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Original article

Noninvasive Fibrosis Profiling in HCV-Positive Patients: A Tertiary Care Perspective

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Abstract

Background*: Hepatitis C virus (HCV) infection remains a major public health concern due to its progression toward chronic liver disease, cirrhosis, and hepatocellular carcinoma. Early detection and staging of hepatic fibrosis are critical for clinical management, yet liver biopsy, the conventional gold standard method poses risks and has limited feasibility in resource-constrained settings.*

Methods*: This study evaluated the diagnostic performance of two widely used noninvasive serum fibrosis indices, Aspartate Aminotransferase-to-Platelet Ratio Index (APRI), and Fibrosis-4 (FIB-4), in predicting liver fibrosis among HCV-positive patients in a tertiary care hospital in Telangana, India.*

Results*: Out of 10,500 individuals screened, 113 (1.07%) were confirmed HCV positive. The majority were males (56.6%), with the highest prevalence in the 51–60-year age group. Liver fibrosis staging revealed that 44.2% had no fibrosis, 11.5% mild fibrosis, 39.8% moderate fibrosis, and 4.4% severe fibrosis. Age, AST, ALT, and bilirubin levels showed significant positive correlations with fibrosis, while platelet count and serum albumin were inversely correlated. The mean APRI and FIB-4 scores progressively increased with fibrosis severity, peaking at 2.673 and 12.164, respectively, in patients with cirrhosis. ROC analysis demonstrated higher diagnostic accuracy of FIB-4 compared to APRI across all fibrosis stages, with both indices showing excellent performance for severe fibrosis prediction (AUROC >0.98). Viral load, however, showed no significant association with fibrosis stage.*

Conclusion*: The findings underscore that FIB-4 and APRI serve as reliable, cost-effective, and noninvasive alternatives to biopsy for staging liver fibrosis in HCV patients, with FIB-4 demonstrating superior predictive utility. These indices can enhance patient stratification and guide management decisions, especially in resource-limited settings.*

Keywords *- HCV, FIB-4, APRI, Liver Fibrosis, ELISA, RT-PCR, Truenat, FibroScan, Noninvasive*

Introduction

Hepatitis C Virus (HCV) is one of the major bloodborne chronic viral infections. HCV infection can lead to mild to major illness or life-threatening complications, such as cirrhosis of the liver and hepatocellular carcinoma. According to the WHO, it was estimated that more than 5 crore people are living with HCV infection, another 10 lakhs of people are getting infected every year globally, and 2.4lakh people died of HCV or its related complications during 2022 alone.[1]Because of its insidious onset, HCV infections are left undiagnosed, and it is documented that less than 20% of the HCV- infected people know that they are harbouring the virus in their body.[2] An unsettling fact is that 75- 80% of the HCV-infected people remain asymptomatic and will be unaware of their infection.[3,4] In India, it is estimated that more than 50 lakh people are living with HCV.[1]

It is worth noting that 30% of the HCV-infected patients show spontaneous clearing of the virus without any medical intervention, and the remaining 70% may develop chronic HCV infection.[5] It is also worth noting that HCV prevalence rates are highest in chronic kidney disease patients due to their frequent need of dialysis. Apart from haemodialysis patients, IV drug abusers and healthcare workers due to needlestick injuries are at a higher risk. To prevent HCV transmission among dialysis patients, it is very important to screen them for HCV infection periodically. Enzyme Linked Immunosorbent Assay (ELISA) is the most used diagnostic technique to

screen for HCV status among large populations. If positive in the screening test, Nucleic Acid Amplification Technology (NAT) is employed to detect both qualitative and quantitative levels of HCV RNA. Further clinical decisions are made based on a combination of invasive and noninvasive methods, along with radiological investigations. Invasive methods, although they provide valuable insight into the liver health status, are not feasible, and it is sometimes not recommended to perform procedures like liver biopsies frequently. Noninvasive (direct and indirect) assessments are the preferred choice given their simplicity and ease of performance with less ambiguous results compared to biopsies.

The risk of liver cirrhosis increases manifold in chronic HCV-infected people. In this context, it is important to identify the seroprevalence of HCV infections and their liver health status by performing direct biological methods like Fibrotest, FibroMeter, Hepa score, and indirect biological methods such as Fibrosis Indices (FIB-4 Index), Aspartate Aminotransferase-to-Platelet Ratio Index (APRI), and Age-Spleen Platelet ratio. These indices help the physician in staging the liver disease and give a valuable insight into the treatment options, disease course, and prognosis. Hence, the current study aimed to find the seroprevalence of HCV and viral load in patients and to assess their FIB-4 index and APRI score.

