Apri As A Predictor For Sustained Virological Response In Chronic Hepatitis C Patients Genotype 4

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Abstract: Background &Aim: To evaluate the aspartate aminotransferase (AST) to platelet ratio index (APRI) as a predictive factor of sustained viral response in chronic hepatitis C naive patients with genotype 4. **Patients &Methods:** We conduct this prospective study on chronic hepatitis C naïve patients who were evaluated to start therapy with peg interferon a-2a (180 µg per week) and ribavirin (> 75 kg: 1200 mg and < 75 kg: 1000 mg) for 48 weeks and responders were followed for 24 weeks after end of treatment. Odds ratio (OR) and 95% confidence interval (CI) were calculated to assess the relationship between each risk factor and the sustained virological response (SVR). **Results:** One hundred and twenty patients were followed prospectively. The mean ± SD of age in our subjects was 35.8 ± 12.5 years; weight 76 ± 12.7 kg , AST 63.8±44.7 IU/mL, alanine aminotransferase (ALT) 74.5± 60 IU/mL, creatinine; 0.96±0.26 mg/dl and platelets 202612±88343/mm^3. The mean hepatitis C virus RNA viral load was 3143683±6643988 IU/mL. APRI showed a significant positive correlation with increasing fibrosis stage (r= 0.41, $P < 0.05$). By both univariate and multivariate analysis; initial viral load >600,000 iu/ml and advanced hepatic fibrosis were negative predictors for SVR. **Conclusion:** APRI is a good estimator of hepatic fibrosis. It could be used to decrease the number of liver biopsies; however it is not useful to predict SVR in patients with chronic hepatitis C genotype 4.

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1. Introduction

Hepatitis C virus (HCV) is a major public health problem that accounts for high proportion of liver diseases throughout the world[1]. According the WHO estimate 170 million individuals of the world population are infected with Hepatitis C virus (HCV)[2].

HCV can result in progressive hepatic injury and fibrosis, culminating in cirrhosis and end-stage liver disease. Chronic hepatitis C is a major indication for liver transplantation and increases the incidence of hepatocellular carcinoma[3].

The current treatment of choice for chronic hepatitis C (CHC) is combination of pegylated interferon (Peg-IFN) and ribavirin (RBV)[4]. However, non-response to this therapy remains common with approximately 50% of patients achieving sustained viral response (SVR)[5,6,7].

Limited treatment efficacy, high costs, and significant side effects have prompted the development of methods to predict treatment outcome[8.9.10]. Previous studies declared many negative predictors for SVR among HCV patients genotype 4 treated with peg interferon and ribavirin such as age, pretreatment viral load, and stage of fibrosis[11,12,13].

Percutanous liver biopsy has been the gold standard for grading and staging liver disease; recently however, non-invasive methods have been developed to determine stage of hepatic fibrosis such as transient electrograph, fibrotest, and the aspartate aminotransferase (AST) to platelet ratio index (APRI)[14,15] is one of several markers that have been anticipated to measure liver fibrosis. It is proposed as a simple and non-invasive predictor in the evaluation of liver fibrosis status [14]. APRI has been used in the evaluation of patients with CHC with high accuracies in identifying the presence of significant fibrosis and cirrhosis[14,15,16,17]. Previous studies have not explored the usefulness of non-invasive tests like APRI to assess liver fibrosis for the prediction of SVR in hepatitis C naive patients[3].

Thus we designed the present study with the aim to elucidate the role of APRI as a predictive factor of SVR in Chronic hepatitis C patients with genotype 4.

2. Methods & Patients:

Patients eligible for HCV antiviral therapy were recruited from National Liver Institute, Menofyia University, Egypt, in an ongoing,

prospective trial from May 2007 to January 2009. Treatment naive CHC patients were included if they were between 18 and 60 years and had positive HCV RNA by real time PCR (Cobas Amplicor HCV v2.0, Roche Molecular Systems) with liver biopsy consistent with chronic hepatitis and significant fibrosis. All patients were having HCV genotype 4. Exclusion criteria included evidence for coexisting liver disease, concurrent infection with hepatitis B virus or HIV, presence of hepatocellular carcinoma, decompensated cirrhosis, patients on hemodialysis, significant systemic disorders, uncontrolled thyroid disease, a current or past history of alcohol abuse, major psychiatric conditions, or previous liver transplantation. Patients with baseline anemia (hemoglobin <13 g/dL for men and <12 g/dL for women), absolute neutrophil count (ANC) <1500/mm3, platelet count <75,000 /mm3 or creatinine >1.5 mg/dL were also excluded.

Pregnancy and lactation were not allowed and the use of a reliable method of contraception during the period of combination therapy was suggested. The study was conducted in conformance with the principles of the Declaration of Helsinki. The institutional review board of the hospital approved the protocol and consent forms. All participants provided written informed consent.

