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Research Article

### A COMPARISON OF SENSITIVITY AND SPECIFICITY OF TRANSIENT ELASTOGRAPHY I.E. FIBRO SCAN WITH AST TO PLATELET INDEX (APRI) AND FIB-4 IN CHRONIC HCV INFECTED PATIENTS, A RETRO PROSPECTIVE CROSS SECTIONAL STUDY AT LAHORE GENERAL HOSPITAL, LAHORE, PAKISTAN

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#### Abstract:

**Background:** Hepatitis C is a leading cause of liver fibrosis, cirrhosis and cirrhosis associated complications. In this study, we compared readily available non-invasive fibrosis indexes with fibro scan for the fibrosis staging and predicting its progression in Pakistani population.

**Methods:** The retrospective cross sectional study was conducted in medicine unit 1&2 and hepatitis clinic of Lahore General Hospital, Lahore starting from February 12, 2018 to January 8, 2019. We studied 1464 HCV infected patients which were got CBC, LFTs, ELISA, PCR and fibro scan done to perfectly diagnose ongoing hepatitis C infection. In order to differentiate HCV fibrosis progression, we compared the effectiveness of readily available AST to Platelet Index (APRI), and FIB-4 with fibro scan

**Results:** Readily available serum indexes AST to Platelet Index (APRI) and FIB-4 were able to stage liver fibrosis in advanced stages of fibrosis (F4 especially) with correlation coefficient indexes 0.462, and 0.131 with considerable specificities and sensitivities. For APRI >1.5, it did predicted F4 stage with sensitivity of 87.6 % and specificity of 74.8%. For Fib-4 > 3.25, it did predicted F4 stage with sensitivity of 72.3% and specificity of 53.2%.

**Conclusions:** Readily available and cheap serum indexes, AST to Platelet Index (APRI) and FIB-4 accurately predicted distinguished between cirrhotic and non- cirrhotic stages in HCV infected patients in comparison to the costly and rarely available Fibro scan score.

**Keywords:** Hepatitis C, Blood Platelets, Fibro scan score.

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## INTRODUCTION:

Hepatitis is a greek word derived from "Hepa" means Liver and "itis" means inflammation. Hepatitis C is one of the major cause of death among individuals almost affection 71 million people worldwide. It is one of the leading causes of liver cirrhosis and hepatocellular carcinoma which ultimately results in deaths of individuals[1].

According to a survey almost 700000 people die from Hepatitis C related diseases making it more prevalent than liver cancer and cirrhosis which results in deaths of 167000 and 326000 people respectively[2].

Hepatitis C is caused by HCV which results in both acute and chronic disease. It spreads from multiple routes but majorly it results from Blood contact, transfusions, vertical transmission, needle stick injuries, Sexual contact and also from intravenous drugs use[1,3].

Hepatitis C causes inflammation of liver which results in severe right quadrant pain, followed by jaundice and ultimately results in hepatomegaly. . Lymphocytes infiltrate the portal tract and with chronic inflammation and infection, hepatocytes die. Liver cells and parenchyma are irritated and liver quickly needs to replace them. Some come to fibrosis and cirrhosis or alternatively hepatocytes go into frenzy and reproducing cells become malignant leading to hepatocellular carcinoma. Hep C infection leads to development of cryoglobulins or serum proteins containing IgM that precipitate and cool our temperature (3, 4). If it remains untreated it results in chronic disease which disrupts liver parenchyma and eventually hepatocytes die and if it remains undiagnosed and untreated it ultimately causes cirrhosis and cancer which is deadly[4,5,6].

Out of 71 million people affected, Pakistan has the world's second highest prevalence rate of Hep C and among Pakistani Population majority of population is from rural areas i.e, more than 60%.Due to lack of awareness, health facilities and poor financial conditions people do not go for regular screening of specific tests like PCR,ELISA,LFTs and Fibro scan etc. As a result most of symptoms are left undiagnosed[7].

This research was conducted to assess that how far AST to Platelet Index (APRI) and Fib-4 can replace Transient Electrography i.e, Fibroscan in predicting advanced stages of liver fibrosis in Hepatitis C patients.With advancement in medical era, DAA has achieved 95% cure rate, but the goal is to make the

world Hepatitis C free with cost effective treatment and awareness so World may celebrate a Hepatitis C free day[8].