Materials and Methods

Ethical approval

Ethical approval for this study was obtained from the Institutional Ethics Committee of Meenakshi Medical College Hospital and Research Institute vide reference ICE//004/Microbiology dated 12/02/2021. Permission to collect patient data and sera samples for testing was granted by the medical superintendent of the District Hospital, Khammam. (Currently, as the Government General Hospital).

Inclusion criteria

Patients of all age groups above 18 years, and both sexes visiting District Hospital Khammam were screened for HCV infection, and the ones who tested positive were included in the study.

Exclusion criteria

Patients below 18 18-year-old age. Patients who tested negative for HCV infection and patients with existing liver ailments like fatty liver and hepatocellular carcinoma were excluded from the study.

Study design and study population.

A descriptive cross-sectional study was conducted at Government General Hospital, Khammam, Telangana, India. This Study included 113 HCV-positive patients from 10,500 patients who underwent screening as part of differential diagnosis, including patients undergoing dialysis, surgery patients, patients with abnormal LFT reports, presenting symptoms like febrile illnesses, healthy blood donors, close contacts of HCV-positive cases, and other high-risk populations from January 2022 to December 2024. Clinical details were obtained through questionnaires from each infected case. Written informed consent was obtained from each participant, and confidentiality was maintained.

Baseline Investigations, ELISA screening, and viral Load detection

The baseline investigation data, like the Complete Blood Picture, Liver Function Tests, which include ALT, AST, Serum Bilirubin, and Albumin, Radiological examination data (Ultrasound Scanning), and demographic information obtained from the patients, were recorded before sample collection. A set of blood samples, such as 2ml of EDTA and 2ml of plain, was collected from each patient by following aseptic protocol. Caution was taken for dialysis patients; samples were collected before Heparin administration.

HCV ELISA test

The HCV antibody tests were performed as per the manufacturer's protocol[6] (ErbaLisa HCV Gen 4 Ag & Ab, Transasia, Mumbai). The HCV Gen4 Ag-Ab is a two-step solid-phase enzyme immunoassay principle for the simultaneous qualitative detection of HCV antigens and HCV antibodies in human serum. The kit consists of a pre-coated monoclonal antibody and antigen on microwells. The HCV core antigens include Core, NS3, NS4, NS5, and Anti-HCV antibodies, which capture specific targets from patient serum or plasma. In the testing procedure, test specimens, along with blank, positive, negative controls, and diluted Conjugate-1 (conjugated anti-HCVcAg antibodies) were added to the wells. The wells were incubated at 37ºC to facilitate the antigen and antibody binding. After incubation, wells were washed with washing buffer to remove the unbound material. Then conjugate -2, which contains conjugated anti-human IgG antibodies, was added to the wells to form an antigen-antibody complex, and the wells were incubated at 37ºC, followed by the second wash using washing buffer. Later, a chromogenic substrate-TMB was added to the wells to produce colour. Then the reaction was

stopped by adding a stop solution. Optical density was measured at 450nm, and the results were calculated and interpreted against control assays.

RT-PCR analysis

The quantification of viral load in the samples was detected through Real Time PCR by following the manufacturer's protocol[7] (Truenat HCV Qualitative and Quantitative, Molbio Diagnostics, Goa). A chip-based real-time reverse transcriptase PCR (RT-PCR) designed to assess qualitative and quantitative detection of HCV RNA. It consists of a micro-PCR chip, freeze-dried reagent micro tubes. Followed by the RNA extraction, 6µL of purified RNA was added to the reagent microtube and allowed the pellet to dissolve completely without agitation. From this, 6µL of the clear reaction mixture was transferred into the central well of the Truenat HCV Chip. The prepared chip was then loaded into the Truelab Real Time Quantitative micro-PCR Analyzer, which automatically initiated the amplification upon confirmation. Amplification was monitored in real-time, with fluorescence curves generated for both the HCV RNA target and the internal positive control (IPC). A positive result was indicated by exponential amplification crossing the threshold with a corresponding cycle threshold (CT) value, while the IPC ensures assay validity. The analyser calculated the viral RNA copies/ml based on the CT Value and fluorescence.

