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ORIGINAL ARTICLE

Comparison of Fibrosis-4 with FibroScan for Liver Fibrosis Assessment in Non-Alcoholic Fatty Liver Disease Patients: A Cross-sectional Study

Fahad Kakar, Arif Rasheed Siddiqui, Saad Khalid Niaz, Syed Afzal ul Haq Haqqi, Zea ul Islam Farrukh, Muhammad Danish Ashraf Wallam, Muhammad Umar Farooq, Sayed Rohail Ahmed Rizvi

Department of Gastroenterology, Patel Hospital, Karachi, Pakistan.

Correspondence to: Dr. Fahad Kakar, Email: drfahadkhanfk@gmail.com, ORCiD: 0009-0008-8672-1699

ABSTRACT

Objective: To compare the efficacy and accuracy of the Fibrosis-4 (FIB-4) index with FibroScan in assessing liver fibrosis in patients with non-alcoholic fatty liver disease (NAFLD).

Methods: This cross-sectional study was conducted at Patel Hospital, Karachi, Pakistan, from October 2023 to April 2024. All known cases of NAFLD or non-alcoholic steatohepatitis (NASH) aged ≥18 years, regardless of gender, were included. FIB-4 scores were measured using age, platelet level, aspartate transaminase (AST), and alanine transaminase (ALT). FibroScan categorized liver fibrosis into stages F0 to F4 with specific stiffness ranges: F0 (1–6 kPa), F1 (6.1–7 kPa), F2 (7.1–9 kPa), F3 (9.1–10.3 kPa), and F4 (≥10.4 kPa).

Results: Of the 146 patients, the median age was 52.00 (IQR: 47.00–54.00) years. Based on FibroScan results, 61 (41.8%) patients were classified as F1, 35 (24.0%) as F2, 30 (20.5%) as F3, and 20 (13.7%) as F4. The diagnostic performance of FIB-4 showed an area under the curve of 0.83 (95% CI: 0.76–0.90). The optimal cut-off for FIB-4 was 1.28 with sensitivity, specificity, positive predictive value, negative predictive value, and overall diagnostic accuracy of 98.0%, 65.6%, 59.7%, 98.4%, and 76.7%, respectively. Spearman's correlation test (ρ) was applied and a significantly moderate correlation was found between FibroScan and FIB-4 ($\rho = 0.50$, $p < 0.001$).

Conclusion: FIB-4 demonstrated higher accuracy and diagnostic performance in determining liver fibrosis in NAFLD patients compared to FibroScan.

Keywords: Aspartate Aminotransferases, Alanine, Fibrosis, Liver Cirrhosis, Non Alcoholic Fatty Liver Disease, Transaminase .

INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) is the most common liver disease worldwide, affecting approximately two billion people. It has rapidly spread, earning the name "silent epidemic" and is a major cause of chronic liver diseases including non-alcoholic fatty liver and simple steatosis.[1,2] These conditions can progress to non-alcoholic steatohepatitis (NASH), cirrhosis, and eventually end-stage liver disease and/or hepatic cancer.[3-5]

Evidence indicates that individuals with NAFLD are at increased risk for cardiovascular issues such as hypertension, ischemic heart disease, abnormal heart rhythm, and heart muscle disease.[6] This highlights the importance of consistent monitoring of NAFLD patients by gastroenterologists to detect emerging concerns. Additional investigations that provide added value beyond ruling out fibrosis are needed to monitor and treat NAFLD patients, preventing progression to more severe disease forms. This method would also reduce the need for unnecessary liver biopsies.

Liver biopsy is the foremost method for identifying fat accumulation and fibrosis in NAFLD patients but is limited by impracticality for repeated monitoring.[7] Although blood tests or a combination of diagnostic techniques have been employed to evaluate liver fibrosis and injury, none are without limitations. FibroScan, a noninvasive bedside test that provides instant results, has gained traction because of its simplicity and widespread acceptance among patients.[8,9] Consequently, Liver biopsy may eventually be substituted by fibroScan as the gold standard.[8] However, its widespread adoption is hindered by factors such as limited accessibility, high cost, and the need for specialized expertise, particularly in low-

income countries like Pakistan.[10] Alternatively, the Fibrosis-4 (FIB-4) index offers a simple and cost-effective method for evaluating liver fibrosis, utilizing readily available parameters such as patient age, platelet count, aspartate transaminase (AST), and alanine transaminase (ALT).[11-12]

