

Research Article

Simplified Cirrhosis Staging Algorithm for HCV Treatment Scale-up in Community Setting in Punjab, Pakistan

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Abstract

Background: Pakistan has a high prevalence of the hepatitis C virus (HCV), but there is insufficient evidence and limited access to HCV treatment.

Objectives: This study aimed to evaluate the diagnostic accuracy of non-invasive tests, including simple blood tests and hepatic ultrasonography (USG), in diagnosing cirrhosis among Hepatitis C (HCV) patients compared to Fibro-scan.

Methods: This retrospective cross-sectional study was conducted over one year from March 2022 to March 2023 at the Hepatitis Prevention and Treatment Clinic (HPTC), Lahore, Pakistan. The study included 844 HCV patients with positive polymerase chain reaction (PCR) results. Various parameters were analyzed, including liver function tests, Fibrosis-4 (FIB-4) index, AST to Platelet Ratio Index (APRI), USG results, and Fibrosis scores on Fibro-scan. A Liver Stiffness Measurement (LSM) of ≥ 12.5 kPa on Fibro-scan indicated cirrhosis. Statistical analysis was performed using SPSS version 26.0, and diagnostic performance was assessed through sensitivity, specificity, predictive values, and ROC curve analysis.

Results: Based on LSM values, 28% of the patients were cirrhotic. Significant differences were observed in several parameters between cirrhotic and non-cirrhotic patients. When using APRI ≥ 1.50 or Fib-4 index ≥ 1.45 as cutoff values for cirrhosis, the combination showed sensitivity, specificity, and negative predictive values of 62% (C.I. 55.5-68.2%), 97% (C.I. 95.4-98.1), and 87%, respectively.

Conclusion: A combination of APRI and FIB-4 demonstrated good diagnostic accuracy for determining cirrhotic status in HCV patients, while USG-documented chronic liver disease showed limited value in improving correct cirrhosis categorization.

Keywords: Liver Cirrhosis, Hepatitis C, Ultrasonography, Aspartate Aminotransferases, Platelet Count.

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Received: 30-09-2025 | **Accepted:** 31-12-2025

Introduction

Pakistan is among the most populous countries affected by hepatitis C virus (HCV) infection. A community-based survey estimated the national prevalence of hepatitis C virus (HCV) infection in Pakistan to be approximately 4.8%, with a higher prevalence reported in Punjab province (6.7%), indicating a substantial regional burden. These findings are consistent with more recent estimates highlighting the significant HCV burden in Pakistan^{1,2,3}. The consequences of this pervasive HCV presence are stark,

manifesting as escalated instances of liver-related conditions such as decompensated liver disease and hepatocellular carcinoma (HCC), alongside a broader spectrum of non-liver complications and mortality rates. These tribulations are acutely felt in low and middle-income countries (LMICs) like Pakistan, underscoring the pressing need for transformative measures.⁴

Within this backdrop of adversity, the advent of highly efficacious, concise, and well-tolerated direct-acting antiviral (DAA) treatments presents an important opportunity. This confluence of advancements aligns harmoniously with the World Health Organization's (WHO) goal to eliminate HCV by the year 2030.⁵ Pakistan is poised to play a pivotal role in this global vision. Realizing this ambition hinges on the monumental task of scaling up HCV treatment, aiming to extend its reach to hundreds of thousands of patients annually. A



Production and Hosting by KEMU

<https://doi.org/10.21649/jspark.v4i4.790>
2959-5940/© 2024 The Author(s). Published by Journal of Society of Prevention, Advocacy and Research (JSPARK), King Edward Medical University Lahore, Pakistan.
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shift from exclusive specialist centers to community clinics run by proficient general practitioners emerges as a potent approach. However, several challenges hinder this progress, including high costs, limited availability of tools for staging liver fibrosis, and a large proportion of undiagnosed individuals in the population.⁶