## MATERIALS AND METHODS:

This study was carried out at Hepatitis Clinic, Lahore General Hospital / Ameer Ud Din Medical College, Lahore ,Pakistan. We explained the whole process of our study for the clarification of patient's concepts about our study. Informed consent was obtained from patients who were willing to be involved in research. It was cross-sectional study. This study was carried out from 11 Feb 2017 to 29 Dec 2018.

Patients of chronic viral hepatitis C infection were identified among the patients visiting Hepatitis Clinic, Lahore General Hospital, Lahore, who were only positive for HCC antibodies by detecting HCV RNA by Polymerase Chain Reaction (PCR) and then, HCV genotype was established. HBV/HCV and HCV/HIV co-infected patients and on which any clinical findings of liver cancer were present, were not included in the study. Total 1898 patients were engaged over this period. Quantitative determination of the Fibro scan score (Liver Stiffness Index; LSI), baseline viral load obtained by PCR and biomarkers ( liver function tests (LFTs), albumin, bilirubin and Complete Blood Count ( CBC ) were done. The fibrosis stages of patients were determined from fibro scan score following Metavir System using. We considered results of Fibroscan reliable if IQR/med. was less than 30%. Then we took consecutive 10 readings of fibroscan and considered average of these readings as our fibroscan score value. Then we used Ziol transient elastography breaking points for staging of fibrosis according to Metavir System of fibrosis. 2.5 -8.8 fibroscan vaue reffered as F0-F1, 8.9-9.6 fibroscan vaue reffered as F2, 9.7-14.6 fibroscan vaue reffered as F3 and above 14.6 were labelled as F4 using Metavir System of fibrosis stages. The patients were assessed for readily available serum fibrosis indices; AAR,APRI,FI, FIB-4, API, Pohl score, FCI and our newly developed NFI. The study was approved by Institutional Ethical Review Board (IERB) ), LGH.

The following formulas were used to review the predicted scores with particular cut-off values.

- AST to ALT Ratio (AAR) =  $\text{AST(IU/l)}/\text{ALT(IU/l)}$   
If  $\text{AST}/\text{ALT} \geq 1$ , significant cirrhosis.
- AST to Platelet index (APRI) =  $\left[ \frac{\text{AST(IU/l)}}{\text{ALT}_{\text{ULN}}(\text{IU/l})} \times 100 \right] / \text{platelet count}(109/l)$   
If  $\text{APRI} < 0.5$ , no or minimal fibrosis; if  $\text{APRI} > 1.5$ , significant fibrosis.

**Statistical analysis:**

SPSS windows version 22 was used to analyze the data. p value of less than 0.05 was considered statically significant. To signify the marked association between stages of liver fibrosis and continuous variables, Spearman's rank correlation was used. We used student t-test to relate arithmetic means and parameters. Various univariate analysis was performed for multiple biomarkers. Receiver Operating Curves (ROC) and AUROC were performed to infer the diagnostic precision of the

serum fibrosis indexes along with their cutoff points, sensitivities and specificities.

**RESULTS:**

1464 patients were included in our study. Among them 1014(69.3%) patients are female and 450(30.7%) are male shown in table.1. According to data of marital status 1367(93.4%) patients are married while 94(6.6%) are unmarried. As for the occupation, 613 patients are the housewives, 738 are the laborers and 113 are the working ladies.

Table 1: Showing Distribution of Gender of 1464 Patients

	Frequency	Percent	Valid Percent	Cumulative Percent
Valid Female	1014	69.3	69.3	69.3
Male	450	30.7	30.7	100.0
Total	1464	100.0	100.0	

Table 2: Shows marital status of Patients

	Frequency	Percent	Valid Percent	Cumulative Percent
Valid Married	1367	93.4	93.4	93.4
Unmarried	94	6.6	6.6	99.6
Total	1464	100.0	100.0	

As for genotype, 1069(73%) patients are 3a, 380(26%) are 1b and 15(1%) are 1A.

Table 3: Shows Genotype of 1464 patients

	Frequency	Percent	Valid Percent	Cumulative Percent
Valid 3a	1069	73.0	73.0	73.0
1b	380	26.0	26.0	99.0
1A	15	1.0	1.0	100.0
Total	1464	100.0	100.0	

The determination of fibrosis stage among HCV infected patients depicts that among 1464 patients 899(61.4%) patients are in fibrosis stage F0-F1 stage,

87(5.9%) patients are in F2 stage, 218(14.9%) patients in F3 and 260(17.8%) patients are in F4 leading cirrhosis.

