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A Comparison of Sensitivity and Specificity of AST to Platelet Index (APRI) and FIB-4 with Transient Elastography i.e. Fibro Scan in Chronic HCV Infected Patients

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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 scans for fibrosis staging and predicting its progression in Pakistani population.* ***Methods:*** *The retro prospective cross-sectional study was conducted in medicine unit 1 and 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 was 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 predict F4 stage with sensitivity of 87.6% and specificity of 74.8%. For Fib-4> 3.25, it did predict F4 stage with sensitivity of 72.3% and specificity of 53.2%.* ***Conclusion:*** *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

INTRODUCTION

Hepatitis is a Greek word derived from “Hepa” means Liver and “itis” means inflammation. Hepatitis C is one of the major causes of death among individuals almost 71 million people affected 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 7,00,000 people die from Hepatitis C related diseases making it more prevalent than liver cancer and cirrhosis which results in deaths of 1,67,000 and 3,26,000 people respectively [2].

Hepatitis C is caused by HCV which results in both acute and chronic diseases. It spreads from multiple routes but majorly it results from Blood contact, transfusions, vertical transmission, needle stick injuries, and Sexual contact and also from intravenous drug use [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. Hepatitis C infection leads to development of cryoglobulins or serum proteins containing IgM that precipitate and cool our temperature [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 cause cirrhosis and cancer which is deadly [5,6].

Out of 71 million affected people, Pakistan has the world’s second-highest prevalence rate of Hepatitis 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 how far AST to Platelet Index (APRI) and Fib-4 can replace Transient Electrography i.e, Fibro Scan 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 the research. It was cross-sectional study. This study was carried out from 11 February 2017 to 29 December 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. A total of 1,898 patients was 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 followed by using METAVIR System. We considered results of Fibro Scan reliable if IQR/med. was less than 30%. Then we took consecutive 10 readings of Fibro Scan and considered average of these readings as our Fibro Scan score value. Then we used Ziol transient Elastography breaking points for staging of fibrosis according to METAVIR System of fibrosis. 2.5-8.8 Fibro Scan value referred as F0-F1, 8.9-9.6 Fibro Scan value referred as F2, 9.7-14.6 Fibro Scan value referred as F3 and above 14.6 were labeled 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 [9].

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

- AST to ALT Ratio (AAR)=AST(IU/l)/ALT(IU/l)

  If AST/ALT ≥ 1, significant cirrhosis.

- AST to Platelet index (APRI)=[{AST(IU/l)/ALT_ULN(IU/l)} × 100]/platelet count (109/l)

  If APRI<0.5, no or minimal fibrosis; if APRI > 1.5, significant fibrosis.

Statistical Analysis

SPSS windows version 22 was used to analyze the data. The 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 cut off points, sensitivities, and specificities.

RESULTS

A total of 1464 patients were included in our study. Among them 1014 (69.3%) patients were female and 450 (30.7%) were male shown in Table 1. According to data of marital status 1367 (93.4%) patients were married while 94 (6.6%) were unmarried. As for the occupation, 613 patients were the housewives, 738 were the labourer and 113 were working ladies (Table 2). As for genotype, 1069 (73%) patients are 3a, 380 (26%) are 1b and 15 (1%) are 1A (Table 3).

Table 1 Distribution of gender of 1464 patients

Gender	Frequency	Percentage	Valid Percentage	Cumulative Percentage
Female	1014	69.3%	69.3%	69.3%
Male	450	30.7%	30.7%	100%
Total	1464	100%	100%	

Table 2 Marital status of patients

Marital Status	Frequency	Percentage	Valid Percentage	Cumulative Percentage
Married	1367	93.4%	93.4%	93.4%
Unmarried	94	6.6%	6.6%	99.6%
Total	1464	100%	100%	

Table 3 Genotype of 1464 patients

Genotype	Frequency	Percentage	Valid Percentage	Cumulative Percentage
3a	1069	73%	73%	73%
1b	380	26%	26%	99%
1A	15	1%	1%	100%
Total	1464	100%	100%	

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).

Table 4 Stage of fibrosis among patients

Fibrosis Stages	Frequency	Percent	Valid Percent	Cumulative Percentage
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%
Total	1464	100%	100%	

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 Table 5.