Noteworthy strides have been made in the quest for non-invasive liver markers, with markers such as AST to Platelet ratio (APRI) and the Fibrosis-4 index exhibiting a commendable correlation with cirrhosis estimates derived from liver biopsies.⁷ Regrettably, their utility as standalone methods for classifying cirrhosis is hampered by limited sensitivity.⁸ Even liver biopsy, traditionally regarded as the gold standard for assessing liver fibrosis, is compromised by its dependence on the sampled tissue's size and its random nature, potentially yielding misleading results. Amid these challenges, the liver stiffness measurement (LSM) method executed through Fibroscan emerges as a promising avenue for diagnosing cirrhosis.⁹ However, its prohibitive cost and the need for specialized expertise restrain its broader application. Meanwhile, abdominal ultrasonography (USG), focusing on liver texture and indicators of portal hypertension, emerges as a viable alternative with high specificity for detecting cirrhosis.¹⁰

The Hepatitis Prevention and Treatment Program (HPTP), including the Hepatitis Prevention and Treatment Clinic (HPTC) and its network of clinics across Punjab, supports data collection and treatment scale-up. While Fibroscan is available at HPTC, most community clinics lack access to this facility. Although APRI and FIB-4 are established markers, their combined use within a simplified diagnostic approach for cirrhosis identification in community settings remains insufficiently evaluated. Our study therefore evaluates an algorithm based on APRI and FIB-4 for cirrhosis identification, using Fibroscan as the reference standard, and assesses the role of USG. The proposed simplified staging algorithm classifies patients as low-risk when both APRI and FIB-4 are below established thresholds, high-risk when both exceed thresholds, and recommends Fibroscan or specialist assessment only for discordant cases. This approach is intended to reduce dependence on Fibroscan in community-based HCV treatment programs.

Methods

This retrospective cross-sectional study reviewed records from March 2022 to March 2023 of HCV RNA-positive patients attending the HPTC in Lahore, Pakistan. Ethical approval was obtained from Pakistan Kidney and Liver Institute and Research Centre Lahore Pakistan (IRB#DS1221). The study included treatment-naïve patients with complete baseline laboratory data prior to initiation of HCV therapy, and treatment-experienced patients with available baseline data at least six months after completion of therapy. Exclusion criteria included patients consuming over 30 grams of alcohol per week and those testing positive for Hepatitis B surface antigen.

The analysis included 844 patients meeting inclusion criteria during the study period, all having complete baseline liver function tests, complete blood counts, and liver stiffness measurement (LSM) values. Among these, 327 patients had ultrasonography (USG) records available. USG was not routinely performed for all patients because this was a retrospective programmatic dataset collected across multiple referral pathways. Patients without archived USG reports were retained for APRI/FIB-4 analyses, while USG analyses were restricted to patients with available imaging records. This may introduce selection bias and is acknowledged as a study limitation.

Hepatic parenchymal stiffness as recorded in patient files was measured using Fibroscan (Echosens, Paris, France) based on transient elastography. Certified technologists performed measurements, with at least 10 valid readings per patient and an interquartile range (IQR) $\leq 30\%$ considered acceptable. Fibroscan (LSM ≥ 12.5 kPa) was used as a reference standard for cirrhosis classification, based on its validated correlation with liver biopsy findings¹¹

USG findings as documented in records were obtained using the Aplio 500 system (Toshiba). Chronic liver disease (CLD) was defined as coarse liver texture along with at least two of the following: increased gall bladder wall thickness, dilated portal vein, splenomegaly, varices, or ascites.¹²

AST, ALT, total bilirubin, albumin, platelet count, APRI, and FIB-4 index values were analyzed. APRI and FIB-4 were calculated using standard formulas, and validated cutoff values for cirrhosis were applied.^{13,14}

Data were entered and cleaned using Epi-Data version 3.1 and analyzed using SPSS version 26.0. Categorical variables were presented as frequencies (%), and continuous variables as median (IQR). Because continuous variables were not normally distributed, comparisons between groups were performed using the Mann-Whitney U test rather than the independent-samples t-test. Chi-square test was used for categorical variables. A p-value < 0.05 was considered statistically significant. Receiver Operating Characteristic (ROC) curve analysis was performed and 95% confidence intervals (95% CI) were calculated for AUROC, sensitivity, specificity, PPV and NPV where applicable.

