ORIGINAL ARTICLE

Comparison of Sensitivity and Specificity of Aspartate Aminotransferase to Platelet Index (APRI) and FIB-4 with Transient Elastography: Fibro Scan in Chronic Hepatitis C Virus Infected Patients

HAKIM ALI ABRO[1], ASMA HAMEED[2], MEHWISH EJAZ[3], *HAMID KHALIL*[4]
[1]*Professor of Medicine, Chandka Medical College/Shaheed Mohtarma Benazir Bhutto Medical University, Larkana*
[2]*Senior Registrar, Department of Medicine Unit 2, Sandeman Provincial Hospital/Bolan University of Medical & Health Sciences Quetta*
[3]*House Officer, Department of Medicine, Fatima Memorial Hospital Lahore*
[4]*Assistant Proffesor Of Cardiology , Punjab Institite Of Cardiology , Lahore*
Correspondence to Prof. Hakim Ali Abro Email: abrohakim@gmail.comCell 0300-3402414

ABSTRACT

Aim: To compared readily available non-invasive fibrosis indexes with fibro scan for the fibrosis staging and predicting its progression in Pakistani population.
Study Design: Retrospective cross-sectional study
Place and Duration of Study: Department of Medicine, Chandka Medical College Hospital, Larkana from 1st July 2019 to 31st December 2019.
Methodology: One thousand four hundred and sixty four hepatitis C virus (HCV) infected patients were got complete blood count, liver function tests, enzyme-linked immunosorbent assay, polymerase chain reaction 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 aspartate aminotransferase (AST) to Platelet Index (APRI) and FIB-4 with fibro scan.
Results: Readily available serum indexes AST to Platelet Index 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%.
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.
Key words: 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 cause of death among individuals almost affection 71 million people worldwide. It is one of the leading causes of liver cirrhosis and hepatocelullar 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[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 causes cirrhosis and cancer which is deadly[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].

METHODOLOGY

This retrospective cross-sectional study was conducted at Department of Medicine, Chandka Medical College Hospital, Larkana from 1st July 2019 to 31st December 2019. Patients of chronic viral hepatitis C infection were identified who were only positive for HCC antibodies by detecting HCV RNA by Polymerase Chain Reaction (PCR)

Received on 14-01-2020
Accepted on 17-06-2020

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 not included. Total 1898 patients were engaged over this period. Quantitative determination of the Fibro scan score (Liver Stifness 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 ZioI transient elastography breaking points for staging of fibrosis according to Metavir System of fibrosis. 2.5-8.8 fibroscan value referred as F0-F1, 8.9-9.6 fibroscan value referred as F2, 9.7-14.6 fibroscan 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.

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 analyses were 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

There were 1014 (69.3%) female patients female and 450 (30.7%) were male patients. 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. As for genotype, 1069 (73%) patients are 3a, 380 (26%) are 1b and 15(1%) are 1A. 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 1). 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 shown in Table 2.

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 for Fib-4 score showed a statistically significant relationship with Person's correlation coefficients (R) values=0 .458 (P value = 0.0001). 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). 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 is 0. 131) in different stages of fibrosis in Hepatitis C (Fig. 2). 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 3, Figs. 3-4).

Table 1: Demographic information of the patients

Variable	No.	%
Gender		
Male	450	30.7
Female	1014	69.3
Marital status		
Married	1367	93.4
Unmarried	94	6.6
Genotype		
3a	1069	73.0
1b	380	26.0
1A	15	1.0
Stage of Fibrosis		
F0 – F1	899	61.4
F2	87	5.9
F3	218	14.9
F4	260	17.8

Table 2: Mean ± standard deviation of the different variables

Variable	Mean±SD
Age	40.57±13.04
Baseline viral load	1031912.81±6684292.11
Albumin	3.5473±
Bilirubin	1.24±1.34
AST	73.88±66.93
ALT	80.40±193.56
Platelet count	613020.59±2607641.77
Alkaline phosphatase	301.37±137.36
APRI	0.61±0.54
Fib-4	1.13±0.67

