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Simple non-invasive markers as a predictor of fibrosis and viral response in chronic hepatitis C patients

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Background/aims: *Chronic hepatitis C has a high prevalence and leads to development of cirrhosis and hepatocellular carcinoma. Liver fibrosis staging is one of the main factors that influence the decision to indicate therapy for chronic hepatitis C carriers. Several simple laboratory tests, scores and indices have been proposed for the non-invasive prediction of hepatic fibrosis in patients with chronic hepatitis C. The purpose of this study was to evaluate non-invasive liver fibrosis tests as a predictive factor of fibrosis and non-sustained viral response (relapse/non-responder) in chronic hepatitis C naive patients.* ***Materials and Methods:*** *We performed a retrospective case-control study with utilization of non-invasive liver fibrosis test, platelet count, aspartate aminotransferase/alanine aminotransferase ratio, age-platelet index and aspartate aminotransferase to platelet ratio index, as a predictor of non-sustained viral response in chronic hepatitis C naive patients between July 2008 and August 2010 in İzmir Atatürk Training and Research Hospital.* ***Results:*** *We observed non-invasive liver fibrosis test to be highly effective in predicting non-sustained viral response patients, especially with age-platelet index (Accuracy=73%, OR=6.93, 95% CI, 2.41-19.8). A strong relationship was shown with multivariate analysis between non-sustained viral response and some non-invasive liver fibrosis tests such as viral load (OR=4.51, 95% CI, 1.16 –17.6, p=0.03) and age-platelet index (OR=11.8, 95% CI, 2.25-62.15, p=0.004).* ***Conclusions:*** *If non-invasive tests could be standardized according to age, gender, race, and body mass index and individualized according to the fibrosis, then a nearly full correlation of non-invasive liver fibrosis test with histologic results could be obtained, stage of fibrosis could be predicted initially, sustained viral response/non-sustained viral response could be estimated, and the need for a repeat biopsy could be eliminated.*

Key words: Chronic hepatitis C, fibrosis, non-invasive tests, non-sustained viral response

Kronik hepatit C hastalarında fibrozis ve viral yanıtı öngörmede basit non-invaziv belirteçler

Amaç: *Kronik hepatit C'nin prevalansı yüksek olup, sirozis ve hepatosellüler karsinom gelişmesine neden olur. Kronik hepatit C taşıyıcılarında tedavi kararını etkileyen esas faktörlerden biri karaciğer fibrozisinin derecesidir. Kronik hepatit C hastalarında hepatik fibrozisi non-invaziv olarak öngörmede, bir kaç basit laboratuvar test, skor ve indeks önerilmektedir. Bu çalışmanın amacı, kronik hepatit C hastalarında tedaviye cevapsızlığı (relaps/non-responder) ve fibrozisi öngörmede non-invaziv karaciğer fibrozis testlerini değerlendirmekti.* ***Gereç ve Yöntem:*** *İzmir Atatürk Eğitim ve Araştırma Hastanesinde Temmuz 2008 ile Ağustos 2008 tarihleri arasında naiv kronik hepatit C hastalarında platelet sayısı, aspartat aminotransferaz/alanin aminotransferaz oranı, yaş platelet indeksi ve aspartat aminotransferaz/platelet oranı gibi, non-invaziv karaciğer fibrozis testleri kaydedilerek retrospektif vaka kontrol çalışması yapıldı.* ***Bulgular:*** *Non-invaziv karaciğer fibrozis testlerini tedaviye cevapsız hastaları öngörmede, özellikle yaş-platelet indeksi olmak üzere, oldukça etkin saptadık (Doğruluk=73%, OR=6.93, 95% CI, 2.41-19.8). Yapılan çoklu analizde tedaviye cevapsızlık ve viral yük, yaş-platelet indeksi gibi bazı non-invaziv karaciğer fibrozis testleri arasında güçlü bir ilişki saptadık.* ***Sonuç:*** *Non-invaziv testler yaş, cinsiyet, ırk, vücut kitle indeksi ve fibrozise gore bireyselleştirilebilirse, histolojik sonuçlarla tama yakın korelasyon sağlanabilir, fibrozisin derecesi başlangıçta öngörülebilir, tedaviye cevap/cevapsızlık tahmin edilebilir ve tekrarlayan biyopsi ihtiyacı ortadan kalkabilir.*

Anahtar kelimeler: Kronik hepatit C, fibrozis, non-invaziv testler, non-SVR

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INTRODUCTION

Chronic hepatitis C (CHC) has a high prevalence and leads to development of cirrhosis and hepatocellular carcinoma. The most important issue is the therapeutic decision-making based on histopathological results. Knowledge of the stage of liver fibrosis is essential for determining prognosis and decisions for antiviral treatment (1,2).