The Aspartate Aminotransferase to Platelet Ratio Index (APRI) is calculated by the formula[8]:

APRI = [AST *(IU/L)*/**(ULN)/ platelet count (*10^9 /L)] x 100**

ULN = Upper limit of Normal AST level in IU/L

The APRI is a simple, noninvasive method that identifies significant hepatic fibrosis using standard laboratory tests. It is based on the understanding that as the liver fibrosis increases along with higher portal blood pressure, it results in reduced thrombopoietin production by hepatocytes, greater platelet sequestration in the spleen, and reduced clearance of AST.

The FIB-4 is an index that accurately distinguishes between mild and moderate fibrosis using standard laboratory tests. Furthermore, it has the potential to decrease the necessity for liver biopsies in as many as 70% of patients[7]. It is calculated by the formula[9]:

FIB-4 = AST*(IU/ml)* *** age***(years)*/**platelet count (*10^9 /L) * ALT**$^{1/2}$ *(IU/ml)*

Descriptive statistical analysis was employed to assess the statistical significance. Qualitative data were expressed as numbers (%) and compared using Fisher's exact test or Pearson's chi-square test. A *p-value* of <0.05 was considered significant. Statistical analysis was conducted using the SPSS 25.0 statistical package. The diagnostic performance of fibrosis prediction markers APRI and FIB-4 in distinguishing severe fibrosis from mild-to-moderate fibrosis was assessed using area under the receiver operating characteristic curve (AUROC) analysis.

Results

Out of 10,500 individuals screened for HCV, 113 (1.07%) tested positive. Among them, male preponderance was observed at 56.63%, (64 individuals). The remaining 43.3% (49 individuals) were women (Figure 1).

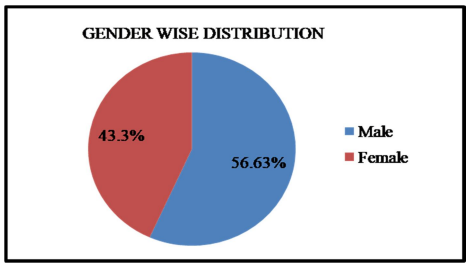


Figure 1. Frequency distribution of HCV-positive individuals according to gender.

The most affected occupational group in the study was housewives (36%), followed by private employees (27.43%), agriculture workers (26.54%), business personnel (7.1%) and drivers (2.65 %)
(Figure 2).

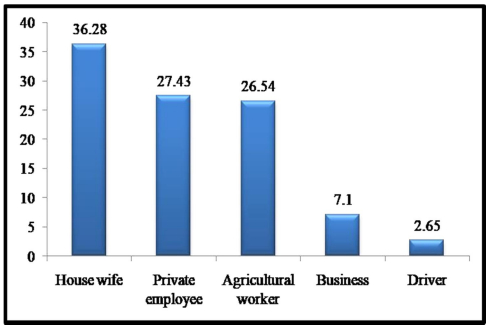


Figure 2. Frequency distribution of HCV-positive individuals according to occupation

The most affected age group was between 51 and 60 years (35.4%), followed by the 41 to 50 years age range at 24.7% (Figure 3).

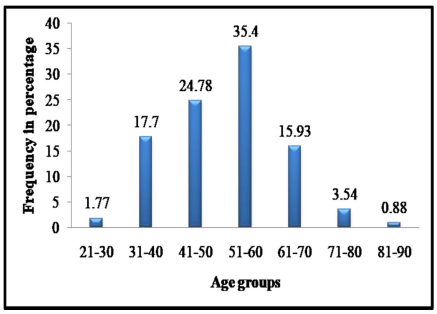


Figure 3. Distribution of HCV-positive patients age-wise

Liver fibrosis assessment revealed that 44.2% had no fibrosis or cirrhosis, 11.5% exhibited mild fibrosis, 39.8% had moderate fibrosis, and 4.4% had severe fibrosis or cirrhosis (Figure 4). Age and the presence of fibrosis show a significant association (p=0.0002) and a higher prevalence in older age groups (Table 1).