Results

The study included 844 HCV patients, with a median age of 41 years (IQR: 33–50). Among them, 444 (52%) were female. Cirrhosis was identified in 237 (28%) patients, while 607 (72%) were non-cirrhotic based on Fibroscan results. Significant differences were observed between cirrhotic and non-cirrhotic groups in age, BMI, platelet count, albumin, total bilirubin, AST, ALT, CAP, LSM, APRI, and FIB-4 ($p < 0.05$). No significant differences were observed in gender, treatment history, diabetes,

hypertension, or steatosis ($p > 0.05$) (Table 1).

Cirrhotic patients had higher median age (47 vs. 38 years), higher BMI, and altered laboratory parameters compared to non-cirrhotic patients. Non-invasive fibrosis scores (APRI, FIB-4, LSM) were significantly higher in cirrhotic patients ($p < 0.001$) (Table 1).

Ultrasound findings (Table 2) showed that cirrhotic patients more frequently had chronic liver disease (22.8% vs. 1.3%), splenomegaly (47% vs. 7%), coarse liver texture (83% vs. 33%), and portal vein dilation (14% vs. 1.3%) ($p < 0.05$). Fatty liver frequency did not differ significantly between groups ($p = 0.215$).

The diagnostic performance of APRI and FIB-4 for cirrhosis is presented in Table 3. At APRI ≥ 1.50 , sensitivity was 76% (95% CI: 70.1–81.2%) and specificity was 84% (95% CI: 80.7–86.9%), with PPV of 65% and NPV of 90%. At APRI > 2.0 , specificity

increased to 91% with reduced sensitivity (60%). For FIB-4 ≥ 1.45 , sensitivity was 82% and specificity was 79%, with PPV of 61% and NPV of 92%. Higher cutoffs (FIB-4 > 3.25) demonstrated higher specificity (98%) but lower sensitivity (41%).

ROC analysis demonstrated good diagnostic performance for both APRI and FIB-4, with AUROC values of 0.88 and 0.87, respectively (Fig. 1).

Using combined cutoff values of APRI ≥ 1.50 and FIB-4 ≥ 1.45 , sensitivity was 62%, specificity 97%, PPV 89%, and NPV 87%. When either APRI ≥ 1.50 or FIB-4 ≥ 1.45 was used, sensitivity increased to 96%, with specificity of 66%, PPV of 52%, and NPV of 98%.

Among patients with available USG data, chronic liver disease and splenomegaly were more frequently observed in cirrhotic patients. No additional diagnostic parameters beyond sensitivity and specificity were included for USG.

Table 1. Profile of study participants by cirrhosis status among patients visited at HPTC, Lahore, Pakistan

Determinants	Cirrhotic (n=237)	Non-Cirrhotic (n=607)	Overall (844)	Test	P- value
Age (median IQR)	47(39-55 SD+)	38 (30-48 SD+)	41 (33-50 SD+)	Z=9.87	<0.001
Age (Years)					
<25	2(0.84%)	57 (9.3%)	59 (7%)	$\chi^2=45.32$	<0.001
25-49	135(57%)	417 (68.7%)	552 (65.4%)		
>50	100(42.2%)	133 (22%)	233 (27.6%)		
Gender					
Male	121 (51%)	283 (47%)	404 (48%)	$\chi^2=1.48$	0.225
Female	116 (49%)	324 (53%)	440 (52%)		
Genotype					
Genotype 1	27 (13%)	55 (9%)	82 (9.7%)	$\chi^2=12.56$	<0.001
Genotype 3	203 (86%)	537 (88.5%)	740 (87.7%)		
Others¥	7 (1%)	15 (2.5%)	22 (2.6%)		
Treatment					
Experience	29 (12.3 %)	61 (10 %)	90 (11%)	$\chi^2=0.89$	0.345
naive	207 (87.7 %)	546 (90 %)	753 (89%)		