Treatment regime:

They were treated with Peg-IFN α-2a 180 mcg weekly with ribavirin in dose of 1000 mg orally if patient was less than 75 kg and 1200 mg if the patient weighed greater than or equal to 75 kg. For 48 ws

Follow-up

All subjects were monitored during peg-interferon, ribavirin treatment in both groups and for a further period of 24 weeks after the end of treatment. They had biweekly outpatient visits during the first month and monthly visits during the rest of the treatment period as well as during the 24-week follow-up period. At each visit, a physical examination was performed, the importance of treatment adherence was explained, adverse effects were recorded, and biochemical tests and blood counts were performed. The efficacy to standard anti viral therapy was defined as undetectable HCV RNA level by PCR at 12 weeks (early virological response EVR),at the end of treatment (ETR) and after 24 weeks follows up (SVR).

APRI calculated according to the formula proposed by **Wai *et al* .,** in 2003, namely, [(AST of the sample/ reference AST) x 100] / platelets count (10^3/ dL)][18]. Fibrosis was established if the APRI was ≥ 1.2.

Dose modifications

Medications doses were modified based on the recommended manufacturers' guidelines for the treatment of Peg-IFN α-2a/RBV-induced hematological side effects [19]. Growth factors such as erythropoietin and granulocyte colony-stimulating factor (G-CSF) were only used beyond the criteria of dose modification

Statistical analysis

Data was statistically analyzed using SPSS (statistical package for social science) program version 17 for windows. Quantitative data are presented as mean ± standard deviation. Qualitative data are presented as relative proportions. Student t-test and Mann-Whitney test were used to compare means for quantitative variables. The association between the categorical variables was assessed by using the chi-square test or Fisher exact test. Odds ratio (OR) and 95% confidence interval (CI) were calculated to assess the relationship between each risk factor. Logistic regression was used to assess the significance of different variables on achieving SVR. A p value < 0.05 was considered statistically significant.

3. Results

One hundred and twenty CHC patients (84 males, 70%) met the inclusion criteria; their mean ages were 39.9 ± 10.6 years. Seventy nine (65.8%) patients completed 48 weeks of treatment. 83 (69.2%) patients achieved EVR; 49 of them reached a complete EVR and 34 showed partial EVR. 68 (56.7%) patients achieved ETR and 51 (42.5%) patients achieved SVR. Basal patients' characteristics are shown in (Table 1).

APRI and fibrosis stage

APRI showed a significant positive correlation with increasing fibrosis stage (r= 0.41, *P* = 0.009). Box plot of AST/ platelet ratio index in relation to the Metavir score is shown in (Figure 1).

Independent factors associated with SVR

Using the univariate analysis; HCV viral level above 600.000 IU/mL, and evidence of advanced fibrosis in liver biopsy (F4) were significantly associated with low rate of achieving SVR (Table 2). This was confirmed by multivariate analysis (Table 3)

4. Discussion:

Recent studies have shown the importance of APRI test to decrease the number of liver biopsies, particularly because patients with an APRI of less than 0.40 have very little chance of having significant fibrosis[3]. For our knowledge this was the first study

to evaluate the APRI as a predictive factor of sustained viral response in patients with chronic hepatitis C genotype 4.

We elucidate the possibility that biopsy could predict treatment response in HCV infected patients; but an indirect measure of fibrosis with APRI is not an option to predict viral response, in addition, viral load still considered as a predictor for viral response.

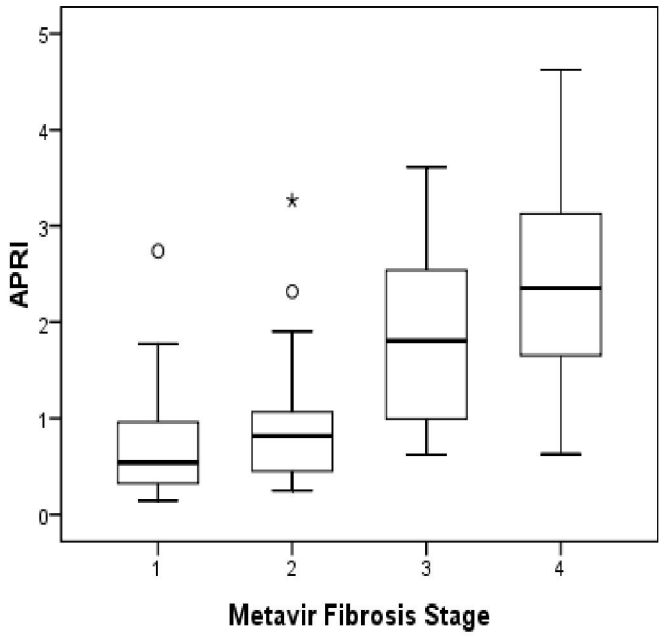
Table (1): Base line and demographic characteristic of patients' cohort.