Sustained virological response (SVR) is defined as the absence of hepatitis C virus (HCV) RNA from serum by a sensitive polymerase chain reaction (PCR) assay, 24 weeks following discontinuation of therapy. Relapse is defined as reappearance of HCV RNA in serum after therapy is discontinued and non-responder as failure to clear HCV RNA from serum after 24 weeks of therapy (3).

There are factors identified as predictors of SVR among patients who received polyethylene glycol-interferon (PEG-IFN) and ribavirin, including HCV genotype other than 1, viral load less than 600,000 IU/ml, age of 40 years or less, body weight of 75 kg or less, and the absence of bridging fibrosis/cirrhosis (4,5). Infection with genotype 2 or 3, low viral load, and absence of advanced hepatic fibrosis have consistently been identified as independent predictors of SVR (6).

To overcome the need to perform liver biopsy and in an attempt to predict the degree of liver fibrosis, a number of non-invasive liver fibrosis tests (NILFTs) have been proposed. These tests have been extensively investigated, especially in patients with CHC (7). Several simple laboratory tests, scores and indices have been proposed for the non-invasive prediction of hepatic fibrosis in patients with CHC (8). Among these tests are platelet count (9), aspartate/alanine aminotransferase (AST/ALT) ratio (8), age-platelet index (10), and AST to platelet ratio index (APRI) score (9).

Liver biopsy is a costly and invasive procedure, associated with pain and discomfort, which renders it not well accepted by patients, especially when it has to be repeated frequently. Furthermore, infrequent but serious complications such as profuse bleeding may occur (11). The purpose of this study was to evaluate NILFTs as a predictive factor of fibrosis and relapse/non-responder (non-SVR) in CHC naive patients.

MATERIALS AND METHODS

Study Design

We performed a retrospective case-control study with utilization of NILFT, platelet count, AST/ALT ratio, age-platelet index and APRI, as a predictor of non-SVR (relapse/non-responder) in CHC naive patients between July 2008 and August 2010 in İzmir Atatürk Training and Research Hospital. We also reviewed retrospectively the medical records of CHC naive patients who were evaluated for therapy with PEG-IFN alpha-2b (1.5 mg/kg per week) or PEG-IFN alpha-2a (180 mg/kg per week) and ribavirin (>75 kg: 1200 mg and <75 kg: 1000 mg). First, we evaluated the sensitivity of NILFTs and the correlation with fibrosis scores, and then we evaluated those NILFT results that were correlated with fibrosis for their prognostic significance in non-SVR patients.

Study Patients

Patients were eligible for the study if they were between the ages of 18 and 75 years, had chronic HCV infection, had no history of treatment of HCV infection, and had HCV RNA- positive serum (at least >50 IU/ml) according to a real time (RT)-PCR (Cobas Amplicor HCV v2.0, Roche Molecular Systems). Patients were excluded if they had poorly controlled psychiatric disease, solid organ transplant, autoimmune condition, thyroid disease, hemoglobin level of 12 g/dl or lower, a neutrophil count of 1500 per cubic millimeter or lower, a platelet count of 75,000 per cubic millimeter or lower, drug abuse within the previous 12 months or alcohol abuse within the previous 6 months, and HBV or human immunodeficiency virus (HIV) co-infection.