Table 5 Determination of fibrosis stages using already used variables

Variables	Minimum	Maximum	Mean	Std. Deviation
Age of Patient	14	100	40.572	13.0495
Baseline Viral Load	119	107911144	1031912.81	6684292.12
Albumin	0.7	15	3.5473	1.49778
Bilirubin	0.5	24	1.2421	1.34103
AST	14	1085	73.885	66.9357
ALT	10	7000	80.403	193.5658
Platelet Count	186000	26800000	613020.595	2607641.78
Alkaline Phosphatase	51	1154	301.373	137.3671
APRI	0	7.52	0.6195	0.54188
Fib-4	0	6.71	1.1305	0.67897
Valid N (listwise)				

By applying the Independent sample T-test, the relationship between stage of fibrosis predicted by Fibro Scan and APRI and Fib-4 was found to be statistically significant ($p>0.05$). Univariate analysis for Fib-4 score showed a statistically significant relationship with Person's correlation coefficients (R value=0 .458) ($p=0.0001$). The Linear Curve Estimation Analysis and Pearson Correlation coefficient showed a positive linear relationship between Stage of fibrosis by Fibro Scan and APRI (R value=0.462) in different stages of fibrosis in Hepatitis C (Figure 1).

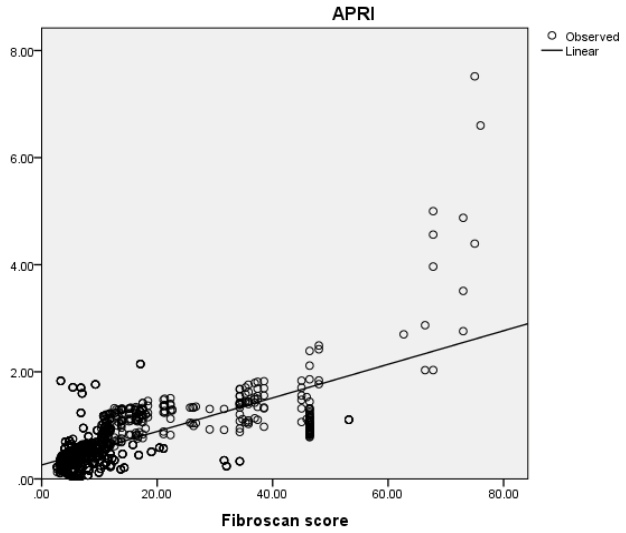

Figure 1 Scatter-plot for APRI vs fibro scan score

The Linear Curve Estimation Analysis and Pearson Correlation coefficient showed a positive linear relationship between Stage of fibrosis by Fibro Scan and Fib-4 (R value=0. 131) in different stages of fibrosis in Hepatitis C (Figure 2).

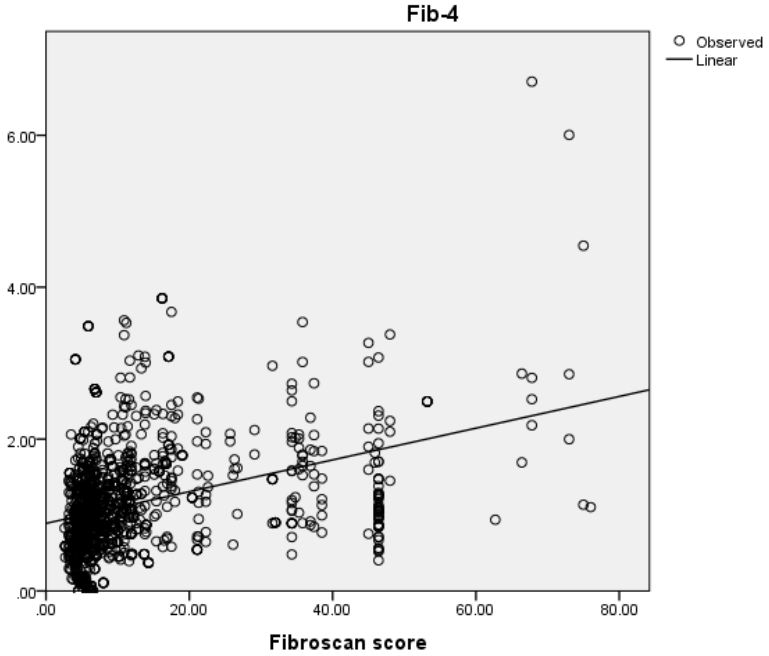

Figure 2 Scatter-plot for Fib-4 vs fibro scan score

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 (Table 6 and Figures 3 and 4).

