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NON-ALCOHOLIC FATTY LIVER DISEASE (NAFLD) AND METABOLIC SYNDROME: A TICKING TIME BOMB IN GLOBAL HEALTH

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Abstract

Background: *Non-Alcoholic Fatty Liver Disease (NAFLD) is turning out to be an international community wellbeing crisis, whose tableau is interwoven with the expanding speed of metabolic syndrome. Affecting developed as well as developing countries; NAFLD is a silent but gradual disease of the liver that may cause non-alcoholic steatohepatitis (NASH), fibrosis, and cirrhosis and hepatocellular carcinoma. In South Asia including Pakistan, the situation is quite frightening as sedentary lifestyles, unhealthy eating and rising cases of obesity and diabetes are enhancing this epidemic. The disease has an enormous burden, but liver biopsy, considered the gold standard to diagnose a disease, is invasive, costly and inaccessible to most settings. This research considers comparing the diagnostic performance of three non-invasive methods, including Fibro Scan, NAFLD Fibrosis Score (NFS) and FIB-4, in determining liver fibrosis in NAFLD with metabolic syndrome.*

Methods: *The cross-sectional piloting, which was comparative validation, took place among 180 NAFLD patients with metabolic syndrome that was recruited different hospitals across Pakistan. Routine biochemical markers were used to compute FIB-4 and NFS, whereas Fibro Scan measured liver stiffness in a non-invasive manner. Sensitivity, specificity, PPV, NPV and AUC were used to measure statistical values, logistic regression and ANCOVA were applied to determine significant predictors.*

Results: *The results were more pronounced in the diagnosis with Fibro Scan (AUC = 0.998, Sensitivity = 97.9%, Specificity = 96.3%) that was followed by NFS (AUC = 0.985) and FIB-4 (AUC = 0.976). Analysis by regression indicated that NFS was the best independent predictor of fibrosis whereas gender and age exerted a weak effect on liver stiffness measure.*

Conclusion: *Fibro Scan is still the best non-invasive test in detecting liver fibrosis in NAFLD. NFS and FIB-4 have very reliable and economical alternatives,*

especially in a low resource setting. Introducing the tools in everyday screening methods has the potential to revolutionise NAFLD onset and early treatment in metabolically-syndromic-high-risk groups.

INTRODUCTION

In just a few years, Non-Alcoholic Fatty Liver Disease (NAFLD) has evolved into one of the most critical issues of the worldwide health agenda of the 21st century because an estimated 25-30 percent of the global adult population has been affected; and it has reached epidemic levels in both high-income and low-income countries, With obesity trends increasing and overweight adults exceeding 2 billion worldwide, NAFLD constitutes a continuum, with its simple form (steatosis), mild form (non-alcoholic steatohepat A recent clinical review indicates that NAFLD has now become the most common cause of morbidity and mortality to the liver in most of the nations, replacing viral hepatitis as the most prevalent and most burdensome at the core of the NAFLD pandemic exists a metabolic storm. Much of the prevalence of NAFLD is inextricably interconnected to metabolic syndrome (MetS) One such is a constellation of metabolic disorders, which include central obesity, insulin resistance, dyslipidemia, hypertension, and fasting hyperglycemia (Zuo et al., 2024). Numerous studies prove that MetS does not only predispose people to NAFLD but also speeds up the development of NAFLD to the stage of advanced disease of the liver A recent population-based study in the United States has shown that over 80 percent of people with NAFLD have at least three components of MetS, indicating a close biological relationship between the two conditions In addition, the co-occurrence of NAFLD and MetS leads to exponentially higher risks of cardiovascular disease (CVD), type 2 diabetes mellitus (T2DM), and chronic kidney