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

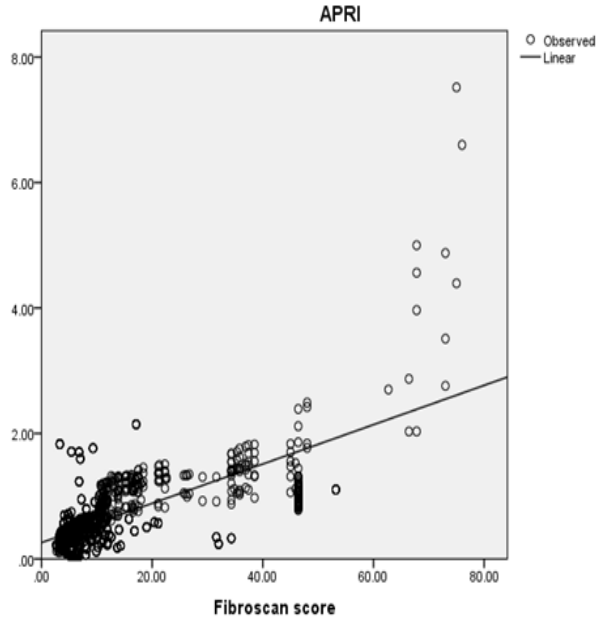


Fig.2. Scatter-plot for Fib-4 vs fibro scan score

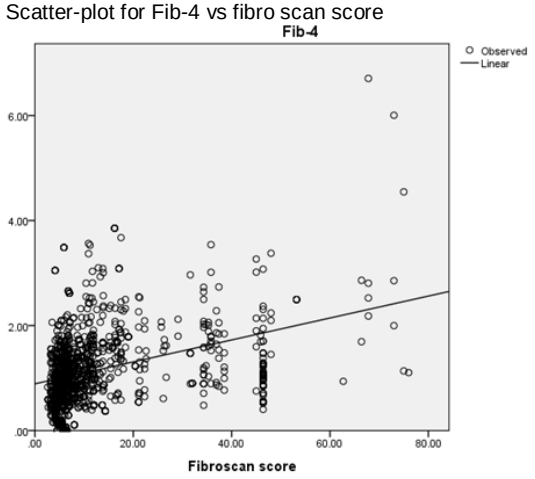


Table 3: ROC curve analysis for validation of serum APRI, and FIB-4HCVinfectedpatients

Stage	Cutoff value	Spe %	Sen %	AUC
APRI				
F0–F3	<0.5	68.0	56.2	0.54
F4-F5	87.6	74.0	0.864	
FIB-4				
F0–F3	<1.45	65.4	51.0	0.521
F4-F5	>3.25	72.3	53.2	0.801

Diagonal segments are produced by ties

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

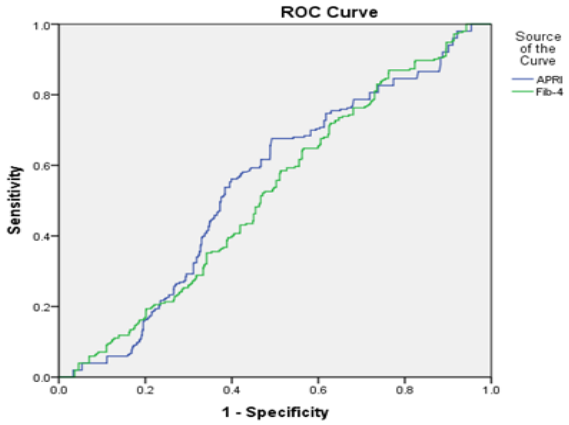
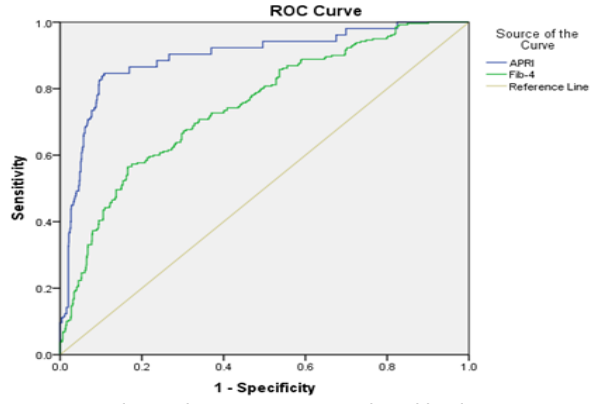