Table 1. Association of age and Liver Fibrosis

		Liver Fibrosis		Total	p-value
Age Distribution		No	Yes		0.0002
	21-30	0 (0%)	2 (100%)	2 (100%)	
	31-40	10 (50%)	10 (50%)	20 (100%)	
	41-50	13 (46.42%)	15 (53.57%)	28 (100%)	
	51-60	18 (45%)	22 (55%)	40 (100%)	
	61-70	7 (38.88%)	11 (61.11%)	18 (100%)	
	71-80	2 (50%)	2 (50%)	4 (100%)	
	81-90	0 (0%)	1 (100%)	1 (100%)	
Total		50 (46.9%)	63 (53.09%)	113 (100%)	

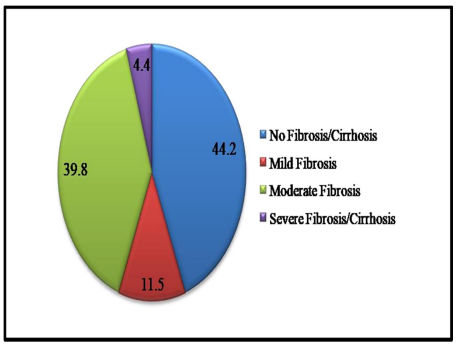


Figure 4. Frequency distribution of the severity of liver fibrosis Table 1. Association of age and Liver Fibrosis

The most common risk factor was therapeutic injections, at about 80%, followed by blood transfusions at 26.5% and a history of dialysis at 25.7%. Other reported factors included past surgeries (23%), invasive dental treatment (7.1%), and tattoos (7.1%) (Figure 5).

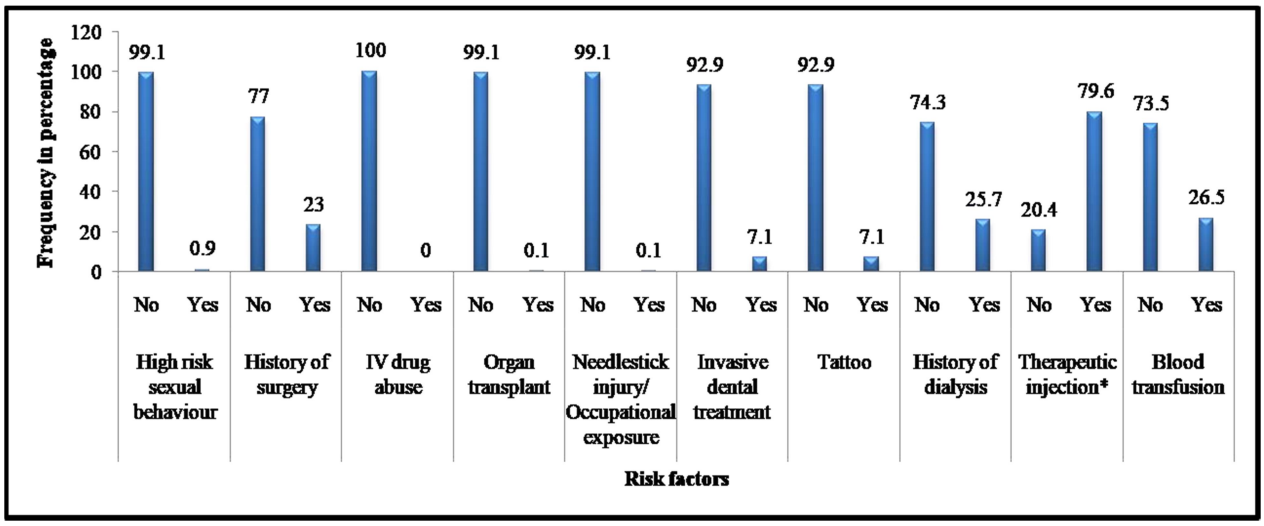


Figure 5. Frequency distribution of modes of transmission of Hepatitis C Virus

Intravenous drug users are not found in the study. The relationship between baseline investigations and fibrosis showed significant associations between liver fibrosis and AST, ALT, bilirubin, and platelet count (Table 2).

