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Can Biomarkers Predict Liver Cirrhosis in Chronic Hepatitis C?

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Abstract: ***Aim: To assess the accuracy of simple available laboratory tests (ALT, AST, platelet count, AST /ALT ratio AST to platelet ratio index: APRI) in predicting of liver fibrosis in chronic hepatitis C, in comparison to the predictive accuracy obtained by elastography. Methods: Two hundred and sixty five patients suffering from chronic hepatitis C (CHC) were included in this study. They included patients enrolled from the Hepatology Department of University Hospital Center "Mother Theresa" in Tirana. Fibrosis results obtained from elastography were assigned a score from 0 to 4 score as per METAVIR scoring. Results of serum ALT, AST levels and platelets were expressed as AAR and APRI. Results: One hundred and twenty nine (48.7%) patients showed no evidence of fibrosis on elastography 87 (32.8%) patients showed fibrosis, and 49 (18.5%) as cirrhosis. There was a significant correlation between the degree of fibrosis and AST levels, AST/ALT ratio, platelet count and APRI. The AUROC curve for predicting significant cirrhosis was 0.631 for AST levels, 0.342 for platelets, 0.642 for AAR and 0.668 for APRI (p <0.05). Conclusion: In conclusion, the results of our study demonstrate a diagnostic role of AAR and APRI as a simple non-invasive test for diagnosis of liver cirrhosis.***

Keywords: HCV, biomarker, predict, liver cirrhosis

1. Introduction

More than 170 million people are chronically infected with hepatitis C virus (HCV) worldwide. Patients with chronic HCV may develop decompensated liver disease and hepatocellular carcinoma and the risk is highest among patients with advanced fibrosis[1].

Chronic hepatitis C patients with significant fibrosis progress almost invariably to cirrhosis over a 10-20 years period and antiviral treatment is strongly recommended On the other hand patients with no or minimal fibrosis at presentation appear to progress slowly and thus treatment could possibly be delayed or withheld [2,3].

Because antiviral treatment is costly and may be associated with significant side effects, the indication for antiviral therapy has to be evaluated carefully. Antiviral treatment is indicated for most patients infected with the easier-to-treat HCV genotypes 2 or 3. In contrast, the decision for treatment in the more difficult-to-treat HCV genotype 1–infected patients should be based on additional prognostic factors, such as the degree of hepatic fibrosis at the time of examination.

While liver biopsy was until recently considered as the gold standard for defining the degree of hepatic fibrosis,. novel non-invasive methods, including serum biomarkers, transient elastography and combination algorithms, aregradually being incorporated into new guidelines and are becoming standard of care [4]

Many studies have been undertaken to evaluate the use of readily available laboratory tests to predict significant fibrosis or cirrhosis in patients with CHC[5]-[8]. So, the APRI consisting of 2 readily available laboratory results (AST levels and platelet count), can predict significant fibrosis and cirrhosis in treatment-naïve CHC patients with a high degree of accuracy [7].

In this study we tried to evaluate the accuracy of the readily available laboratory tests (AST/ALT ratio and APRI) in diagnosing liver fibrosis in treatment-naïve CHC patients. We compared the accuracy of correlation between the results of simple lab tests and transient elastographyoffers an accredited non-invasive method for theassessment of liver fibrosis.Itis performed by using *Fibroscan*, a device composed of anultrasound transducer probe that is mounted on the axis of a vibrator, with the degree of liver fibrosis predicted by them[4].

2. Methods

This transversal study was conducted on 265 adult patients suffering from CHC for a period of ten years. The diagnosis of CHCwas established by the presence of HCV antibody on ELISA and confirmed by the presence of HCV RNAusing qualitative polymerase chain reaction assays.

Demographic and clinical information of the patients including, age, sex, laboratory results and liver elastography reports were obtained from their medical records.

