inflammation than in those with less severe inflammation especially in more advanced stages. In a study by Vispo et al. (19), patients with ALT >100 IU/L had higher liver stiffness measurements than those with ALT <100 IU/L regardless of the stage of fibrosis. This indicates that intense hepatic necroinflammation leads to overestimation of the stage of fibrosis with using TE (19).

It is clear that decrease in AST levels is the result of resolution of hepatic necroinflammation after achieving SVR. In the present study, AST and ALT levels decreased in all 3 patient groups. However, the decrease in AST and ALT levels were more significant in patients who achieved SVR. Besides the decrease in AST levels, increased platelet levels also contribute to the decrease in APRI scores in patients who achieved SVR (14). The main reason for increased platelet levels after SVR seems to be decrease in portal venous pressure. Despite the persistence of liver fibrosis, resolution of hepatic oedema associated with hepatic necroinflammation might lead to decrease in portal venous pressure and increase in platelet levels (20). In the present study, platelet levels increased in patients who achieved SVR with DAA + ribavirin and did not change in those who achieved SVR with PEG IFN + ribavirin. In contrast, platelet levels decreased in patients who did not achieve SVR. The decrease in APRI in patients who achieved SVR can be attributed to decreased AST levels along with increased or stable platelet levels.

According to the aforementioned studies and our study, it is clear that not only fibrosis but also hepatic necroinflammation influence APRI and the other noninvasive scores in CHC. All of these scores can overestimate the stage of fibrosis in patients with high necroinflammatory activity, while they can underestimate in those with low histological necroinflammatory activity in any given stage. If high APRI scores had indicated only the stage of liver fibrosis, the decrease in APRI scores would have indicated the regression of fibrosis and even cirrhosis immediately after SVR.

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Study Limitations

Our study has some limitations. The study included small number of patients and was retrospective. Moreover, patients did not have paired liver biopsy samples after treatment. Therefore, correlation between APRI and the stage of liver fibrosis after treatment can not be assessed. However, the stage of liver fibrosis is not expected to change as early as 24 weeks after treatment.

Conclusion

In conclusion, non-invasive fibrosis scores including APRI should not be the indicator of only the stage of fibrosis. Hepatic necroinflammation also influences APRI score by increasing AST levels and decreasing platelet levels. After successfull treatment of CHC, APRI scores decrease significantly; however, this can not correspond to regression of significant fibrosis and cirrhosis.

Ethics

Ethics Committee Approval: Local Ethic Committee approval was taken from the University of Health Sciences Turkey, Haydarpaşa Numune Training and Research Hospaital (approval number: 771/12/2018-14).

Informed Consent: It wasn't obtained.

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Authorship Contributions

Concept: Ö.B., F.G., Design: Ö.B., F.G., Supervision: F.G., Materials: C.S., Data Collection or Processing: S.Ö., H.Ş., M.K., E.K., A.G.D.S., Analysis or Interpretation: S.Ö., H.Ş., M.K., E.K., A.G.D.S., Literature Search: C.S., Writing: Ö.B., C.S.

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