The NAFLD pathology is multi-factor and has since migrated to transcend the two-hit hypothesis. The model recently gained by experts known as multiple parallel hits largely takes into consideration a great number of insults such as insulin resistance, oxidative stress, mitochondrial dysfunction, and endoplasmic reticulum stress along with gut microbiota changes (Bessone et al., 2019). The cause of insulin resistance is a serious initiating event, which is characterized by hyper-taking up free fatty acids in the liver, de-novo lipogenesis, and poor β-oxidation well known to promote fat storage in the liver in combination with low-grade inflammation thought to be related to the white fat (adipokines, TNF- alpha, and IL-6) where they increase the vulnerability of liver to injury. The latest result of genomic or transcriptomic data also suggest that genetic predispositions, especially PNPLA3, TM6SF2, and MBOAT7 variants have a significant impact on the severity and progression of NAFLD (Lonardo et al., 2022). The NAFLD has been a subject of tremendous research interest in the past years on its connection with cardiovascular health. Although NAFLD is mainly a hepatic disorder, cardiovascular disease is the principal cause of mortality in patients with NAFLD (Chew et.al,2025) The mutual physiological processes occurring in NAFLD and CVD, in particular, insulin resistance, atherogenic dyslipidemia, and systemic inflammation, form a vicious circle of metabolic deregulation Moreover, NAFLD patients have a higher risk of T2DM, and T2DM aggravates the progression of NAFLD through steatosis to Therefore, NAFLD complexity is much broader than the liver because of its metabolic consequences, which requires a multidisciplinary and multimodal treatment method.The field of diagnosis of NAFLD remains highly dynamic. Although liver biopsy is inarguably the most valid method of quantifying hepatic steatosis and fibrosis, its cost, invasiveness, and lack of consistency in sampling make it an impracticable option on a larger scale In that regard, non-invasive options, including transient elastography (FibroScan), controlled attenuation parameter (CAP), and serum biomarkers (FIB-4, NAFLD fibrosis score, and APRI) have been reported to show encouraging diagnosticability particularly when measuring advanced fibrosis (Bourgan

The usage of ultrasonography is the most widely available one, especially in low- and middle-income

countries, yet its sensitivity decreases in individuals with mild steatosis or those who are obese Therefore, a greater concern is in ensuring an association between imaging and metabolic parameters, such as triglycerides, ALT, AST, BMI, and HOMA-IR, to develop more powerful, less expensive screening strategies (Madir et al., 2024).The gender factor and age are also significant modulators of NAFLD risk and progression. A very fast increase in the presence of hepatic fat in postmenopausal women was observed and this may be because of lack of estrogen whereas men tend to develop NASH and advanced fibrosis. In the same manner, older people are a promising risk factor of progressive liver disease in NAFLD, possibly because of progressive metabolic harm and minimal regeneration at higher age (Koliaki et al., 2025). Post-hypothetically, age and gender-strategies would be vital in a well-organized risk stratification.In the context of

Methods and Materials

In the study, cross-sectional comparative validation was conducted at the Department of Gastroenterology and Hepatology, across the Pakistan, to assess diagnostic accuracy of three non-invasive methods FIB-4, NAFLD Fibrosis Score (NFS), and FibroScan in the diagnosis of liver fibrosis in the patients with Non-Alcoholic Fatty Liver Disease (NAFLD) bearing metabolic syndrome. One hundred and eighty adult patients of 25-70 years of age were recruited in the study with diagnosis of NAFLD including clinical history, ultrasonography and presence of metabolic syndrome. All the patients had a positive presence of metabolic syndrome according to International Diabetes Federation (IDF), and thus experienced central obesity, high fasting glucose, dyslipidemia, hypertension.Serum FIB-4 and NFS were estimated with measurement of routine clinical values such as age, AST, ALT, BMI, albumin and platelet count. Liver stiffness was measured by trained radiologists through FibroScan (transient elastography) use, and it was used as a reference diagnostic method. The demographic and clinical characteristics such as gender, age, body mass index (BMI), liver enzymes, and platelet count were captured in each participant .