Non-Invasive Liver Fibrosis Tests and Liver Histology

Platelets were counted on a Cell-Dyn 4000 System (Abbott Diagnostics, Abbott Park, IL, USA). The international normalized ratio (INR) was measured on an Acl-Futura-Plus (Instrumentation Laboratory, Barcelona, Spain). Serum total cholesterol, ALT, AST and gamma-glutamyl transpeptidase (GGT) activities were measured with Roche reagents in a Roche-Hitachi Modular-P800 clinical chemistry module (Roche, Mannheim, Germany). AST upper normal limits were 34 IU/L. The AST/ALT ratio is the ratio of AST to ALT. The APRI index was determined according to Wai et al. (9) as follows: (actual AST concentration divided by its upper normal limit)/platelet counts (10^9 /L)x100. Age-platelet index was calculated by adding up scores awarded to the following patient laboratory results (possible value of 0-10): age (in years) <30=0, 30-39=1, 40-49=2, 50-59=3, 60-69=4,

>70=5; and platelet count (10^9 /L): >225=0, 200-224=1, 175-199=2, 150-174=3, 125-150=4, <125=5 (10). For all these tests, blood was collected under fasting conditions.

Grading and staging scores were calculated according to the method of Ishak et al. (12). All histological studies were performed by a single experienced histopathologist.

Statistical Analysis

Statistical analysis of data was performed using the Statistical Package for the Social Sciences (SPSS) for Windows (version 17.0) and the MedCalc program version 7.6 (MedCalc Software, Mariakerke, Belgium). Continuous variables were presented as medians (range) and categorical variables as frequencies. Differences in the indices of NILFT among the two study groups were determined by Mann-Whitney U test. The associations between categorical variables were investigated by means of the Pearson chi-squared test. The diagnostic performances of NILFT in identifying patients with significant liver fibrosis were assessed by plotting receiver operating characteristic (ROC) curves and calculating the areas under the ROC curves (AUROC). Sensitivity, specificity, positive and negative predictive values (PPV, NPV), accuracy and odds ratio (OR) of NILFT were also calculated. To adjust for the effects of potential confounders, we used logistic regression models. Values of $p \leq 0.05$ were considered significant.

RESULTS

Patients

We evaluated 212 patients, and 55 of them developed SVR. We observed non-response in 20 patients and relapse in 14 patients. The drugs were withdrawn because of side effects in 9 patients. Fifty-two patients are still continuing therapy. A total of 62 patients were not given therapy for the following reasons: low biopsy scores in 4 patients, spontaneous clearance in 4 patients at clinical follow-up, and various reasons in 54 patients, such as severe neuropsychiatric disorders, severe depression, autoimmune diseases, and advanced age, etc. Patients were allocated into two groups as patients with SVR and non-SVR (relapse/non-responders). Twenty-seven (49%) patients were female and 28 (51%) were male in the SVR group, while 12 (35%) were female and 27 (65%) were male in the non-SVR group ($p>0.5$). The mean age of our subjects was 50.7 (21-68) years in the SVR group and 53.5 (31-68) in the non-SVR group ($p>0.5$). All of them had genotype 1 (Table 1).

There was a statistically significant difference between the two groups regarding ALT levels ($p=0.026$), GGT ($p=0.035$), HCV RNA level ($p=0.017$), liver fibrosis ($p<0.001$), and AST/ALT ratio ($p<0.001$), but no statistically significant difference between groups as to weight (kg), total cholesterol, low-density lipoprotein (LDL), triglyceride, ferritin, AST, and platelet count (Table 1).

Table 1. Demographic, histopathological and laboratory data, and NILFT scores of SVR and non-SVR patients

Variable	SVR (n=55)	Non-SVR (n=34)	p
Age (years)	52.7 (21-68)	53.3 (31-68)	NS
Gender (female/male)	28/27	22/12	NS
Weight (kg)	75.5±13.4	81.6±26.8	NS
Total cholesterol (mg/dl)	160.1±32.3	140.4±38.5	NS
LDL (mg/dl)	91.4±30.6	88.9±52.1	NS
Triglyceride (mg/dl)	118.6±54.2	135.6±38.7	NS
Ferritin (ng/ml)	210.6±287.6	300.5±373.6	NS
AST (U/L)	57.0±50.6	46.6±18.1	NS
ALT (U/L)	76.5±73.1	47.7±17.5	0.026
HCV-RNA (IU/ml)	2049492±3,9x10^6	6533253±1.18X10^7	0.017
Liver biopsy (stage)	1.88±1.66	3.88±1.36	<0.001
Platelet count	235920±77115	191980±56584	NS
AST/ALT ratio	0.79±0.18	1.00±0.30	< 0.001
APRI score	0.86±0.92	0.80±0.40	NS
Age-platelet index	4.00±2.19	5.00±2.09	0.023
GGT (U/L)	73.9±78.7	90.3±71.6	0.035

LDL: Low-density lipoprotein. AST: Aspartate aminotransferase. ALT: Alanine aminotransferase. HCV: Hepatitis C virus. APRI: Aspartate aminotransferase/platelet ratio index. GGT: Gamma glutamyl transferase. NS: Non-specific.