BMI	27 (24-31)	25 (30-48)	26 (22-29)	Z=7.12	<0.001
Platelets count	153 (113-197)	231 (195-272)	216 (174-261)	Z=15.43	<0.001
Albumin	3.50 (3.2-3.9)	3.9 (3.7-4)	3.8 (3.5-4)	Z=12.67	<0.001
Total Bilirubin	0.80 (0.5-1)	0.60 (0.4-0.8)	0.6 (0.4-0.9)	Z=8.95	<0.001
AST	86 (63-129)	46 (36-63)	54 (38-80.36)	Z=14.22	<0.001
ALT	101 (67-151.50)	66 (49-98)	74 (51-112)	Z=10.38	<0.001
CAP	264 (228.5-298.5)	260 (221-296)	261 (223-297)	Z=2.02	0.044
LSM	23 (16-31.5)	6.7 (5.4-8.4)	8 (6-14)	Z=22.15	<0.001
APRI	2.36 (1.56-4)	0.86 (0.63-1.22)	1.04 (0.7-1.9)	Z=18.76	<0.001
Fib4	2.77 (1.68-4.68)	0.94 (0.68-1.34)	1.16 (0.75-2)	Z=17.89	<0.001

Continuous variables (reported as median [IQR]) were compared using the Mann-Whitney U test (Z-values reported). Categorical variables (reported as n [%]) were compared using Pearson's χ^2 test (χ^2 -values reported). All tests were two-tailed, with p-values <0.05 considered statistically significant.

Table 2. Ultrasound findings of study participants by cirrhosis status among patients visited at HPTC, Lahore, Pakistan

USG performed	Cirrhotic (n=171)	Non-Cirrhotic (n=156)	Overall (327)	Test	P- value
Chronic Liver Disease					
Absent	132 (77.2%)	154 (98.7%)	286 (87%)	$\chi^2=42.15$	<0.001
Present	39 (22.8%)	417 (68.7%)	552 (65.4%)		
Space occupying lesion					
Absent	163 (95.3%)	155 (99.4%)	318 (97%)	FET	0.025
Present	8 (4.7%)	1 (.6%)	9 (3%)		
Ascites					
Absent	165 (96.5%)	156 (100%)	321 (98%)	FET	0.02
Present	6 (3.5%)	0 (0%)	6 (2%)		

Varices					
Absent	162 (94.7%)	155 (99.4%)	317 (97%)	FET	0.014
Present	9 (5.3%)	1 (0.6%)	10 (3%)		
Splenomegaly					
Absent	90 (53%)	145 (93%)	235 (72%)	$\chi^2=72.84$	<0.001
Present	81 (47%)	11 (7%)	92 (28%)		
Coarse					
Absent	29 (17 %)	104 (67 %)	133 (41%)	$\chi^2=83.17$	<0.001
Present	142 (83 %)	52 (33 %)	194 (59%)		
Fatty					
Mild	23 (13.5%)	21 (13.5%)	44 (13%)	$\chi^2=3.08$	0.215
Moderate	8 (4.7%)	15 (9.6%)	23 (7%)		
No Fatty	140 (81.9%)	120 (76.9%)	260 (80%)		
Portal Vein (PV)					
Dilated	24 (14%)	2 (1.3%)	26 (8%)	$\chi^2=20.91$	<0.001
Not dilated	147 (86%)	154 (98.7%)	301 (92%)		
Comparisons between cirrhotic and non-cirrhotic groups were performed using Pearson's χ^2 test (for categorical variables) or the Mann-Whitney U test (for continuous variables). Fisher's Exact Test was used where expected cell counts <5. P-values <0.05 were considered statistically significant.					