Table 4: Shows Stage of Fibrosis among Patients

	Frequency	Percent	Valid Percent	Cumulative Percent
Valid F0-F1	899	61.4	61.4	61.4
F2	87	5.9	5.9	67.3
F3	218	14.9	14.9	82.2
F4	260	17.8	17.8	100.0
Total	1464	100.0	100.0	

**Determination Of Fibrosis Stages Using Already Used Variables:**

The mean and standard deviations of Age of Patient,

Baseline Viral Load, Albumin, Bilirubin, AST, ALT, Platelet Count, Alkaline Phosphatase, APRI and Fib-4 are given in the table 5.

Table 5: Descriptive Statistics

	N	Minimum	Maximum	Mean	Std. Deviation
Age of Patient	1459	14.0	100.0	40.572	13.0495
Baseline Viral Load	1464	119	107911144	1031912.81	6684292.117
Albumin	1464	.70	15.00	3.5473	1.49778
Bilirubin	1464	.50	24.00	1.2421	1.34103
AST	1464	14.0	1085.0	73.885	66.9357
ALT	1464	10.0	7000.0	80.403	193.5658
Platelet Count	1464	186000.00	26800000.00	613020.5949	2607641.77863
Alkaline Phosphatase	1464	51.0	1154.0	301.373	137.3671
APRI	1464	.00	7.52	.6195	.54188
Fib-4	1464	.00	6.71	1.1305	.67897
Valid N (listwise)	1459				

By applying Independent sample T test, the relationship between stage of fibrosis predicted by FibroScan and APRI and Fib-4 was found to be statistically significant ( $p > 0.05$ ).

#### Univariate analysis:

Univariate analysis for Fib-4 score showed a statistically significant relationship with Person's

correlation coefficients (R) values=0.458 (P value = 0.0001).

#### Linear Curve Estimation Analysis:

The Linear Curve Estimation Analysis and Pearson Correlation coefficient showed a positive linear relationship between Stage of fibrosis by FibroScan and APRI (R value is 0.462) in different stages of fibrosis in Hepatitis C.

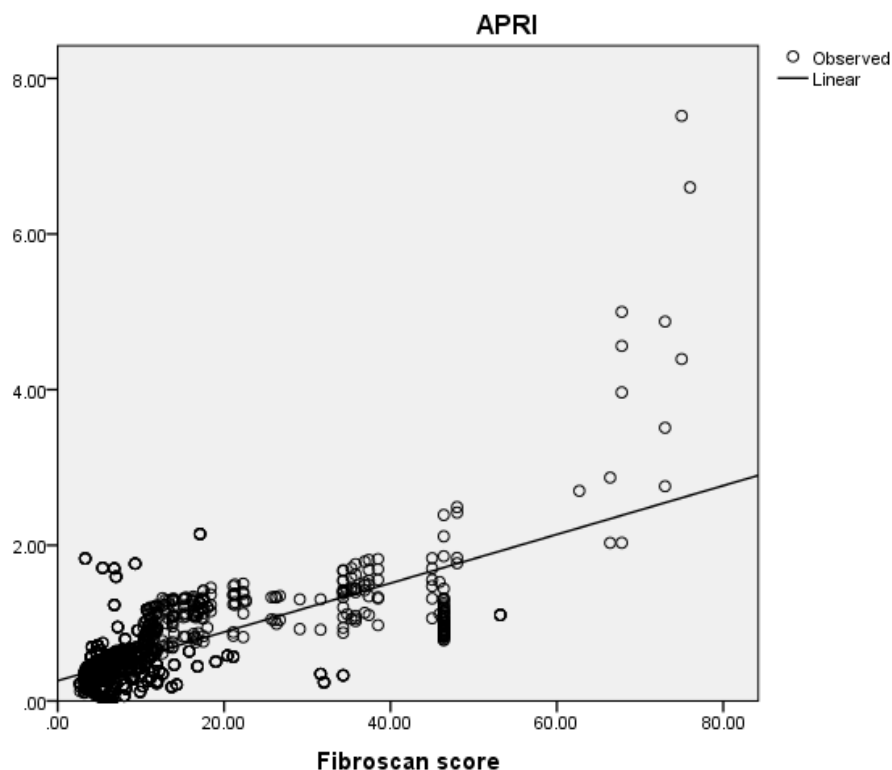


Fig.1. Scatter-plot for APRI vs fibro scan score

The Linear Curve Estimation Analysis and Pearson Correlation coefficient showed a positive linear relationship between Stage of fibrosis by FibroScan and Fib-4 (R value is 0.131) in different stages of fibrosis in Hepatitis C.