The Relation between NILFT and Advanced Fibrosis

We observed a correlation between liver fibrosis (Ishak fibrosis scores 5 and 6) and NILFT. Correlation coefficients were determined for platelet count, AST/ALT ratio, APRI score, and age-platelet index, r=0.39 (p<0.001), r=0.18 (p=0.021), r=0.42 (p<0.001), and r=0.44 (p<0.001), respectively (Figure 1). We calculated sensitivity, specificity, PPD, NPD, accuracy, and OR of NILFT for advanced liver fibrosis (Table 2). The results were as follows: sensitivity 38%, specificity 76%, PPV 24%, NPV 87%, accuracy 70%, OR=2.03 (95% confidence interval [CI], 0.61-6.80) for APRI; sensitivity 75%, specificity 76%, PPV 14%, NPV 98%, accuracy 76%, OR=9.67 (95% CI, 1.27-70.9) for platelet count (<120,000); sensitivity 30%, specificity 100%, PPV 100%, NPV 22%, and accuracy 42% for AST/ALT ratio (>0.62); and sensitivity 43%, specificity 84%, PPV 62%, NPV 72%, accuracy 69%, and OR=4.11 (95% CI, 1.47-11.4) for age-platelet index (>5) (Table 2).

Non-SVR Patients and NILFT Findings

We evaluated NILFT in predicting non-SVR patients. The results were as follows: sensitivity 23%, specificity 59%, PPV 9%, NPV 82%, and accuracy 54% for APRI (>1.5); sensitivity 67%, specificity 63%, PPV 91%, NPV 20%, and accuracy 63% for platelet count (<120,000); sensitivity 42%, specificity 79%, PPV 70%, NPV 74%, and accuracy 73% for AST/ALT ratio (cut-off value >0.62); sensitivity 55%, specificity 85%, PPV 70%, NPV 74%, and accuracy 73% for age-platelet index (cut-off value >5); and sensitivity 62%, specificity 67%, PPV 40%, NPV 83%, and accuracy 65% for high fibrosis score (Ishak fibrosis scores 5 and 6), respectively (Table 3).

In non-SVR patients, AST/ALT ratio (AUC=0.722, p<0.001), age-platelet index (AUC=0.643, p=0.024), HCV-RNA (AUC=0.654, p=0.017), and liver fibrosis (AUC=0.767, p<0.001) were shown to be statistically significant. There was no statistical difference in terms of APRI score (AUC=0.54, p=0.48) and platelet count (AUC=0.389, p=0.78) in non-SVR patients (Figure 2).

Independent Factors Associated with Non-SVR

The final multiple logistic regression model, including the following factors, was entered in the binary logistic regression analysis: gender, age (<40 years vs >40 years), body weight (<75 kg vs >75 kg), pretreatment viral load (<600,000 IU/ml vs >600,000 IU/ml), pretreatment ALT (<28 IU/L vs >28 IU/L), pretreatment APRI score (<1.5 vs >1.5), pretreatment platelet count (<120,000/L vs 120,000/L), pretreatment age-platelet index (<5 vs ≥6), and pretreatment AST/ALT ratio (<0.62 vs >0.62). Gender, viral load (>600,000 IU/ml), platelet count (<120,000/L) and age-platelet index (>5) increased the odds of a non-SVR independently and significantly: gender (OR=0.21, 95% CI, 0.05-0.88, p=0.03), age >40 years (OR=0.41, 95% CI, 0.06-2.64, p=0.35), weight >75 kg (OR=1.25, 95%

Table 2. The relation between NILFT and advanced fibrosis (Ishak Fibrosis Score)

Variables	Sensitivity	Specificity	PPV (%)	NPV (%)	Accuracy (%)	OR (95% CI)
APRI score (>1.5)	38	76	24	87	70	2.03 (0.61-6.80)
Platelet count (<120,000)	75	76	14	98	76	9.67 (1.27-70.9)
AST/ALT ratio (>0.62)	30	100	100	22	42	Inf (1.44-)
Age-platelet index (>5)	43	84	62	72	69	4.11 (1.47-11.4)

AST: Aspartate aminotransferase. ALT: Alanine aminotransferase. HCV: Hepatitis C virus. APRI: Aspartate aminotransferase/platelet ratio index. PPV: Positive predictive value. NPV: Negative predictive value. OR: Odds ratio. CI: Confidence interval.