Table 3. Accuracy of APRI, Fib4 and ultra-sound score in predicting Liver cirrhosis in Hepatitis C patients in Punjab.

APRI	Fibro scan		Sensitivity	Specificity	PPV	NPV
	Cirrhosis	No Cirrhosis				
>0.50	235	524	99	14	31	98
≤0.50	2	83				
>1.00	213	231	90	62	48	94
≤1.00	24	376				
>1.50	181	96	76	84	65	90
≤1.50	56	511				
>2.00	143	52	60	91	73	86
≤2.00	94	555				
Fib4						
>1.45	194	125	82	79	61	92
≤ 1.45	43	482				
>3.25	98	11	41	98	90	81
≤3.25	139	596				
>3.25	98	11	70	98	90	92
≤1.45	43	482				
>3	107	11	45	98	91	82
≤3	130	596				
Coarse						
Present	143	52	83	67	73	78
Absent	29	104				

Chronic Liver Disease						
Present	39	2	23	97	89	54
Absent	132	154				

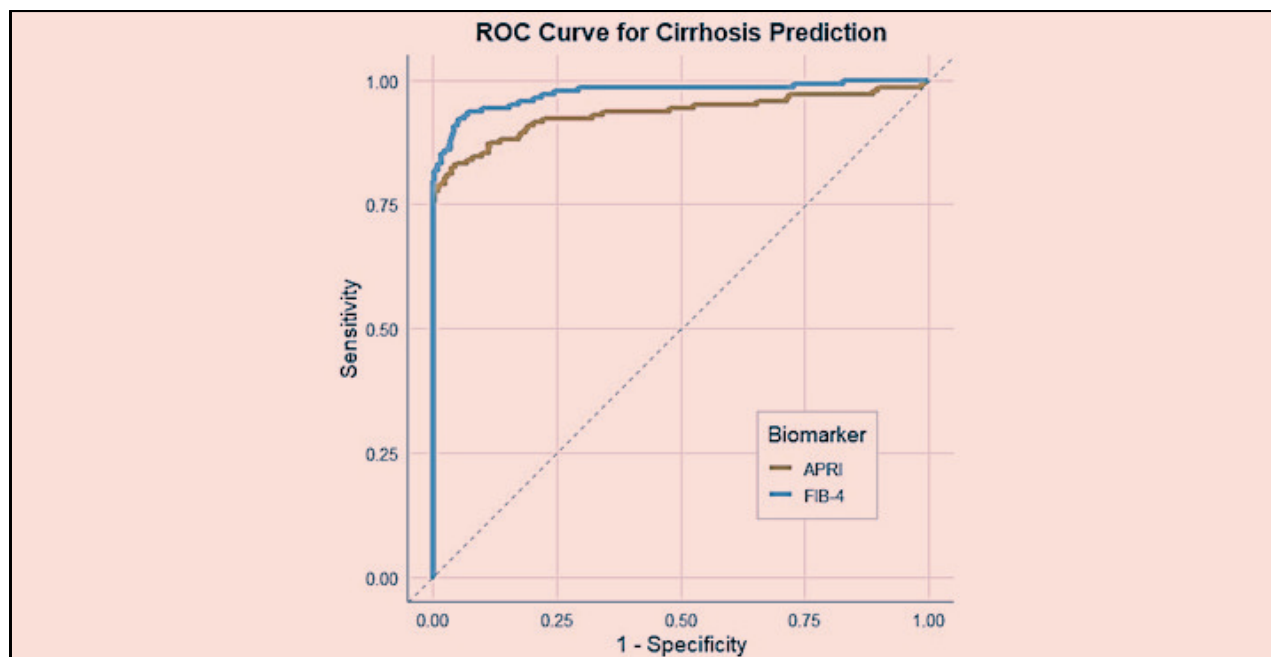


Figure 1: ROC curve for Cirrhosis Prediction

Discussion

The reduction in the cost of direct-acting antivirals (DAAs) in developing countries provides an opportunity to expand HCV treatment in resource-limited settings, contributing to the WHO elimination targets.¹⁵ Simplification of diagnostic and staging approaches is essential to facilitate treatment initiation. Current guidelines from EASL and WHO recommend the use of non-invasive serological markers for fibrosis staging.¹⁶ However, APRI and FIB-4, when used individually, have limited sensitivity and may not be sufficient as standalone tools for clinical decision-making.¹⁷ In the current study of 844 HCV RNA-positive patients, APRI and FIB-4 demonstrated good diagnostic performance for cirrhosis identification when compared with Fibroscan.³ At predefined cutoff values (APRI ≥ 1.50 and FIB-4 ≥ 1.45), both markers showed balanced sensitivity and specificity, consistent with previously reported studies.¹⁸ Similar studies have reported sensitivity ranging from 70–85% and specificity from 75–90% for APRI and FIB-4 at comparable thresholds, supporting the robustness of these findings.¹⁹ Our findings are in agreement with a previous study reporting that lower APRI and FIB-4 values are useful for excluding cirrhosis due to their high negative predictive value.^{20,21} This is particularly relevant in high-burden settings such as Pakistan, where genotype 3 predominance and limited

access to Fibroscan necessitate reliable rule-out strategies. These observations support the role of APRI and FIB-4 as initial screening tools, especially in resource-limited settings.