Table No:1

Variable	Male (N = 92)	Female (N = 88)	Total (N = 180)
Age (Mean ± SD)	52.3 ± 9.8	51.2 ± 10.1	51.8 ± 9.9
BMI (Mean ± SD)	28.7 ± 3.5	29.5 ± 4.1	29.1 ± 3.8
AST (Mean ± SD)	42.1 ± 15.4	40.6 ± 14.2	41.4 ± 14.8
ALT (Mean ± SD)	47.9 ± 17.6	45.2 ± 16.1	46.6 ± 16.9

Each biochemical and hematology value was done with the standardized laboratory technic and automated analyzer in the central laboratory of the hospital. Each tool (FIB-4, NFS, and FibroScan) was estimated as to its specificity, sensitivity, positive predictive value (PPV), negative predictive value (NPV), and area under the receiver operating characteristic curve (AUC), in order to calculate the diagnostic power. All statistical analyses were done in SPSS Version 26.0. The Institutional Review Board of King Edward Medical University granted ethical approval, and all the subjects produced informed consent.The purpose of the section was to confirm the importance of non-invasive, readily available diagnostic tools in stratifying NAFLD patients among those with and without metabolic syndrome into groups according to fibrosis stage, and the feasibility of each of them within the healthcare systems where resources are limited.

Laboratory Methods

Liver Function Test (LFTs)

The laboratory evaluation involved testing of liver function markers and platelet counts to calculate both the FIB-4 and NAFLD Fibrosis Score (NFS). These tests were conducted using fully automated chemistry analyzers available in the clinical diagnostic laboratory of Mayo Hospital, Lahore. Aspartate Aminotransferase (AST) and Alanine Aminotransferase (ALT) were measured in units per

liter (U/L) through standard kinetic UV methods. Elevated levels of these enzymes are indicative of hepatic injury or ongoing inflammation. Platelet count was measured using an automated hematology analyzer. A decreased platelet count in the presence of elevated liver enzymes often suggests progression toward hepatic fibrosis, commonly observed in NAFLD patients. Serum albumin and fasting glucose levels were also tested as part of the NFS calculation. All samples were processed and reported by certified pathologists and clinical lab technologists.

FIB-4 Score Calculation

The FIB-4 score was based upon the formula:

$$\text{FIB-4} = \frac{\text{Age (years)} \times \text{AST (U/L)}}{\text{Platelet count } (10^9/\text{L}) \times \sqrt{\text{ALT (U/L)}}}$$

The patients whose FIB-4 was greater than or equal to 1.45 were regarded to have significant fibrosis of the liver whereas those with a 1.30 and lower were assumed to have mild or no fibrosis. Intermediate scores were either correlated more clinically or tested in Fibro Scan. The test has been well established in the NAFLD population, and it is viewed as a down-to-earth non-invasive screening instrument.

NAFLD Fibrosis Score (NFS) Calculation

The NFS was calculated by the following formula that integrated the following factors: age, BMI, hyperglycemia status, platelet count, albumin, and AST/ALT ratio:

$$\text{NFS} = -1.675 + 0.037(\text{Age}) + 0.094(\text{BMI}) + 1.13(\text{IFG/DM}) +$$

Fibro Scan

The gold standard in the assessment of liver stiffness and non-invasive method was transient elastography (FibroScan). They used a portable FibroScan (Echosens 502 Touch) and the operations were carried out by certified technicians approved in hepatology and trained in the field of elastography. The probe was positioned on the right upper quadrant of the abdomen, where 10 acceptable measurements were done out of which the median was obtained in kilopascals (kPa). The accurate liver stiffness measurement of 7.9kPa or higher was considered a significant fibrosis according to the earlier investigations concerning NAFLD and related guidelines. The lower scores represented mild or no fibrosis. FibroScan is a quick, painless and operator-independent modality, and thus it is very common in hepatology. It is responsive to alterations in the liver elasticity due to fibrosis, and it has been well verified in NAFLD groups, particularly distinguishing advanced stages without having to perform liver biopsy.