Table 3. The predictive values of NILFT in detecting non-SVR

Variables	Sensitivty	Specificity	PPV (%)	NPV (%)	Accuracy (%)	OR (95% CI)
APRI score (>1.5)	23	59	9	82	54	0.43 (0.12-1.60)
Platelet count (<120,000)	67	63	12	96	63	3.40 (0.68-16.8)
AST/ALT ratio (>0.62)	42	79	91	20	48	3.87 (1.09-13.5)
Age-platelet index (>5)	55	85	70	74	73	6.93 (2.41-19.8)

AST: Aspartate aminotransferase. ALT: Alanine aminotransferase. HCV: Hepatitis C virus. APRI: Aspartate aminotransferase/platelet ratio index. PPV: Positive predictive value. NPV: Negative predictive value. OR: Odds ratio. CI: Confidence interval.

CI, 0.35–0.40, p=0.72), ALT >28 IU/L (OR=0.59, 95% CI, 0.10-3.51, p=0.56), viral load >600,000 IU/ml (OR=4.51, 95% CI, 1.16–17.6, p=0.03), APRI >1.5 (OR=0.24, 95% CI, 0.04-1.49, p=0.13), platelet count <120,000 (OR=0.04, 95% CI, 0.002-0.88, p=0.04), age-platelet index >5 (OR=11.8, 95% CI, 2.25-62.15, p=0.004), and AST/ALT ratio >0.62 (OR=0.48, 95% CI, 0.08 - 2.90, p=0.43) (Table 4).