The combined use of APRI and FIB-4 further improved diagnostic accuracy, particularly in increasing sensitivity and negative predictive value, which is important for ruling out cirrhosis. These findings are consistent with earlier studies that have suggested combining non-invasive markers to improve diagnostic performance.^{9,10} We also evaluated the role of ultrasonography (USG) in cirrhosis identification. Although USG findings such as splenomegaly and coarse liver texture were more frequent in cirrhotic patients, their additional diagnostic value beyond APRI and FIB-4 was limited. This observation is consistent with previous reports indicating that USG has high specificity but limited sensitivity for early cirrhosis detection.^{10,22} These findings highlight the potential utility of combining simple non-invasive markers for cirrhosis identification in resource-limited settings. The use of APRI and FIB-4 can support clinical decision-making where advanced diagnostic tools are not readily available.

This study has several limitations that should be acknowledged. The retrospective nature of the study design introduces potential selection bias. Additionally, the inclusion of patients from a single-center cohort in

Lahore may limit the generalizability of the findings. The use of ultrasonography for cirrhosis assessment may introduce variability due to operator dependence and differences in sensitivity. Furthermore, non-invasive markers such as APRI and FIB-4 rely on laboratory parameters (e.g., AST and platelet count), which may be influenced by technical variability and comorbid conditions. Additional limitations include incomplete availability of USG records (327/844 patients), lack of systematic comparison between patients with and without USG data, and potential selection bias inherent to retrospective analyses. These factors may affect the generalizability of the USG findings.

Conclusion

In this study, APRI and FIB-4 demonstrated good diagnostic accuracy for identifying cirrhosis among HCV patients when compared with Fibroscan. At predefined cutoff values, these markers showed balanced sensitivity and specificity, with high negative predictive value for excluding cirrhosis. The combined use of APRI and FIB-4 improved diagnostic performance, while ultrasonography showed limited additional value in cirrhosis classification.

Conflict of interest: Authors declare no conflict of interest.

Funding source: No funding was obtained for this study.

Ethical Approval: Ethical approval was obtained from Pakistan Kidney and Liver Institute and Research Centre Lahore Pakistan (IRB#DS1221).

Authors' Contributions:

MR, AK, AK: Involved in conceptualization of study and writing original draft

NW, RG, MK, HB: Involved in data extraction, analysis and final review

JM, TY: final review and editing

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