Laboratory results performed within one week from the date of elastography were used for analysis. If more than one set of laboratory test results were available, the results next to the time of elastography were used. Results of serum aminotransferase (ALT, AST) levels were expressed as ratio-s. The AST to platelet ratio index (APRI) was calculated according to the following equation devised by Wai et al [7].

$$\text{APRI} = \frac{\text{AST level (/ULN)}}{\text{Platelet count } (10^9/\text{L})} \times 100$$

The grade of activity and stage of fibrosis were scored as per published METAVIR criteria, [9] assigning a score of 0 to 4, where F0 = no fibrosis, F1 = portal fibrosis without septa, F2 = portal fibrosis with few septa, F3 = numerous septa without cirrhosis, and F4 = cirrhosis. We have combined the F1 and F2 classification under the classification "fibrosis".

All patient data were analyzing using SPSS 16.0. The patient characteristics were described in numbers and percentage. Spearman correlations were computed between results of the elastography and other laboratory markers (AST, ALT, platelet count and APRI). Receiver operator characteristic curves (ROC) were generated to assess the validity of these markers in diagnosing liver fibrosis reliably in all patients. In the ROC analysis had been included only biomarker which has been significantly correlated with the stage of fibrosis.

3. Results

Twohundred and sixty five patients were included in the study. The mean age of the patients was 42.76 ± 13.4 years; 140 (52.8%) were male and 125 (47.2%) females. One hundred and twenty nine (48.7%) patients showed no evidence of fibrosis on elastography (METAVIR F0, F0-F1, F1), 87 (32.8%) patients showed fibrosis (METAVIR F2, F2-F3), and 49 (18.5) as cirrhosis (METAVIR F3, F4, F3-F4).

The demographic and laboratory characteristics are shown in Table 1.

Table 1: The demographic and laboratory characteristics of the sample

Age (years)	42.76 ± 13.4
Sex	
Male (%)	52.8
Female (%)	47.2
ALT (U/L)	92.26±74.16
AST (U/L)	73.8±73.9
Platelets X10 ^{9}/L	209.5±82.9
ALT/AST ratio	0.83±0.43
APRI ratio	1.24±1.41
Elastography data on liver	
no fibrosis	48.7%
fibrosis	32.8%
cirrhosis	18.50%

The value of AST and the ratios derived are significantly higher among patients with the hepatic cirrhosis, meanwhile the platelets count is lower significantly among patients with hepatic cirrhosis (table 2).

Table 2: The mean of the AAR, APRI, AST, ALT and platelets by the liver status

Hepatic status	No Fibrosis	Fibrosis	Cirrhosis	p-value *
AAR (mean +SD)	0.78±0.4	0.81±0.3	1.0±0.6	0.023
APRI (mean +SD)	1.05±1.4	1.1±0.8	1.9±1.9	0.013
AST (mean +SD) U/L	69.5±79.4	69.6±44.8	92.4±78.1	0.01
ALT (mean +SD) U/L	87.5±68.1	92.5±67.2	104.5±97.6	0.234
Platelets (mean +SD) X10 9	219.8±73.4	212.4±93	177.8±80.9	0.017

*ANOVA
a p<0.05 is considered significant

Correlation studies between the stages of fibrosis and values of different laboratory markers revealed a significant difference (Table 3)

Table 3: Correlations of fibrosis detected on elastography and biomarkers/ratio-s

Biomarkers/ratio	Coefficient of correlation
AST	0.216*
ALT	0.089
Platelets count	-0.216*
AAR ratio	0.187*
APRI	0.25*

*. Correlation is significant at the 0.05 level (1-tailed).

The area under the receiver operator curve (AUROC) for predicting significant fibrosis in patients was 0.631 for AST levels, 0.541 for ALT level 0.643 for AST/ALT ratio and 0.668 for APRI (p <0.05 for all the biomarkers (Figure1 and table 3). the AUROC was significant for patient groups, and thus a best cutoff for ROC can be calculated easily.