Fig. 4: ROC Curve for APRI and Fib-4 for F4



Diagonal segments are produced by ties

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 2nd most common form is 1a[11,12] and exactly corresponding of what we observed in this study. Genotype 3awas in86% 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.[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 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[17] 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% and specificity 72.3% with AUC=0.801.[18,20]

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.

REFERENCES

1. Attaullah S, Khan S, Ali I. Hepatitis C virus genotypes in Pakistan: a systemic review. Virol J 2011.
2. Thampanitchawong P, Piratvisuth T. Liver biopsy: complications and risk factors. World J Gastroenterol 1999.
3. Ahmad W, Ijaz B. A comparison of four fibrosis indexes in chronic HCV: Development of new fibrosis-cirrhosis index (FCI). BMC Gastroenterol 2011
4. Schmid P, Bregenzer A, Huber M, Rauch A, Jochum W, Müllhaupt B,et al. Progression of Liver Fibrosis in HIV/HCV Co-Infection: a comparison between Non-Invasive Assessment Methods and Liver Biopsy. PLoS ONE 2015;10(9):e0138838.
5. Crossan C, Tsochatzis EA, Longworth L, 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 Technol Assess 2015;19:409
6. Association for the Study of the Liver, European. EASL Clinical Practice Guidelines: Management of hepatitis C virus infection. J Hepatol 2014
7. EASL-ALEH Clinical Practice Guidelines: Non-invasive tests for evaluation of liver disease severity and prognosis. J Hepatol 2015; 63: 237–26
8. Adams LA, Sterling RK. Developing a new algorithm to diagnose advanced liver fibrosis: A lift or a nudge in the right direction? J Hepatol 2017.
9. Fallatah HI. Noninvasive biomarkers of liver fibrosis: an overview. *Adv Hepatol* 2014;2014.
10. Boursier J, deLedinghen V, Zarski JP, Fouchard-Hubert I, Gallois Y, Oberti F, et al. Comparison of eight diagnostic algorithms for liver fibrosis in hepatitis C: new algorithms are more precise and entirely noninvasive. Hepatology 2012;55(1):58-67.
11. Zarski JP, Sturm N, Guechot J, Paris A, Zafrani ES, Asselah T, et al. Comparison of nine blood tests and transient elastography for liver fibrosis in chronic hepatitis C: the ANRSHCEP-23 study. J Hepatol2012;56(1):55-62.
12. . Giannini C, Brechot C. Hepatitis C virus biology. J Virol 2003,10:S27-S38.
13. Alter MJ: Epidemiology of hepatitis C. Hepatology 1997; 26:62S-65S.
14. Raja NS, Janjua KA: Epidemiology of hepatitis C virus infection in Pakistan. J Microbiol Immunol Infect 2008, 41:4-8.
15. Idrees M, Riazuddin S. Frequency distribution of hepatitis C virus genotypes in different geographical regions of Pakistan and their possible routes of transmission. BMC Infect Dis 2008; 8: 69.
16. Serag HB. Hepatocellular carcinoma and hepatitis C in the United States. Hepatology 2002, 36:S74-S83.
17. Hussain A, et al., Role of ischemic heart disease (ihd), cerebral vascular accidents (CVA), dietary pattern and body mass index (bmi) in developing secondary systemic hypertension. Indo Am J P Sci 2018; 05(11).
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. J Cardiovasc Dis Diagn 2018; 6: 343.
19. Can We Replace Transient Elastography i.e. Fibro scan with cheap biomarkers? a cross-sectional study at Lahore General Hospital, Lahore. Indo Am J P Sci 2019; 06(05).
20. Hussain A, 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 Am J P Sci 2019; 06(05).