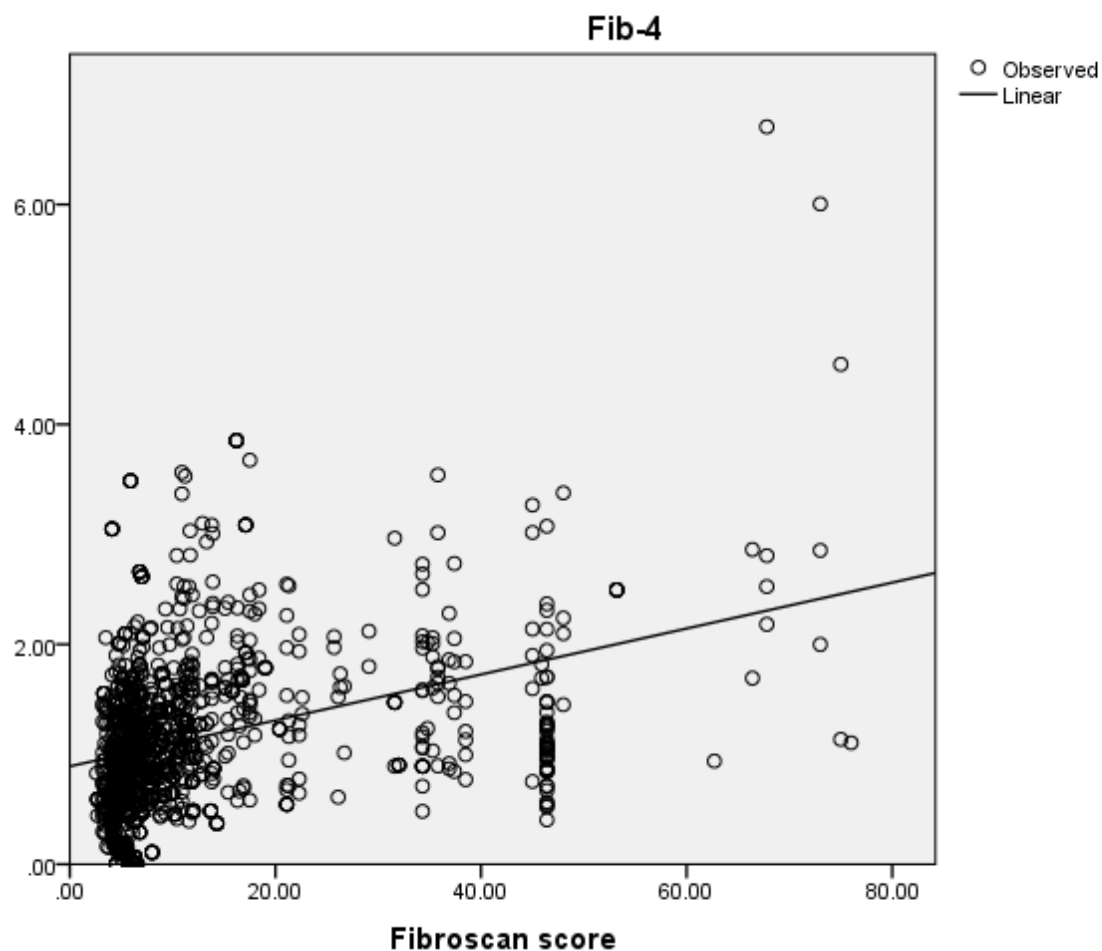


Fig.2. Scatter-plot for Fib-4 vs fibro scan score

**ROC Curve analysis:**

ROC Curve analysis for validation of serum AST platelet ratio APRI, and Fibrosis 4 were performed and sensitivity and specificity along with cutoff points were calculated ([Table3](#)).

