

FREQUENCY OF NON-ALCOHOLIC FATTY LIVER DISEASE (NAFLD) RELATED CIRRHOSIS IN DIABETES MELLITUS USING ASPARTATE AMINOTRANSFERASE TO PLATELET RATIO INDEX (APRI) AND FIBROSIS-4 SCORE

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ABSTRACT

Background: Diabetes mellitus is a metabolic disorder characterized by high blood sugar levels. This results from the body's inability to properly use insulin, leading to impaired carbohydrate metabolism and overproduction of glucose.

Objectives: To study the frequency of NAFLD related cirrhosis in Diabetes Mellitus (DM) using APRI and fibrosis-4 (FIB-4) score.

Methods: We conducted a descriptive cross-sectional study to include 180 individuals of DM with NAFLD presenting at Pakistan Railways Hospital, Rawalpindi from 21st July, 2024 till 20th January, 2025. Patients were included by non-probability consecutive sampling between 18 to 75 years of age. Venous sample was taken for fasting blood glucose, random blood glucose, ALT, AST and platelets. APRI and fibrosis-4 scores were calculated. A higher and lower cut off value of >3.25 and <1.45 for FIB-4 and APRI values of >1.5 and <0.5 were taken as the higher and lower cut off for identifying individuals with cirrhosis. Scores that had come in between these cut off were taken as inconclusive. SPSS version 26.0 was used for data analysis.

Results: Out of 180 individuals, 56 (31.1%) were male and 126 (68.9%) were female. The mean age was 59.90 ± 9.71 years. NAFLD-related cirrhosis was detected in 18 individuals (10%) using the APRI score and in 26 people (14.44%) using the FIB-4 score. Among patients with Grade 1 NAFLD, cirrhosis was present in 16 (8.88%) and 24 (13.33%) patients based on the APRI and FIB-4 scores, respectively. No cases of cirrhosis were observed in Grade 2 NAFLD. In Grade 3, cirrhosis was observed in 2 patients (1.11%) according to each scoring system.

Conclusion: This study emphasizes the demand for routine screening of diabetic and NAFLD patients for advanced fibrosis to enable timely intervention or referral to hepatology specialists.

Keywords: NAFLD, diabetes mellitus, APRI, FIB-4

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INTRODUCTION

Diabetes mellitus (DM) pertains to a group of metabolic disorders that impact carbohydrate metabolism, causing glucose to be poorly utilized for energy and excessively produced because of abnormal gluconeogenesis and glycogenolysis, resulting in elevated blood sugar levels.¹ The diabetes prevalence has been consistently noticing an upward trajectory over the past thirty years, and the disease burden is projected to increase alarmingly by 2030.²

Nonalcoholic fatty liver disease (NAFLD) is constituted by the surplus lipids deposition in the liver, associated with insulin resistance without excessive alcohol intake and is closely linked to type 2 diabetes (T2DM), obesity and other elements of metabolic syndrome. The prevalence of NAFLD is rising, and it is now the primary risk factor of hepatocellular carcinoma (HCC).³ NAFLD affects nearly 30% of adult population globally, inclined more towards those with metabolic disorders, particularly those with highly raised body mass index (BMI).⁴ NAFLD not only affect obese individuals but also affect those who are not obese.⁵ The subgroup analysis found that NAFLD is most common in obese individuals (74.08%), followed by those with diabetes (58.47%) and hypertension (47.43%). Diabetic patients are prone to develop fatty liver two times more in comparison to the general population of Pakistan. This is due to high sugar levels in blood, which promote triglyceride production, and reduced production as well as reduced release of very low-density lipoproteins, both of which promote fat deposition in the liver.⁶

NAFLD and DM are metabolic disorders that frequently co exists. It has been found that diabetics have by two-fold greater risk of NAFLD development. It affects up to 25% of the adult population leading to a continuum of liver diseases that ranges from simple lipid deposition (benign steatosis), to inflammation (nonalcoholic steatohepatitis (NASH), fibrosis, cirrhosis, liver failure, and ultimately it can lead to hepatocellular carcinoma (HCC).⁷ Multiple studies have persistently found that NAFLD, specifically in its more severe stages, enhances the chances of mortality from all causes. Among all patients of NAFLD, cardiovascular diseases (CVDs) are the top most common, then cancers take their place after it outside the liver and also liver-related sequential conditions. Additionally, there is increasing evidence that NAFLD significantly raises the danger of serious heart and other heart problems, like arrhythmias, heart valve calcification and cardiomyopathy, regardless of conventional cardiovascular etiological factors.⁸

In 2020, experts suggested a new terminology of fatty liver disease for what we now call it as 'metabolic associated fatty liver disease (MAFLD)' to give better understanding of the underlying mechanisms. The presence of DM, metabolic dysregulation, and overweight/obesity are the three criteria that must be met in addition to the evidence of hepatic steatosis.⁹

American Diabetes Association recommends screening DM patients with fatty liver or raised alanine transferase (ALT) for clinically significant hepatic fibrosis. NAFLD related fibrosis in DM found in 21% of patients. Liver biopsy, despite being investigation of choice, has its limitations like its invasive nature and surgical related complications and is reserved for those with indeterminate results. Therefore, there comes the

contribution of non-invasive biomarkers of cirrhosis like APRI and FIB-4.¹⁰

The core strategy for managing NAFLD in patients now revolves around guided lifestyle modifications, emphasizing the adoption of regular physical activity and healthier dietary habits. It is associated with improvements in the histological features of NASH.¹¹ In this study, we intended to detect NAFLD-related cirrhosis in diabetes patients to enable early recognition, targeted treatment, and prevention of disease progression.