Table 2. Descriptive statistics and the association between blood investigation parameters and fibrosis

Blood Investigations	Min	Max	Mean ±SD	Median	Inter Quartile Range	Pearson Correlation
HCV Viral Load	0	5000000	398312 ± 971133.016	12000	179585	0.159
Serum Albumin	0.8	6	3.717 ± 0.719	3.8	0.5	-0.185
NLR	1	20	3.017 ± 3.267	2	1	-0.072
AST	8	312	39.763 ± 40.865	29.5	26	0.369**
ALT	1	145	30.771 ± 26.616	23	26	0.302**

Platelets	14700	2340000	227627.193 ± 223139.979	200000	120000	-0.256*
Haemoglobin	3.9	15	10.48 ± 2.34	10	3.9	0.143
Serum Bilirubin	0.2	3.2	0.715 ± 0.503	0.6	0.5	0.429**

** = Correlation is significant at the 0.01 level. * = Correlation is significant at the 0.05 level

According to APRI, FIB-4, NLR scores, for people without fibrosis, the average APRI score was 0.231, while those with fibrosis had a higher average of 0.697. The average FIB-4 score was 0.861 in those without fibrosis and 3.257 in those with fibrosis. Both scores increased with worsening fibrosis. In severe fibrosis or cirrhosis, the APRI score was highest at 2.673, as was the FIB-4 score at 12.164. NLR values ranged from 1 to 20 (mean 3.017 ± 3.267) but showed no significant correlation with fibrosis stage (r = -0.072, p = 0.446), indicating limited diagnostic value for staging liver disease in HCV patients (Tables 3 and 4).

Table 3. Association between APRI, FIB-4 and Liver Fibrosis

	Liver Fibrosis	
	No	**Yes**
APRI		
Sample Size	**50**	**63**
Mean ± SD	**0.231 ± 0.329**	**0.697 ± 0.709**
Median	**0.15**	**0.471**
Min-Max	**0.056-2.37**	**0.158 – 4.25**
Inter Quartile range	**0.145**	**0.383**
FIB-4		
Sample Size	**50**	**63**
Mean ± SD	**0.861 ± 0.304**	**3.257 ± 3.449**
Median	**0.89**	**2.12**
Min-Max	**0.161 – 1.42**	**0.7 – 19.28**
Inter Quartile range	**0.44**	**1.25**

Table 4. Association between APRI and FIB-4 with levels of fibrosis

Severity of fibrosis			
	Mild	**Moderate**	**Severe**
APRI			
Sample Size	13	45	5
Mean ±SD	0.323 ± 0.11	0.585 ± 0.33	2.673 ± 1.02
Median	0.265	0.506	2.655
Min-Max	0.158 – 0.51	0.18 – 1.47	1.522 – 4.25
Inter quartile range	0.17	0.326	0.80
FIB-4			
Sample Size	13	45	5
Mean ±SD	1.679 ± 0.69	2.723 ± 1.49	12.164 ± 6.91
Median	1.75	2.23	14.72
Min-Max	0.7 – 2.81	1.21 – 7.63	4.41 – 19.28
Inter quartile range	0.84	1.04	12.03

Overall, factors such as age, AST, ALT, and bilirubin increased along with fibrosis severity, whereas platelet count and albumin levels decreased. Interestingly, NLR, HCV viral load did not appear to have a significant association with the stage of fibrosis (Table 5).

Table 5. Correlation between variables and liver fibrosis

Variable	Correlation coefficient	p-value
Age	0.277**	0.003
HCV Viral load	0.159	0.093
Haemoglobin	0.143	0.131
Platelets	-0.256**	0.006
ALT	0.302**	0.001
AST	0.369**	0.0001
Serum Bilirubin	0.429**	0.0001
NLR	-0.072	0.446
Serum Albumin	-0.185	0.05