This study addresses the pressing need for non-invasive methods to assess liver fibrosis in NAFLD patients. Current gold standard techniques like liver biopsy are invasive and impractical for continuous monitoring.[6] By comparing the FIB-4 index and FibroScan, this research aims to identify effective and cost-efficient alternatives. Understanding the comparative efficacy of these methods can guide clinicians in making informed decisions regarding patient care and treatment strategies. Moreover, this study can potentially reduce the burden of invasive procedures on patients and healthcare systems while improving the accuracy and accessibility of liver fibrosis assessment in NAFLD. Thus, this research is pivotal in advancing the field of hepatology and addressing the clinical challenges associated with NAFLD management.

METHODS

This prospective cross-sectional study was carried out at Patel Hospital Karachi, Pakistan from the period of October 2023, to April 2024. Ethical clearance was acquired from the institutional review board of Patel Hospital Karachi (Registration number: PH/IRB/2023 /040). Additionally, patients were provided with detailed information about the potential risks and benefits of the study, and their informed consent was obtained.

All known case of NAFLD or NASH having age ≥18 years of either gender were included through non-probability consecutive sampling technique. Exclusion criteria were severe liver illness, cerebral congestion, cardiac arrest, hepatotoxic medication use at the time of the study, refusal to give consent, or incomplete data.

By using OpenEpi sample size calculator taking correlation between FibroScan and AST/ALT 0.25,[13] significance level (α) was taken as 0.05, power (1 - β) as 80%. The estimated sample size was 123. However, to overcome the issue of missing data, 146 patients were included.

Demographic information, including age and gender, was collected. Laboratory parameters like AST and ALT were obtained from hospital records. FIB-4 was calculated as {age (years) × AST (IU/L)} / {platelet count (10^9 /L) × ALT (IU/L) 1/2 }. FibroScan is a non-invasive method used to evaluate hepatic fat accumulation and liver stiffness accurately. The test results, obtained from the Gastroenterology department, were categorized into five categories: "F0" ranged from "1–6 kPa", "F1" ranged from "6.1–7 kPa", "F2" ranged from "7.1–9 kPa", "F3" ranged from "9.1–10.3 kPa", and "F4" ranged from "≥10.4 kPa". Patients were divided into two groups based on their kPa values. Group I consisted of individuals with mild to moderate fibrosis, ranging from F0 to F2, while group II included those with advanced fibrosis, encompassing F3 and F4 stages.

Statistical Package for the Social Sciences (SPSS) version 20.0 was used for data entry and analysis. Quantitative variables such as age, AST, ALT, AST/ALT ratio, FIB-4 score, and FibroScan score (kPa) were reported as median (IQR). Frequency and percentages were determined for categorical variables like gender and FibroScan categories. Inferential statistics were explored using Spearman correlation (ρ) to identify the relationship between FIB-4 and FibroScan ratio stratified on the basis of age and gender. Additionally, Receiver Operating Characteristic (ROC) curves were generated to ascertain the area under the curve (AUROC), cut-off scores, and sensitivity. Positive predictive value (PPV), negative predictive value (NPV), and diagnostic accuracy were calculated for these cut-offs. A p-value of ≤0.05 was considered statistically significant.

RESULTS

The study included 146 patients with a median age of 52.00 years (IQR: 47.00–54.00). There were 101 (69.2%) males and 45 (30.8%) females. Based on FibroScan results, 61 (41.8%) patients were classified as F1, 35 (24.0%) as F2, 30 (20.5%) as F3, and 20 (13.7%) as F4. The median AST and ALT levels were 42.0 (42.00 – 45.25) U/L and 39.0 (35.00 – 40.00) U/L, respectively (Table 1).

A significant moderate correlation was found between FibroScan score and FIB-4 ($\rho = 0.50$, $p < 0.001$). After stratifying by age and gender, a strong correlation was observed only in patients over 52 years old ($\rho = 0.70$, $p < 0.001$) (Table 2).