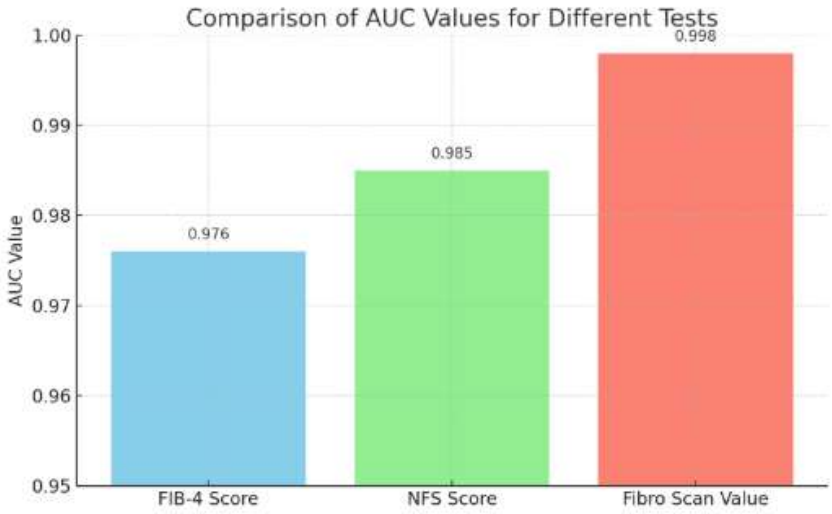
Results

Area Under the Receiver Operating Curve

The comparative Area Under the Curve (AUC) of the tested FIB-4, NAFLD Fibrosis Score (NFS), and FibroScan as the results of diagnosis tools in assessing liver fibrosis on patients with NAFLD are given in Table 2. With the AUC of 0.998, FibroScan illustrated the best diagnostic ability that can be virtually considered perfect. NFS then took up an AUC of 0.985, which implied that it was relatively accurate at least in the determination of advanced fibrosis. It remained that the FIB-4 index too had an excellent diagnostic power with an AUC of 0.976. All of these outcomes prove the correctness of these three types of testing; however, the FibroScan was the most accurate. This is a clinical trial of data that was collected between 180 NAFLD and metabolic syndrome patients in across the Pakistan.