** = Significant correlation. *p*-value <0.05 is significant.

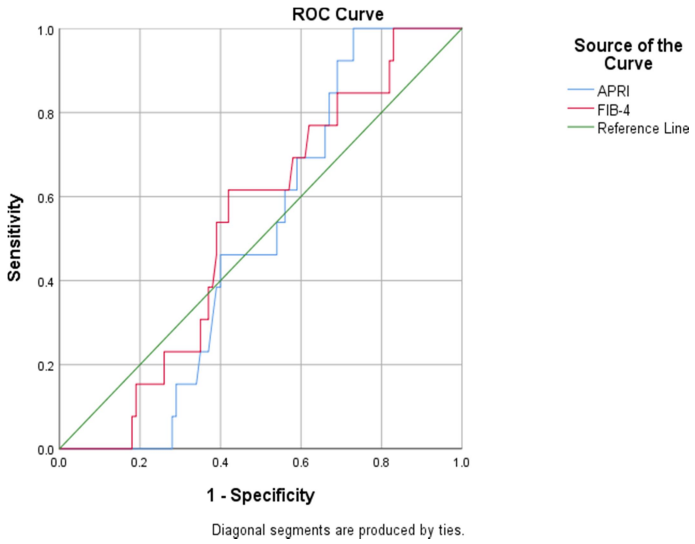
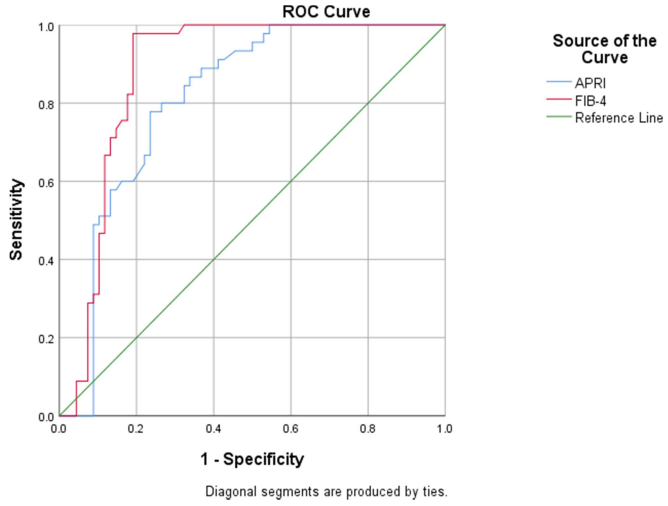


Figure-6. ROC curves for comparison of diagnostic accuracies of APRI and FIB-4 for diagnosing mild fibrosis.

Figure-7. ROC curves for comparison of diagnostic accuracies of APRI and FIB-4 for diagnosing moderate fibrosis.



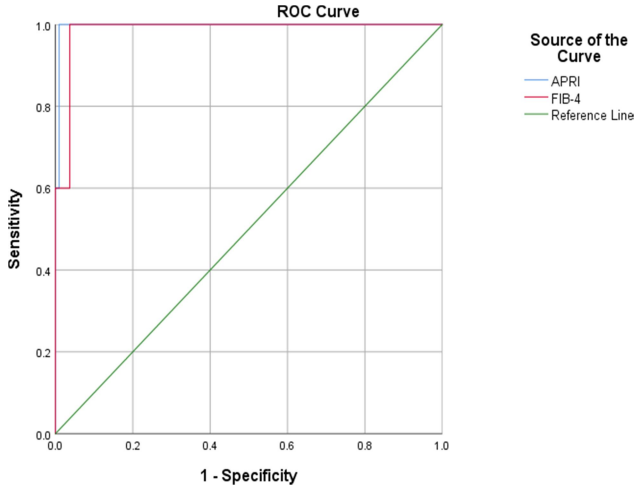


Figure-8. ROC curves for comparison of diagnostic accuracies of APRI and FIB-4 for diagnosing severe fibrosis.

The Area Under Curve (AUC) for FIB-4 and APRI in predicting mild fibrosis is 0.533 and 0.499, respectively. Moderate accuracy: FIB-4 may be slightly better (Figure 6). Whereas the AUC for FIB-4 and APRI in predicting moderate fibrosis is 0.879 and 0.812 shows respectively good accuracy; FIB-4 likely superior, (Figure 7). The AUC for FIB-4 and APRI in predicting severe fibrosis is 0.985 and 0.996, exhibiting High accuracy; both scores are reliable, FIB-4 preferred (Figure 8).

Discussion

Due to the advancements in the treatment modalities and options available for HCV treatment, the number of people living with chronic HCV infection is increasing. Although the survival rate is increasing, this itself poses a higher risk of liver fibrosis due to the viral infection. The risk of liver cirrhosis increases manifold in chronic HCV-infected people. Invasive liver fibrosis assessment methods, like liver biopsy is not an option in a weak chronic HCV-infected person. Liver biopsy also poses greater risks of complications later in life.[10] Hence, noninvasive methods are the preferred choice of tests to assess the liver fibrosis. Imaging methods such as real time shear wave elastography and magnetic resonance elastography are accurate in liver fibrosis assessments but are costly and not available in tier two towns and rural areas. Hence, noninvasive markers such as the FIB-4 index and the ALT to platelet ratio are often selected to assess liver fibrosis status. This study was conducted to assess the reliability of FIB-4 and APRI indices to accurately predict liver fibrosis in HCV-infected patients.