The diagnostic performance of FIB-4 showed an AUROC of 0.83 (95% C.I: 0.76–0.90). The optimal cut-off for FIB-4 was 1.28 with a sensitivity of 98.0%, specificity of 65.6%, PPV of 59.7%, NPV of 98.4%, and diagnostic accuracy of 76.7%. After stratification, the diagnostic performance of FIB-4 in females showed an AUROC of 0.95 (95% CI: 0.89–0.99) with an optimal cut-off of 1.28, sensitivity of 100.0%, specificity of 71.8%, PPV of 59.1%, NPV of 100.0%, and diagnostic accuracy of 80.0% (Table 3).

Table 1: Baseline characteristic of the study participants (n =146)	
Age (years), Median (IQR)	52.00 (47.00 – 54.00)
Age (years)	**n (%)**
≤ 52	93 (63.7)
>52	53 (36.3)
Gender	
Male	101 (69.2)
Female	45 (30.8)
FibroScan Results	
F1	61 (41.8)
F2	35 (24.0)
F3	30 (20.5)
F4	20 (13.7)

-Quantitative variable described by median (IQR), Categorical variables described by frequencies (percentages)

Table 2: Correlation of FIB-4 with FibroScan ratio stratified on the basis of age and gender (n = 146)

	FIB-4 with FibroScan Score ρ (p-value)	**FIB-4 with AST/ALT Ratio ρ (p-value)**
Total	0.50 (<0.001)*	-0.02 (0.737)
Age, years		
≤ 52	0.70 (<0.001)*	0.03 (0.753)
>52	0.34 (0.012)*	-0.06 (0.628)
Gender		
Male	0.43 (<0.001)*	-0.03 (0.718)
Female	0.63 (<0.001)*	-0.15 (0.325)

AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, FIB-4: Fibrosis -4, ρ: Correlation coefficient
*p-value ≤ 0.05 (Spearman's correlation)

Table 3: Diagnostic performance of FIB-4 for the differentiation of severe fibrosis (F3 and F4) from moderate fibrosis (F1 - F2) (n =146)

Indices	**AUC (95% C.I)**	**p-value**	**Optimal cut-off**	**Sensitivity (%)**	**Specificity (%)**	**PPV (%)**	**NPV (%)**	**DA (%)**
FIB-4	0.83 (0.76-0.90)	<0.001	1.28	98.0	65.6	59.7	98.4	76.7
Age, years								
≤ 52	0.91 (0.85-0.97)	<0.001	1.28	96.8	73.7	65.9	97.8	81.7
>52	0.75 (0.62-0.88)	0.003	1.28	100.0	51.4	51.4	100.0	67.9
Gender								
Male	0.76 (0.66-0.85)	<0.001	1.28	97.3	62.5	60.0	97.5	75.2
Female	0.95 (0.89-0.99)	<0.001	1.28	100.0	71.8	59.1	100.0	80.0

AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, FIB-4: Fibrosis -4, PPV: Positive predicted value, NPV: Negative predicted value, DA: Diagnostic accuracy, AUC: Area under the curve, C.I: Confidence Interval

DISCUSSION

NAFLD is a common chronic liver condition globally, and its incidence is increasing in Pakistan.[14-16] Evaluating liver fibrosis is essential in managing NAFLD, as it indicates disease advancement and prognosis. This study compared the biochemical score FIB-4 with FibroScan in assessing liver fibrosis in NAFLD patients.

According to current study findings, a moderate significant correlation between FibroScan scores and

FIB-4 was found which suggests that FIB-4 serves as a dependable marker for liver fibrosis in NAFLD patients. With an AUC of 0.83, FIB-4 demonstrates good diagnostic accuracy in distinguishing between mild to moderate fibrosis (F0-F2) and advanced fibrosis (F3-F4). The optimal cut-off value of 1.28 for FIB-4 exhibits high sensitivity and moderate specificity in identifying advanced fibrosis. These findings align with previous research. For instance, Badawi *et al*. found in their study that patients with advanced fibrosis had higher mean kPa scores, and FIB-4 scores were significantly elevated in patients with advanced fibrosis compared to those with mild to moderate fibrosis. The authors concluded that FIB-4 outperforms FIB-5 as a non-invasive and simple marker for diagnosing advanced fibrosis in NAFLD patients.[17]