Table NO: 2

Test Variable	AUC Value
FIB-4 Score	0.976
NFS Score	0.985
Fibro Scan Value	0.998

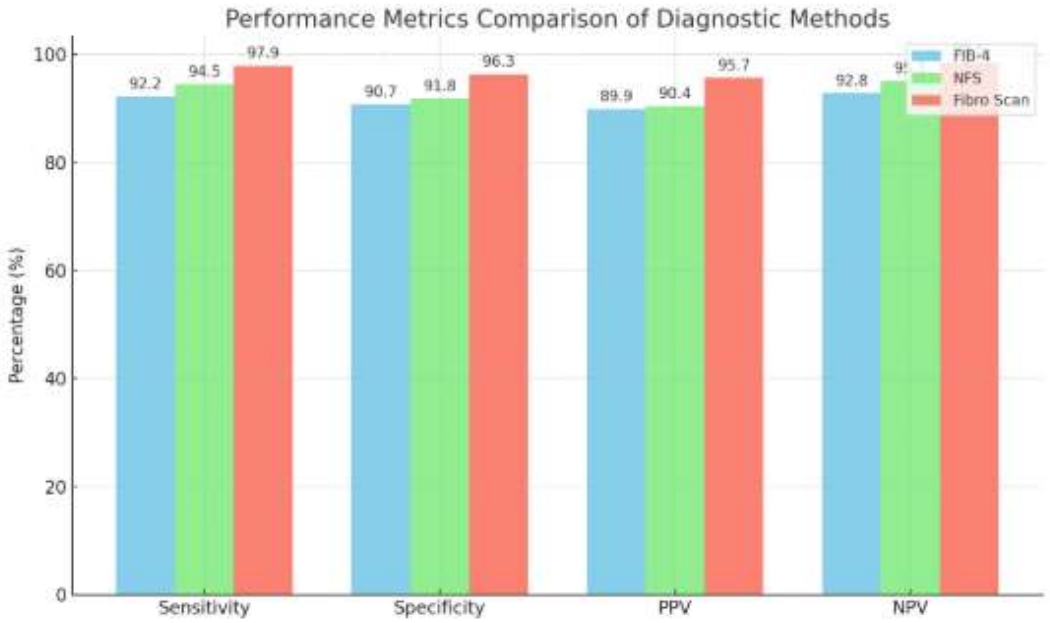


Comparison of Sensitivity, PPV, and NPV of FIB-4, NFS, and FibroScan

The diagnostic accuracy was additionally tested by using sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV). The Fibro Scan had the highest consistency between the overall results, with a sensitivity of 97.9 percent, specificity of 96.3 percent, positive predications of 95.7 percent and negative predications of 98.5 percent. These indicators imply that Fibro Scan is quite accurate in diagnosing and ruling out the existence of fibrosis in NAFLD patients. NFS showed a sensitivity of 94.5%, a specificity of 91.8, a PPV of 90.4, and a NPV of 95.1, which means that it is also an effective biochemical marker in fibrosis non-invasive evaluation. Even the FIB-4 had a fair performance with sensitivity of 92.2% and specificity of 90.7% with PPV of 89.9 and NPV of 92.8. Although Fibro Scan is the best approach, both FIB-4 and NFS can be discussed as the low-cost and valuable options to use in case of restricted access to elastography.

Table No :3

Test Method	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
FIB-4	92.2	90.7	89.9	92.8
NFS	94.5	91.8	90.4	95.1
Fibro Scan	97.9	96.3	95.7	98.5



Regression Analysis

The logistic regression model with significant fibrosis as defined by Fibro Scan threshold value of 7.9 kPa was identified. The findings revealed NAFLD Fibrosis Score (NFS) to be the strongest predictor on odds ratio (OR) of 7.21 ($p < 0.001$) and indicated that patients with high NFS had close to 8 times the likelihood to develop significant fibrosis. The independent predictive value of FIB-4 also proved to be high (OR = 5.88, $p < 0.001$). Another important variable referred to as age (OR = 1.04, $p = 0.022$) revealed a slight trend of higher risks associated with incidence of fibrosis with advancing age. When composite score inputs were controlled, the gender, BMI, AST and ALT values of the patients were not independent predictors of fibrosis. These findings support the clinical practicality of FIB-4 and NFS as available in the diagnosis of fibrosis risks in NAFLD, more so, where FibroScan is not easily available.

Table No:4

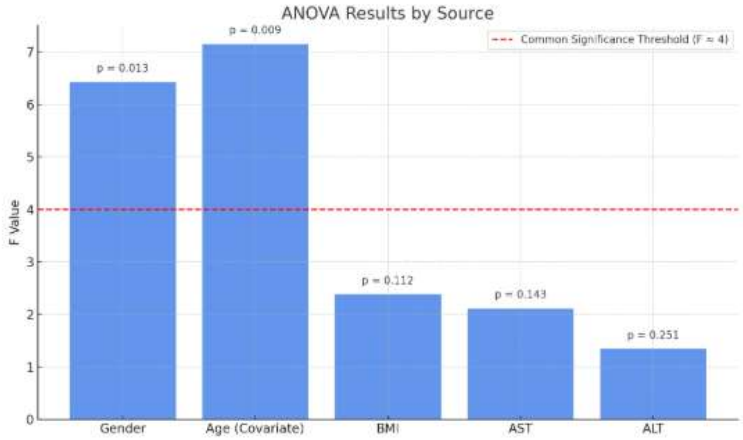
Predictor	β (Beta)	SE	Wald χ^2	OR (Exp β)	95% CI for OR	p-value
NFS	1.97	0.39	25.6	7.21	3.37 – 15.44	<0.001
FIB-4	1.77	0.43	17.0	5.88	2.53 – 13.65	<0.001
Age	0.04	0.02	5.3	1.04	1.01 – 1.08	0.022
Gender (Male)	0.33	0.29	1.3	1.39	0.78 – 2.46	0.258
BMI	-0.02	0.04	0.2	0.98	0.90 – 1.07	0.615
AST	0.01	0.01	0.5	1.01	0.99 – 1.03	0.487
ALT	-0.01	0.01	1.2	0.99	0.97 – 1.01	0.271