Variable	Total patients (n = 120)	SVR patients (n = 51)	Non-SVR patients (n = 69)	*P* value
Age (yr)	38.5 ± 12.5	36.9 ± 12.9	41.1 ± 11.8	0.424
Males (%)	84 (70%)	38 (74.5%)	46 (66.7%)	0.442
Weight (kg)	76.5 ± 12.7	73.7 ± 13.6	78.2 ± 12.1	0.301
Hemoglobin (g/dL)	14.1 ± 2.45	14.4 ±1.8	13.9 ± 2.81	0.511
Platelets (No/µL)	202,612 ± 88,343	212,132± 77,934	185,682 ± 94.113	0.133
Leucocytes (cells/µL)	5.2 ± 2.47	5.5 ± 2.1	4.9 ±2.6	0.512
Glucose (mg/dL)	103 ± 15.54	99 ±17.02	108 ± 13.7	0.243
Creatinine (mg/dL)	0.96 ± 0.26	0.97 ± 0.22	0.94 ±0.52	0.522
Albumin (g/dL)	*4.4 ± 0.51*	4.5 ± 0.41	4.3 ± 0.72	0.476
AST (IU/dL)	63.8 ± 44.7	59.9 ±41.5	72.2 ± 52.3	0.128
ALT (IU/dL)	74.5 ± 60	72.1 ± 56.2	77.2 ± 66.3	0.299
AP (IU/dL)	111.4 ± 37.4	107.2 ±40.3	113.3 ± 33.6	0.623
Baseline viral load (iu/mL)	3143683 ± 6643988	2448973 ± 7433292	3422776 ± 6217684	0.101
APRI	1.024 ± 1.89	0.911 ± 1.65	1.13 ± 1.94	0.092
Fibrosis stage				
F1	26 (21.6%)	12 (23.5%)	14 (20.3%)	
F2	37 (30.9%)	21 (41.2%)	16 (23.2%)	
F3	38 (31.7%)	14 (27.5%)	24 (34.8%)	
F4	19 (15.8%)	4 (7.8%)	15 (21.7%)	0.06

Data are presented as mean ± standard deviation

*P value is between SVR and non- SVR patients

AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; AP: Alkaline phosphatase; APRI: AST to platelet ratio index.



Figure(1): relation of APRI score and Metavir fibrosis stage.

Table(2): Factors associated with SVR (Univariate analysis)

Parameter	Odds Ratio	95% CI	*p* value
Age (> 40 years)	0.75	0.52 - 1.11	0.61
Male gender	1.13	0.36 - 3.41	0.77
Body weight (BW) ≤ 75 kg	0.71	0.62 – 1.02	0.53
Body mass index (kg/m^2)	0.78	0.34 - 1.09	0.74
AST (IU/L)	1.1	0.76 – 2.82	0.09
ALT (IU/L)	1.3	0.59 – 3.21	0.51
Platelets > 150 000/dL	1.9	1.02 – 2.9	0.24
Alkaline phosphatase (IU/L)	1.6	0.78 – 2.01	0.73
Bilirubin (mg/dl)	0.56	0.29 – 1.22	0.18
Viral load > 600 000 IU/mL	0.52	0.31 – 0.97	0.01
APRI	0.79	0.36 – 1.21	0.12
F4 Fibrosis stage	0.61	0.38 – 0.96	0.037
Ribavirin dose (mg/Kg body wt.)	1.73	0.92 – 2.91	0.22

Our findings are comparable with previous reports that evaluate predictors of sustained viral response in chronic HCV patients with genotype 4. Though our results might seem to differ with those of **AL Ashgar *et al* ., 2009**[20], who declared that young age, low AST, and treatment naïve were the predictor of SVR, their study was retrospective in nature with different ethnic and age groups from our study.

In their study, Akuta and colleagues concluded than hepatocytes steatosis is a factor associated with virological non-response; however they measured liver steatosis by obtaining liver biopsy percutaneously, and did not use a non-invasive assessment of liver fibrosis[21].

The APRI is a surrogate for liver fibrosis, and although it seems to perform well, it may not be as accurate as serial liver biopsies. The APRI is subject to fluctuations, because many factors influence AST and platelet levels. It is notable that the APRI has a similar area under the curve (AUC) and positive predictive value for fibrosis as other noninvasive markers[22].

Our study had some limitations, the results may be affected by the relatively small sample size, and also we didn't incorporate hepatic steatosis and insulin resistance which may impact hepatic fibrosis as a predictor of response. Also low APRI score in our population (<1.2) which reflect less marked fibrosis may impair the power of the test as a predictor of response. So there was an imperative need to evaluate these variables in another large, prospective, multicenter study before final conclusion.

In conclusion, APRI, which is a simple non-invasive index for the assessment of liver fibrosis, is associated significantly with the extent of fibrosis .However; APRI does not seem to be the index that might replace the liver biopsy in the majority of patients with chronic viral hepatitis, since it cannot classify correctly 40–65% of cases[21].

Before the wide acceptance of any non-invasive index in clinical practice, it should be evaluated by other groups in several settings other than those in which this index was initially applied, since the results are often found to be inferior to those reported in the initial evaluation.

We are not suggesting that the APRI replace liver biopsy for individual patient management at this time but, rather, that it may be a useful marker to study liver disease progression longitudinally in large populations.

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