In a recent investigation by Ding *et al*. author found a moderate positive correlation between liver stiffness measured via FibroScan and FIB-4. The AUC values for the FIB-4 score indicate fair to good accuracy in distinguishing between mild or severe fibrosis and advanced fibrosis, respectively. These results suggest that the FIB-4 score moderately discriminates liver fibrosis. In their study, FIB-4 index cutoff value was determined as 1.65, with a sensitivity of sixty-eight percent and specificity of ninety percent in diagnosing advanced fibrosis.[18] According to Biberci *et al*. they found that a FIB-4 score cutoff value exceeding 2.16 exhibited the most accurate predictive value for advanced fibrosis.[19] Amernia *et al*. found that the AUC of FIB-4 in distinguishing between stages F3 and F4 from stages F2 and F1 was robust. They suggested that AST to platelet ratio index (APRI) might be the most suitable alternative to FibroScan for identifying significant fibrosis in NAFLD patients. FIB-4 ranked as the second-best option, indicating that if FibroScan is not accessible, APRI and FIB-4 are the optimal indices for evaluating liver fibrosis in NAFLD patients.[13]

FibroScan is widely utilized for assessing liver fibrosis due to its non-invasiveness and reliability. Nonetheless, its accessibility and cost-effectiveness can pose challenges in resource-limited regions like Pakistan. Conversely, FIB-4 is a straightforward and cost-effective tool that can be easily calculated using routine laboratory tests, offering a practical alternative for evaluating liver fibrosis in NAFLD patients, especially where FibroScan is not readily accessible. Moreover, it is noted that obesity can affect FibroScan's efficacy, but this challenge has been addressed with the use of XL probe for individuals with a body mass index over 30 kg/m^2.[10] A previous study in Pakistan reported a significant positive correlation between BMI and liver size,[20] however in the current study BMI was not reported.

The current study has several limitations that need to be acknowledged. Firstly, its cross-sectional design restricts the generalizability of the findings. Moreover, the relatively small sample size might impact the statistical power of the study. Being conducted at a single center, the study's external validity could be limited. Additionally, the absence of histological confirmation of liver fibrosis in all patients is a noteworthy limitation, as liver biopsy is considered the gold standard for fibrosis staging. Despite these limitations, the study possesses several strengths. It stands out as one of the few studies directly comparing the performance of FIB-4 with FibroScan in evaluating liver fibrosis in NAFLD patients. Utilizing FibroScan as the reference standard enhances the credibility of the findings, given its reliability in liver fibrosis assessment. Furthermore, the study's comprehensive analysis of demographic and clinical factors makes the results more reliable.

Future research in this area should focus on prospective studies with larger sample sizes to validate our findings. Longitudinal studies are needed to assess the utility of FIB-4 in monitoring disease progression and treatment response in NAFLD patients. Additionally, studies comparing the cost-effectiveness of FIB-4 and FibroScan in different healthcare settings would provide valuable insights into their practical utility. Finally, the development of non-invasive biomarkers with higher accuracy than FIB-4 for liver fibrosis assessment in NAFLD patients should be a priority for future research efforts.

CONCLUSION

FIB-4 is a valuable tool for assessing liver fibrosis in patients with NAFLD, showing good diagnostic performance compared to FibroScan. Its simplicity, cost-effectiveness, and high sensitivity make it a useful adjunct in the management of NAFLD, particularly in resource-limited settings. Further studies are warranted to validate these findings and explore the utility of FIB-4 in longitudinal monitoring of NAFLD patients.

ETHICAL APPROVAL: The ethical clearance was obtained from the Ethics Committee of Patel Hospital Karachi (Registration number: PH/IRB/2023/040, dated: 12.10.2023).

AUTHORS' CONTRIBUTIONS: FK, ARS, SKN, SAHH, ZIF, MDA, MUF, SRAR: Conception and study design. FK, MDA, SRAR, MUF: Data acquisition, analysis and

interpretation. FK, MDA, SRAR, MUF: Drafting of manuscript. All authors critically reviewed and gave final approval of the manuscript.

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