Table 6 ROC Curve analysis for validation of serum APRI, and FIB-4 HCV infected patients

APRI				
stage	Cutoff value	Spe%	Sen%	AUC
F0-F3	< 0.5	68.0	56.2	0.54
F4	> 1.5	87.6	74.8	0.864
FIB-4				
stage	Cutoff value	Spe%	Sen%	AUC
F0-F3	< 1.45	65.4	51	0.521
F4	> 3.25	72.3	53.2	0.801

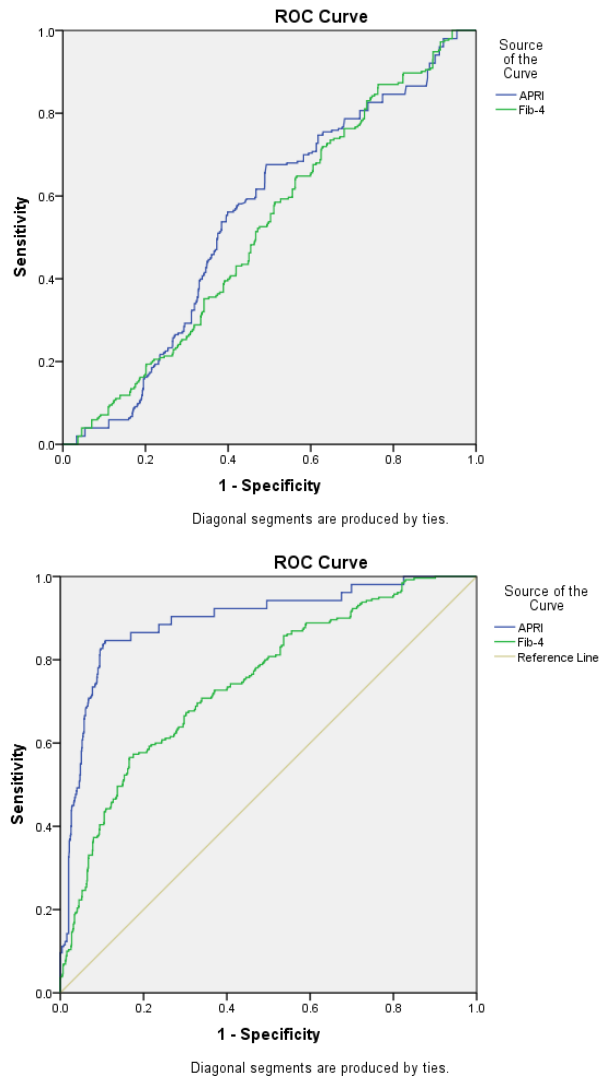


Fig. 3. ROC Curve for APRI and Fib-4 for F3

Fig. 4. ROC Curve for APRI and Fib-4 for F4

**DISCUSSION:**

Hepatitis C leads to liver cirrhosis and liver cancer. Approximately 30 years is the mean infection time for origin of cirrhosis, with people in age group of 10-50 years on risk of cirrhosis [10]. Spread of fibrosis in hepatic tissue is considered as a gold standard for

confirmation of cirrhosis. Several indexes are available for predicting the onset of cirrhosis but not any exclusive and dependable method has yet been established for assessment of fibrosis.

Most common form of hepatitis in Pakistan is



genotype is 3a and 2<sup>nd</sup> most common form is 1a [[3,11],and[12]]and exactly corresponding of what we observed in this study. Genotype 3a was in 86% of patients while rest of them were diagnosed with genotype 1a [13].earlier stages of fibrosis(F1-F2) were diagnosed among much younger patients as compared to later stage of fibrosis (F3-F4) which was present among older people .The results of this study supported the previous researches that subjects with mild fibrosis were found to be younger than the intermediate and advanced fibrosis stages and gender has nothing to do with stage of fibrosis [14].

Our study's results back the latest recommendations by EASL to apply non-invasive tests (NITs) as first line tests in prognostication of liver fibrosis [1,2,17]. According to our conclusions and these new recommendations, liver biopsy is needed only if redundant non-invasive tests show dissension . Blood markers can be used to predict cirrhosis and advanced stages of fibrosis and should be used if TE is not available or cost effective to patient or when diagnostic yield is constrained as in obese patients [13].

At cutoff value <0.5 APRI predicted F0-F3 with 56.2% sensitivity and 68.05% specificity with AUC =0.546 . at cut off value >1.5, F4 was predicted by 74.6% sensitivity and 87.6% specificity having AUC=0.864 .

FIB-4 was invented by Sterling in 2006 [11] and at cutoff value <1.45 ,F0-F3 was having sensitivity 51% & specificity 65.4% with area under curve(AUC) =0.521. At cut-off value > 3.25 ,for F4 sensitivity was 53.2% & specificity 72.3% with AUC=0.801.

### CONCLUSIONS:

Readily available and cheap serum indexes, AST to Platelet Index (APRI) and FIB-4 accurately predicted distinguished between cirrhotic and non- cirrhotic stages in HCV infected patients in comparison to the costly and rarely available Fibro scan score.

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