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

APRI				
Stage	**Cutoff value**	**Specificity%**	**Sensitivity%**	**AUC**
F0-F3	<0.5	68	56.2	0.54
F4	>1.5	87.6	74.8	0.864

FIB-4				
Stage	**Cutoff value**	**Specificity%**	**Sensitivity%**	**AUC**
F0-F3	<1.45	65.4	51	0.521
F4	>3.25	72.3	53.2	0.801

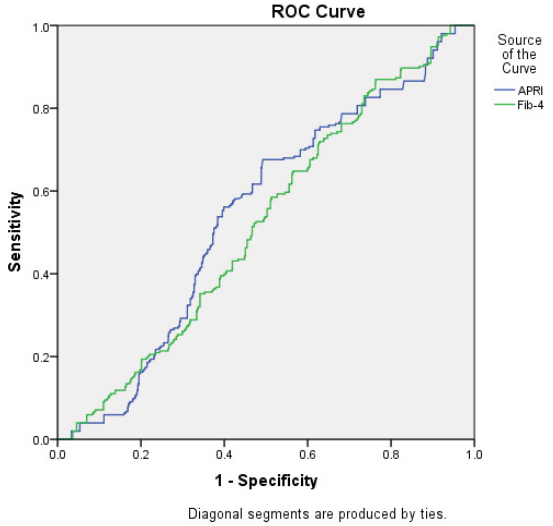

Figure 3 ROC Curve for APRI and Fib-4 for F3

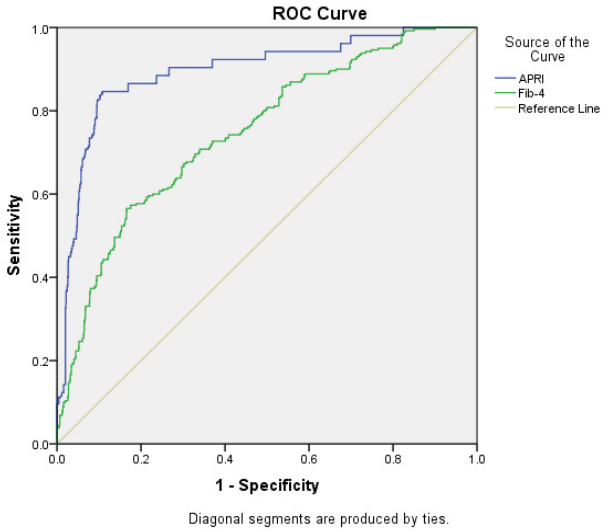

Figure 4 ROC Curve for APRI and Fib-4 for F4

DISCUSSION

Hepatitis C leads to liver cirrhosis and liver cancer. Approximately 30 years is the mean infection time for the origin of cirrhosis, with people in age group of 10-50 years on risk of cirrhosis [10]. The 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.

The most common form of Hepatitis in Pakistan is genotype 3a and the second most common form is 1a [11,12] 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 stages 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 [15]. 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 [16].

At cut off 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 74.6% sensitivity and 87.6% specificity having AUC=0.864. At cut off value <1.45, F0-F3 was having sensitivity 51% and specificity 65.4% with Area under curve (AUC) =0.521. At cut-off value >3.25, for F4 sensitivity was 53.2% and specificity 72.3% with AUC=0.801 [17-20].

CONCLUSION

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.

DECLARATIONS

Conflict of Interest

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

REFERENCES

[1] Attaullah, Sobia, Sanaullah Khan, and Ijaz Ali. "Hepatitis C virus genotypes in Pakistan: A systemic review." *Virology Journal*, Vol. 8, No. 1, 2011, p. 433.

[2] Thampanitchawong, Pornpen, and Teerha Piratvisuth. "Liver biopsy: complications and risk factors." *World Journal of Gastroenterology*, Vol. 5, No. 4, 1999, p. 301.