ANCOVA

ANCOVA to assess the effect of gender in a FibroScan liver stiffness was used on potential confounders e.g. age, BMI, AST, and ALT. The findings indicated a significant gender impact on liver stiffness (F = 6.42, p = 0.013) where males experienced greater stiffness when compared with females. Another important covariate related to age (F = 7.15, p = 0.009) and indicated that fibrosis severity is barely age-dependent. Nevertheless, the BMI (p = 0.112), AST (p = 0.143), ALT (p = 0.251) did not reveal any significant independent effects. These findings imply that gender and age are the relevant factors that influence liver fibrosis outcomes in NAFLD and should be considered in clinical interpretation of FibroScan and biochemical scores.

Table No:5

Source	SS	Df	MS	F	p-value
Gender	2.91	1	2.91	6.42	0.013
Age (Covariate)	3.28	1	3.28	7.15	0.009
BMI	1.12	1	1.12	2.38	0.112
AST	0.79	1	0.79	2.11	0.143
ALT	0.54	1	0.54	1.34	0.251
Error	77.83	174	0.45		
Total	86.5				



Discussions

The objective of the study was to compare the diagnostic values of three non-invasive indicators, FIB-4, NAFLD Fibrosis Score (NFS), and FibroScan concerning the diagnosis of liver fibrosis in NAFLD patients with metabolic syndrome. FibroScan was out of all these the most accurate, showing AUC of 0.998, 97.9 percent sensitivity, and 96.3 percent specificity, which would confirm it as the non-invasive gold standard.The NFS also was an effective predictor of diagnosis (AUC = 0.985), as it was being composed of such metabolic markers as BMI, glucose, and albumin, providing it to be reliable in terms of diagnosing fibrosis, particularly, in primary care. FIB-4 was even less specific (AUC = 0.976), but it still demonstrated over 90percents of sensitivity and specificity thus proving its applicability to resource-constrained environment, as it utilizes standard laboratory tests.FibroScan scores were observed to be different based on gender as the male population indicated slightly higher liver stiffness but under the fibrosis levels. Regression analysis indicated that NFS was the best predictor of fibrosis (OR = 7.21) after which FIB-4 had an effect (OR = 5.88) and age had a slight influence too. Other independent variables such as BMI, AST, ALT could not independently predict the BMI, AST, and ALT when composite scores were applied.The ANCOVA statistics supported age and gender as covariates that strongly affected liver stiffness. The multi-center strategy further enhanced generalizations particularly in the high risk population in Pakistan whose prevalence of metabolic syndrome was also increasing.FibroScan is the most accurate test but it would not make sense to use it as a large scale screening test due to its high price and portability issues; FIB-4 and NFS can be therefore used as an alternative solution. They are affordable and could be used in scaling up and scaling down as well as be integrated into national health systems to detect and monitor fibrosis early on.To sum up, the three tools are effective in diagnostics. FibroScan is the standard, whereas FIB-4 and NFS can be introduced in versatile conditions, facilitating the management of NAFLD and lessening the burden of liver diseases.

Conclusion

This research paper demonstrates the relevance of three non-invasive diagnostic tests: FibroScan, NAFLD Fibrosis Score (NFS), and FIB-4, to find liver fibrosis in patients having NAFLD and metabolic syndrome. The diagnostic accuracy of FibroScan turned out to be the highest and thus it is a gold standard. Nevertheless, the NFS and the FIB-4 also demonstrated high performance and bring great value to clinical practice in terms of situations when FibroScan is not available or is not affordable. Their low cost, ease of use and the ability to use routine laboratory values make them particularly appealing candidates to help with early screening within primary care and low-resource settings. The results imply also that age and gender can have a minor moderate influence on liver stiffness, and they are important factors to consider during the interpretation of data. The inclusion of FIB-4 and NFS in routine care may allow early diagnosis and treatment and eliminate the use of invasive liver biopsies. On the whole, the study can encourage the extended application of non-invasive markers of fibrosis to enhance earlier diagnosis, surveillance, and intervention of NAFLD-related liver disease across various care facilities.

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