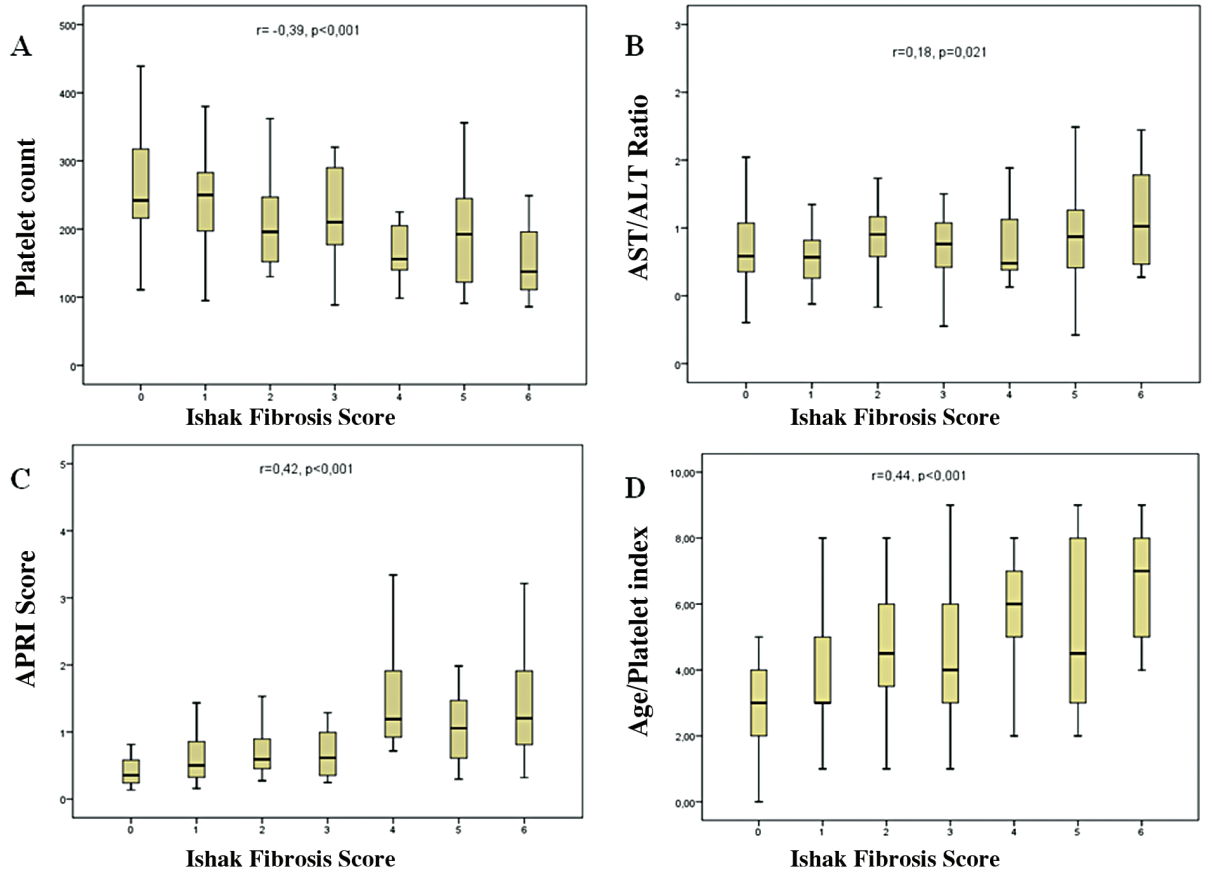

Figure 1. The correlation between platelet count, AST/ALT ratio, APRI score, Age/platelet index and advanced fibrosis

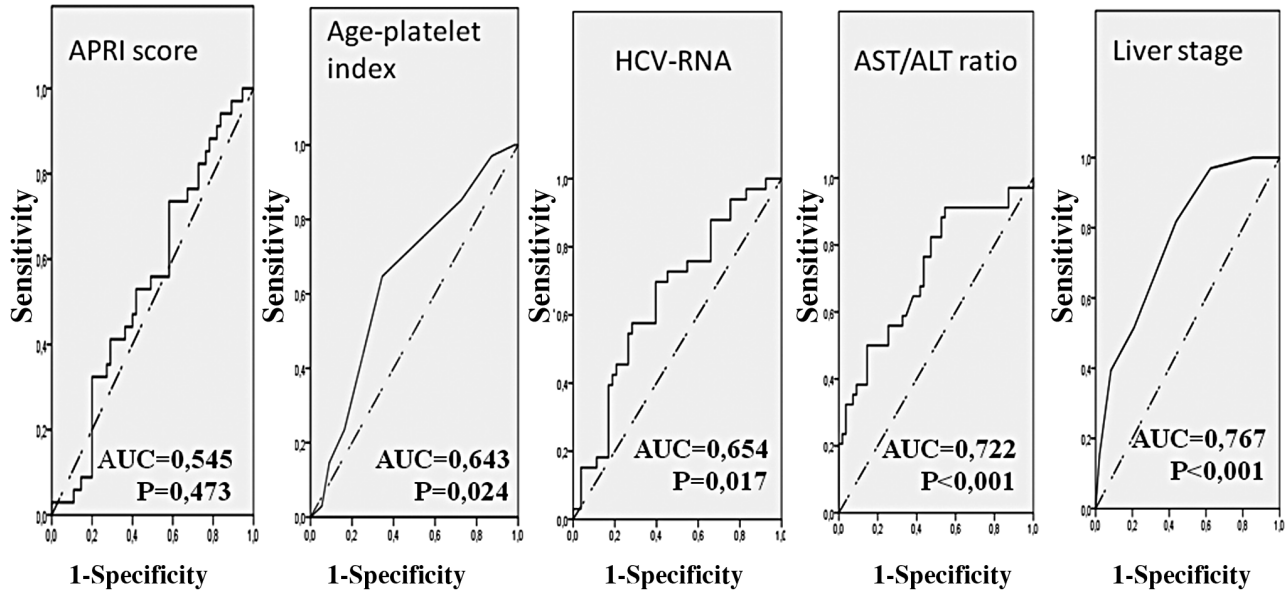

Figure 2. Receiver operating curves (ROC) for APRI, Age/platelet index, HCV-RNA, AST/ALT ratio and liver fibrosis as predictors for non-SVR patients.