METHOD

We conducted a descriptive cross-sectional study to include 180 individuals of DM with NAFLD, both male and female aged 18 to 75 years in the medicine department of Pakistan Railways hospital, Rawalpindi from 21st July, 2024 till 20th January, 2025. Patients were included by non-probability consecutive sampling after getting approval from hospital ethical committee. Patients of type 2 diabetes who have fulfilled diagnostic criteria of American diabetes association and NAFLD were enrolled. NAFLD was considered as suspected if their liver enzymes i.e. ALT and AST are deranged or an abnormal liver appearance was found for any other diagnosis. NAFLD was defined as evidence of hepatic steatosis by standard ultrasonographic criteria i.e. patients were categorized by steatosis grades, with Grade 0 signifying no steatosis and Grade 1,2 and 3 indicating mild, moderate and severe steatosis respectively. Alcohol consumption, other competing cause of hepatic steatosis or co existing cause of chronic liver disease should be excluded.¹² Patients with liver cirrhosis caused by conditions other than diabetes, diagnosed cases of alcoholic liver disease, hepatitis B and C, autoimmune hepatitis, hemochromatosis, hepatocellular carcinoma and gestational diabetes mellitus were excluded. Venous sample was sent to evaluate levels of fasting blood glucose, random blood glucose, ALT, AST and platelet counts in hospital's own laboratory free of cost. APRI was computed by formula i.e. $APRI = \frac{AST [IU/L]/40}{platelet\ count (\times 10^9/L)} \times 100$ and reference ranges for serum ALT was taken as 24 U/L and 19 U/L in men and women respectively as higher cut off and for serum AST, 15-37 U/L was the range taken as normal. Fib-4 score was computed by formula i.e. $Fib-4 = \frac{Age [years] \times AST [IU/L]}{(platelet\ count (\times 10^9/L))^{1/2} \times ALT [IU/L]}$ A higher and lower cut off value of >3.25 and <1.45 for FIB-4 and APRI values of >1.5 and <0.5 were taken as the higher and lower cut off for identifying individuals with cirrhosis. Scores that had come in between these cut off were taken as inconclusive. Cirrhosis was defined by APRI score of >1.5 and Fib-4 score of >3.25.¹³ SPSS version 26.0 was used for data analysis. Continuous

variables like age, BSF, BSR, AST, ALT and platelets were represented as mean and standard deviation. The categorical variables like gender, presence of liver cirrhosis on FIB-4 and APRI and cirrhosis in different grades of NAFLD were represented as frequencies and percentages.

RESULTS

Out of 180 patients, 56 (31.1%) were male and 124 (68.9%) were female. Mean age of patients was 59.90 ± 9.707 years. Clinical profile and biochemical parameters of the patients in the study population are shown in Table 1. Frequency of NAFLD related cirrhosis in diabetics using APRI and Fib -4 score are shown in Table 2. Frequency of cirrhosis in different Grades of NAFLD using APRI and FIB-4 are shown in Table 3.

Table 1. Clinical profile and biochemical parameters of patients in the study population

Sr. No.	Variables	Mean $\pm$ SD
1.	BSF (mg/dl)	189.60 $\pm$ 64.134
2.	BSR(mg/dl)	309.44 $\pm$ 96.230
3.	Platelets ($10^9/\mu$ L)	242.42 $\pm$ 102.48
4.	ALT (U/L)	42.45 $\pm$ 6.58
5.	AST (U/L)	44.23 $\pm$ 7.48

Table 2. Frequency of NAFLD related cirrhosis in diabetics using APRI and Fib -4 score

Sr. No.	NAFLD	APRI	FIB-4
1.	Present	18 (10%)	26 (%)
2.	Absent	162 (%)	154 (%)

Table 3. Frequency of cirrhosis in different Grades of NAFLD using APRI and FIB-4

Sr. No.	NAFLD GRADES	APRI	FIB-4
1.	Grade 1	16 (8.88%)	24 (13.33%)
2.	Grade 2	0	0
3.	Grade 3	2(1.11%)	2 (1.11%)