[3] Ahmad, Waqar, et al. "A comparison of four fibrosis indexes in chronic HCV: Development of new fibrosis-cirrhosis index (FCI)." *BMC Gastroenterology*, Vol. 11, No. 1, 2011, p. 44.

[4] Schmid, Patrick, et al. "Progression of liver fibrosis in HIV/HCV co-infection: A comparison between non-invasive assessment methods and liver biopsy." *PloS One*, Vol. 10, No. 9, 2015.

[5] Crossan, Catriona, et al. "Cost-effectiveness of non-invasive methods for assessment and monitoring of liver fibrosis and cirrhosis in patients with chronic liver disease: systematic review and economic evaluation." *Health Technology Assessment*, Vol. 19, 2015, pp. 1-409.

[6] European Association for Study of Liver. "EASL Clinical Practice Guidelines: Management of hepatitis C virus infection." *Journal of Hepatology*, Vol. 60, No. 2, 2014, p. 392.

[7] European Association for the Study of the Liver. "EASL-ALEH Clinical Practice Guidelines: Non-invasive tests for evaluation of liver disease severity and prognosis." *Journal of Hepatology*, Vol. 63, No. 1, 2015, pp. 237-64.

[8] Adams, Leon A., and Richard K. Sterling. "Developing a new algorithm to diagnose advanced liver fibrosis: A lift or a nudge in the right direction?" *Journal of Hepatology*, Vol. 66, No. 6, 2017, pp. 1111-13.

[9] Hind I. Fallatah. Noninvasive biomarkers of liver fibrosis: an overview. *Advances in Hepatology*, 2014.

[10] Boursier, Jérôme, et al. "Comparison of eight diagnostic algorithms for liver fibrosis in hepatitis C: New algorithms are more precise and entirely noninvasive." *Hepatology*, Vol. 55, No. 1, 2012, pp. 58-67.

[11] Zarski, Jean-Pierre, et al. "Comparison of nine blood tests and transient elastography for liver fibrosis in chronic hepatitis C: The ANRS HCEP-23 study." *Journal of Hepatology*, Vol. 56, No. 1, 2012, pp. 55-62.

[12] Giannini, C., and C. Brechot. "Hepatitis C virus biology." *Journal of Virology*, 2003, Vol. 10, 2003, pp. 27-38.

[13] Alter, Miriam J. "Epidemiology of hepatitis C." *Hepatology*, Vol. 26, 1997, pp. 62-65.

[14] Raja, Nadeem Sajjad, and Khalid Abbas Janjua. "Epidemiology of hepatitis C virus infection in Pakistan." *Journal of Microbiology Immunology and Infection*, Vol. 41, 2008, pp. 4-8.

[15] Idrees, Muhammad, and Sheikh Riazuddin. "Frequency distribution of hepatitis C virus genotypes in different geographical regions of Pakistan and their possible routes of transmission." *BMC Infectious Diseases,* Vol. 8, No. 1, 2008, p. 69.

[16] El-Serag, Hashem B. "Hepatocellular carcinoma and hepatitis C in the United States." *Hepatology*, Vol. 36, 2002, pp. 74-83.

[17] Azhar Hussain et al. "Role of Ischemic Heart Disease (IHD), Cerebral Vascular Accidents (CVA), Dietary Pattern and Body Mass Index (BMI) In Developing Secondary Systemic Hypertension." *American Journal of Pharmaceutical Sciences*, Vol. 5, No. 11, 2008.

[18] Hussain A, Noor HT, Nabi U. "Evaluation of role of increased perceived stress score and body mass index in causing secondary systemic hypertension in patients of Hepatitis C." *Journal of Cardiovascular Diseases and Diagnosis*, Vol. 6, No. 6, 2018, p. 343.

[19] Hussain, Azhar, Zubair, and Tabassum, Saad Muhammad. "Can we replace transient elastography i.e. Fibro scan with cheap biomarkers? A cross sectional study at lahore general hospital, Lahore." *Indo American Journal of Pharmaceutical Sciences,* Vol. 6, No. 5, 2019.

[20] Hussain, Azhar, et al. "Relationship of Derangements in Various Blood Indices and Coagulopathy with Liver Stiffness Index (Lsi) In Various Stages Of Fibrosis In Hepatitis C." *Indo American Journal of Pharmaceutical Sciences,* Vol. 6, No. 5, 2019.