Table 4. Factors associated with non-SVR (multivariate analysis)

	OR	95% CI	p
Gender	0.21	0.05 - 0.88	0.03
Age >40 years	0.41	0.06 - 2.64	0.35
Weight >75 kg	1.25	0.35 - 4.40	0.72
ALT >28 U/L	0.59	0.10 - 3.51	0.56
Viral load <600,000 IU/ml	4.51	1.16 - 17.6	0.03
APRI >1.5	0.24	0.04 - 1.49	0.13
Platelet count <120,000	0.04	0.002 - 0.88	0.04
Age-platelet index >5	11.8	2.25 - 62.15	0.004
AST/ALT ratio >0.62	0.48	0.08 - 2.90	0.43

AST: Aspartate aminotransferase. ALT: Alanine aminotransferase. APRI: Aspartate aminotransferase/platelet ratio index. OR: Odds ratio. CI: Confidence interval.

DISCUSSION

Liver biopsy has been an important reference method for therapeutic decisions regarding CHC, as treatment indication is based on histological findings (F≥2) and/or periportal inflammatory activity ≥grade 2, whether associated with each other or not (7,13-15). Liver fibrosis staging is one of the main factors that influence the decision to indicate therapy for CHC carriers. According to current protocols and guidelines for treating hepatitis C, which reflect the fact that liver disease evolves more slowly in patients who do not have fibrosis or who have minimal fibrosis, treatment does not necessarily need to be started for these patients. In contrast, treatment should be indicated for patients with moderate or more severe fibrosis (F≥2) because of the risk of evolution to cirrhosis and its associated complications (7,13-15). However, biopsy is an invasive method, can be subject to error, and is not free from complications such as bleeding, perforations and even death (16,17). In addition, some authors suggest that liver biopsies may yield false-negative results, as only 1/50,000th of the parenchyma is represented in a sample (1,18). Subjective variations in the interpretation of biopsies occur in 10%-20% of cases, and sample error can also occur. These limitations have generated doubts about the role of biopsies in the management of CHC patients (16,19). Alternative methods for assessing fibrosis have a number of advantages over histology, including low cost, their non-invasive nature and the absence of contraindications, such as severely altered prothrombin activity or thrombocytopenia. Researchers have been trying to find alternative methods for diagnosing fibrosis, and APRI, platelet count, AST/ALT ratio, and age-platelet index are considered several of the simplest and least expensive.

There are factors identified as predictors of SVR among patients who receive PEG-IFN and ribavirin, including HCV genotype other than 1, viral load less than 600,000 IU/ml, age of 40 years or less, and body weight of 75 kg or less. Sixty-five percent of patients with early viral response (EVR) subsequently have a SVR. In addition, the absence of bridging fibrosis/cirrhosis has been significantly associated with SVR (4,5).

In evaluating patients with CHC, the most important issue is whether treatment will be given, taking into account the risk of developing cirrhosis. One of the most important conditions for the clinician is to decide the appropriate treatment option in order to predict the chance of SVR. This study was planned by considering the possibility of NILFT to provide accurate fibrosis scores in CHC patients and the relation between fibrosis and SVR/non-SVR. It is known that the absence of bridging fibrosis/cirrhosis has been significantly associated with SVR. In this context, we thought that NILFT may be the predictive factor in non-SVR patients.

Many articles have evaluated the relationship of liver fibrosis and NILFT, platelet count, APRI score, AST/ALT ratio, and age-platelet index, etc. (9,20-22). Wai et al. (9) were the first to determine a relation between APRI and liver fibrosis scores. That study and follow-up reports showed a wide range of sensitivity, specificity, PPV, and NPV, as 32-85%, 66-90%, 46-90%, and 53-93%, respectively (9,20-22). In our study, we calculated sensitivity as 38%, specificity as 76%, PPV as 24%, NPV as 87%, accuracy as 70%, and OR=2.03 (95% CI, 0.61-6.80) for APRI (>1.5). Many studies related with other NILFT tests, AST/ALT ratio, age-platelet index, and platelet count have been published. These studies displayed a broad range for sensitivity and specificity (10,21,22). The marked differences among these studies can be due to the differences in the systems used to assess fibrosis, cut-off levels, stages compared, age, gender distribution, regional factors, and muscle mass.