DISCUSSION

This study was conducted to reveal that APRI and fib-4 were good early screening tools requiring less resources and skills for identifying cirrhosis in diabetics with fatty liver. This study concluded that APRI and Fib-4 were positive in 10% and 14.44% respectively out of 180 individuals. In Pakistan, the reported prevalence rates of type 2 diabetes mellitus (T2DM) and non-alcoholic fatty liver disease (NAFLD) are 17.1% and 14%, respectively. Among individuals diagnosed with T2DM, the NAFLD prevalence ranges between 32% and 72% [24].¹⁴ The NAFLD prevalence of patients with diabetes was detected to be 56.54% in the years 2008-2018, and 59.74% during

the period 2019-2024.⁴ A statistical pooling of results from 23 studies revealed the NAFLD prevalence in people with diabetes ranging 40.84% to 78.74% and pooled prevalence of 58.47%. In this meta-analysis, it was also explored as prevalence of 11.7% in lean people with NAFLD and 88.0% in obese people with NAFLD among Asian individuals.¹⁵ Approximately 25% of the general population was computed as estimated NAFLD global prevalence, with the rate observed to be nearly twice as high among individuals diagnosed with diabetes¹³. Another meta-analysis showed that the overall NAFLD or MASLD pooled prevalence in individuals with type 2 diabetes was estimated at 65.33% globally. This prevalence demonstrated an upward trend, rising from 55.86% during the period 1990–2004 to 68.81% in the years 2016–2021, with a *P* value of 0.073.¹⁶ Thrombocytopenia (less than $100 \times 10^9/L$ platelets) is present in approximately one-quarter of NAFLD patients. it was further demonstrated that liver damage is a necessary factor, alongside insulin resistance, for its association with thrombocytopenia and that the severity of thrombocytopenia correlates with the extent of hepatic steatosis.¹⁷ Thrombocytopenia in NAFLD has been attributed to mild hypersplenism due to alterations in liver and portal circulation. Additional contributing factors may include reduced thrombopoietin production from liver damage, shortened peripheral blood cell lifespan, and vitamin deficiencies.¹⁸

A substantial number of referrals to hepatologists or gastroenterologists could be avoided by using these non-invasive scores, thereby lowering the number of liver biopsies performed to assess liver fibrosis and reducing the overall cost of this invasive procedure.¹⁹

Aminotransferase levels (AST and ALT) have been linked to histological features like inflammation and steatosis in NAFLD. These enzymes may be mildly to moderately elevated, typically with an AST/ALT ratio <1 , distinguishing NAFLD from alcoholic liver disease. Their values do not actually reflect the severity of inflammation in the liver or fibrosis and they, despite being normal, do not rule out NAFLD. Non-invasive fibrosis scores are useful in identification of NAFLD patients at greater risk of liver-related morbidity or mortality. In one study, Fib-4 outperformed other serological markers in determining NAFLD related advanced fibrosis. A retrospective analysis of 320 NAFLD patients showed that only those classified as high-risk by the APRI score had an increased chance of death or liver transplantation. Non-invasive tools for the assessment of fibrosis and cirrhosis such as FIB-4, NFS, and APRI offer high negative but low positive predictive values. While FIB-4 and NFS demonstrate good accuracy in diagnosis, their performance can be affected by factors like age and diabetes. Elevated fibrosis scores have been linked to higher mortality due to cardiovascular and liver-related

complications. Consequently, these tools are primarily used to rule out advanced fibrosis and reduce the need for unnecessary liver biopsies.²⁰ One study showed APRI score provide useful information related to the extent of insulin resistance and thus, help in managing the glycemic control in the patients of diabetes along with NAFLD.²¹ A study compared noninvasive makers of hepatic fibrosis in people with NAFLD and FIB-4 outperforms other non-invasive markers.²² FIB-4 is more closely aligned with measurements of liver stiffness from Fibro Scan, which could help in providing early detection of NAFLD in resource limited as well as other population.²³ APRI is an important predictor of advanced liver fibrosis and a better alternative in settings where Fibro Scan is not readily available, such as in resource-limited areas.²⁴

LIMITATIONS.

This study was a single-center, cross-sectional study conducted on a limited population of individuals who visited a hospital setting, so the results may not be generalizable.

CONCLUSION

The current study emphasizes the demand for routine screening of patients with diabetes and NAFLD for the detection of advanced fibrosis, allowing for timely interventions such as lifestyle modification or referral to specialists for further management.

ETHICAL APPROVAL

Ethical approval of synopsis was granted by the Institutional Review Committee of Islamic International Medical College vide reference No. Appl. # Riphah /IRC/ 25/1055 dated 05 June, 2024.

CONFLICT OF INTEREST

Authors declare no conflict of interest.

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AUTHOR'S CONTRIBUTIONS

RB: Concept and design, collection and assembly of data and drafting of article

KF: Analysis and interpretation of data

HP: Drafting and critical revision of article

AZ: Data collection and critical revision of article

SK: Statistical expertise and revising it for important intellectual content

MF: Final approval of the manuscript

All Authors: Approval of the final version of the manuscript to be published

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