The current study found a significant correlation between age, serum albumin, serum AST, ALT, and liver fibrosis. It was also found that platelet count, and serum albumin levels were negatively correlated with liver fibrosis (Table-5). A similar observation was found in a study by Al Danaf *et al.*[11] That means patients with liver fibrosis have thrombocytopenia and lower serum albumin. These routine tests are invaluable in predicting the liver fibrosis. An interesting observation seen in this study is that there is no significant correlation between HCV load and the severity of liver damage or fibrosis (Table-5). This indeed proves the known fact that the liver damage is more due to immune- mediated injury rather than the cytopathic effect of the virus. A similar observation was reported by Anand et al.[12] The viral load ranged from undetectable levels to several million copies in the HCV- infected patients. The study unravelled a hotspot of HCV infection in a village where tens of families were infected with HCV due to unsafe injection practices of a quack rural medical practitioner, as alleged by the patients. This revelation further reinforces the importance of universal safety precautions in preventing infections. Out of 10,500 people screened for HCV, 113 tested positives. If we factor out the hotspot village where unsafe needle practice was practiced, the prevalence would have been much lower.

The APRI and FIB-4 indices increased proportionately as the fibrosis of the liver progressed further. Receiver Operator Characteristic (ROC) curve was used to study the sensitivity and specificity of APRI and FIB-4 indices in predicting the severity of liver fibrosis. It was found that the FIB-4 index is better at predicting mild, moderate, and severe fibrosis as compared to any other noninvasive marker, only next to APRI. This observation was also confirmed by various other studies done previously.[9,13,14]It was observed that in mild liver fibrosis, the sensitivity of predicting fibrosis with APRI and FIB-4 is a little less compared to moderate and severe fibrosis. Nevertheless, these indices were useful in differentiating mild/moderate from severe liver

fibrosis and are also reported by Maheshwari *et al* in 2013.[15] The Area Under Curve (AUC) for FIB-4 and APRI in predicting mild fibrosis is 0.533 and 0.499, respectively (Figure 6). Whereas the AUC for FIB-4 and APRI in predicting moderate fibrosis is 0.879 and 0.812, respectively (Figure 7). The AUC for FIB-4 and APRI in predicting severe fibrosis is 0.985 and 0.996, respectively (Figure 8). A value of the Area Under Curve (AUC) for FIB-4 and APRI closer to 1 is considered highly specific and sensitive. This also proves that FIB-4 is a better predictor of fibrosis than APRI.[14] Both FIB-4 and APRI had shown moderate accuracy in predicting moderate fibrosis and high accuracy in predicting severe fibrosis (Table 4).

From the ROC (Receiver Operating Characteristic) curve analysis, it is established that both FIB-4 and APRI are very good in predicting the liver fibrosis and FIB-4 is superior to APRI in every stage of fibrosis prediction. This was also observed in studies conducted by Rungta *et al* in 2021[16] and Khare S *et al* in 2020.[17] Although FIB-4 is superior to APRI, the latter is more suited for resource- limited settings where multiple noninvasive parameters cannot be assessed. The advantage of APRI is that with only two parameters, it can predict liver fibrosis with reasonable sensitivity and specificity. A study by Wong S *et al* found that APRI can be used as an alternative to FibroScan for screening liver fibrosis, and the accuracy of APRI was found to be 78.2% versus the accuracy of FibroScan which stood at 79.7%.[18] However, studies have found that FIB-4 consistently outperforms APRI for advanced fibrosis, with higher AUROC and stronger predictive power. We found similar results in this study too. The study acknowledges the inherent variability of serum fibrosis markers at different stages of liver disease. Furthermore, even when considering liver biopsy as the gold standard, its use is complicated by inter- and intra-observer variability.

Conclusion

Our study found that FIB-4 and APRI are both invaluable markers of liver fibrosis. They can be used as alternatives to liver biopsy, FibroScan and other radiological examination methods, which are both expensive and unavailable in many areas. FIB-4 and APRI indices can be used for staging of liver fibrosis without the need for biopsies. These indices can be used for the prediction of both long-term and short-term prognosis in HCV-infected individuals.

Declarations

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