Table 3: The area under receiver operating curve and the significance for each biomarker/ratios

Test Result Variable(s)	Area	P value*	Asymptotic 95% Confidence Interval	
			Lower Bound	Upper Bound
AST	.631	.004	.544	.718
Platelet count	.341	.001	.252	.430
AAR	.643	.002	.553	.732
APRI	.668	.000	.579	.757

*p<0.05 is considered significant.

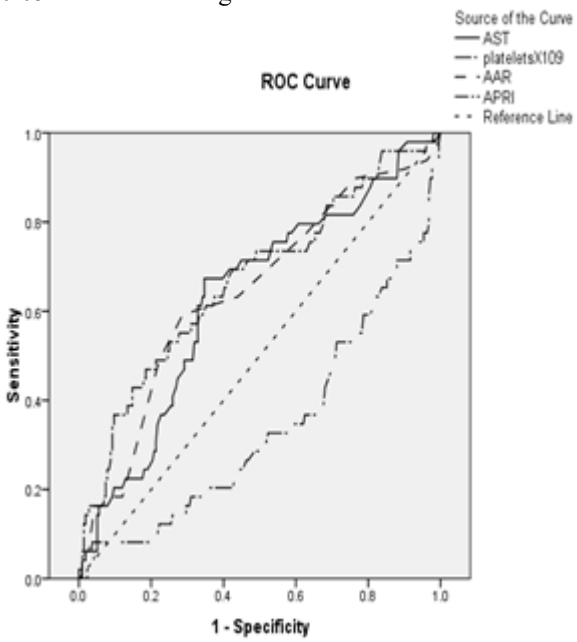

Figure1: Area under the receiver operating curve for predicting hepatic cirrhosis

4. Discussion

In this study we tried to assess the validity of noninvasive, simple, easily available blood tests to predict significant cirrhosis in CHC patients. 265 patients with from viral hepatitis C were included in this study.

The AST levels were higher in patients who showed significant liver fibrosis or cirrhosis than in patients with or no fibrosis and the difference was statistical significance. The previous studies demonstrated that progression of liver

fibrosis may reduce the clearance of AST, leading to increased serum AST levels. The advanced liver disease may be associated with mitochondrial damage, resulting in more marked release of AST, which is present mainly in mitochondria and cytoplasm, whereas ALT is only located in the cytoplasm[10] [12].

A significant difference in the AST/ALT ratio in patients with no fibrosis, fibrosis and cirrhosis were found. Our study results conform to many precious studies which report that AST/ALT ratio may predict the presence of cirrhosis in patients with chronic hepatitis C[13]-[15] but several others have concluded that an AST/ALT ratio >1 may not be as useful for predicting cirrhosis in chronic hepatitis C[5,16,17].

The inverse correlation of platelet count and the degree of hepatic fibrosis in chronic hepatitis C has been noted by several investigators [5],[7]. Thrombocytopenia in patients with advanced hepatic fibrosis may be explained by portal hypertension leading to pooling of platelets in an enlarged spleen, a myelosuppressiveaction of HCV, or reduced hepatic production of thrombopoietin [18].

The AUROC curve for predicting significant hepatic cirrhosis was lower for platelets count (AUROC 0. 341, p = 0.001) than in AST, AAR and APRI (AUROC 0.631, 0.642,0.668 p <0.01). They reliably predict cirrhosis in these patient groups. The inconsistent conclusions among the studies on diagnostic accuracy of noninvasive markers of fibrosis may be explained by the prevalence of cirrhosis in the population under study and that a normal AST value can lead to APRI inaccuracy[19] However, several studieshave demonstrated that APRI was a good estimator of hepatic fibrosis or cirrhosis in patients with CHC[20]-[27].

In conclusion, the results of our study demonstratea diagnostic role of AAR and APRI as a simple non-invasive test for diagnosis of liver cirrhosis

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