However, similar to previous studies, we determined a significant correlation between NILFT and fibrosis. Correlation coefficients between NILFT and platelet count, AST/ALT ratio, APRI score, and age-platelet index were as follows: r= 0.39 (p<0.001), r=0.18 (p=0.021), r=0.42 (p<0.001), and

r=0.44 (p<0.001), respectively (Figure 1). Consequently, we have concluded that NILFT is almost as effective as histological assessment at the first diagnosis, but a combined assessment of these tests could provide better results.

Considering the relation of fibrosis with SVR/non-SVR, NILFT can also be valuable in prognostication of SVR/non-SVR. We found a small number of reports about the relationship between NILFT and SVR/non-SVR (23-28). Absence of EVR, non-white race, AST/ALT ratio ≥1.0, and presence of steatosis ≥5% in liver biopsy are independent predictors of absence of SVR in patients with chronic HCV infection receiving PEG-IFN and ribavirin combination treatment (23). In a study evaluating response to treatment with IFN + ribavirin in CHC patients, although biopsy and transient elastography were reported as strong predictors, the APRI score was not (24). In another study, platelet count and AST/ALT ratio were shown to have no predictive value for SVR, but a cut-off value ≥1 for AST/ALT ratio was evaluated (25). In a study evaluating the association between APRI and EVR, no relationship could be found (26). When response to treatment in CHC patients was evaluated, it was seen that hepatic vein transit time (HVTT) increased (p=0.01) and APRI score decreased (p=0.003) in patients with response (27). Nunes et al. (28) determined the AUROC values of AST/ALT ratio as 0.83 for the 1st year, 0.77 for the 3rd year and 0.72 for the 5th year, and AUROC values of APRI score as 0.90 for the 1st year, 0.88 for the 3rd year, and 0.85 for the 5th year in predicting HCV-related mortality. In our study, among SVR and non-SVR groups, significant differences were determined between the initial ALT levels, HCV RNA levels, liver fibrosis stage, AST/ALT ratio, age-platelet index, and GGT (p=0.026, p=0.017, p<0.001, p<0.001, p=0.023, and p=0.035, respectively) (Table 1).

When the non-SVR group was evaluated, age-platelet index, HCV RNA, AST/ALT ratio, and stage of liver fibrosis revealed a predictive role for determining unresponsiveness (AUC=0.643, p=0.024; AUC=0.654, p=0.017; AUC=0.722, p<0.001; AUC=0.757, p<0.001, respectively) (Figure 2). We observed NILFTs to be highly effective in predicting non-SVR patients, especially with age-platelet index (Accuracy=73%, OR=6.93, 95% CI, 2.41-19.8) (Table 3). Finally, a strong relationship was shown with multivariate analysis between non-SVR and some of the NILFTs such as viral load (OR=4.51, 95% CI, 1.16 –17.6, p=0.03) and age-platelet index (OR=11.8, 95% CI, 2.25-62.15, p=0.004) (Table 4).

In light of these results, NILFT seems to be an accurate predictor for advanced fibrosis and non-SVR. The possible reason why age-platelet index outweighs the other NILFTs in predicting non-SVR is that this index is studied with two different markers, the values of which have been previously demonstrated, and it evaluates in a stratified manner. These markers are in different categories; platelet count is a strong clinical factor while age is an individual factor.

This study has several limitations: the patients were analyzed retrospectively, and the results could have been affected by the small sample size. There are not many studies assessing the utility of non-invasive tests in predicting SVR/non-SVR in hepatitis C naive patients. Despite the limitations of our study, we believe our results show that the age-platelet index is a strong predictor of non-SVR in HCV naive patients.

However, while first biopsy is indispensable in terms of detecting fibrosis and histologic activity and excluding diseases that can be found together with HCV, no precise correlation between histologic results and NILFT has been shown. Prospective studies assessing NILFT in combination with other liver damage parameters (Fibroscan, transient elastography) are necessary. The results of this study can be used to improve the recognition, diagnosis, management, and prognostication of CHC patients.

Finally, if non-invasive tests could be standardized according to age, gender, race, and body mass index and individualized according to the fibrosis, then a full correlation of NILFT with histologic results could be obtained, stage of fibrosis could be predicted initially, SVR/non-SVR could be estimated, and the need for a repeat biopsy could be eliminated.

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