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Association of Microalbuminuria in Patient with Non-Alcoholic Fatty Liver Disease: A Cross-Sectional Study in A Tertiary Care Centre

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Abstract

NAFLD (Nonalcoholic Fatty Liver Disease) is a prevalent chronic liver disorder characterized by metabolic abnormalities. Microalbuminuria have been linked to cardiovascular and renal diseases, but its association with NAFLD remains underexplored. This cross-sectional study assessed urine microalbumin levels in patients diagnosed with NAFLD. Demographic data, NAFLD grading, and microalbuminuria status were analyzed in non-NAFLD and NAFLD groups. Statistical analysis has been performed to evaluate the associations. Males were more common than females among NAFLD patients (n=100), particularly in the age range of 41 to 60. Compared to non-NAFLD controls (0%), NAFLD patients (76%) had a considerably higher prevalence of microalbuminuria. BMI showed no significant association with NAFLD prevalence. NAFLD grading revealed Grade 1 as the most prevalent (52%), followed by Grade 2 (32%) and Grade 3 (16%). Our findings demonstrate a strong association between microalbuminuria and NAFLD, suggesting a potential link with adverse cardiovascular and renal outcomes. Monitoring microalbuminuria in NAFLD patients may aid in risk stratification and management. There is a need to conduct larger population-based-randomized studies.

Keywords: *Cardiovascular Disease, Microalbuminuria, Metabolic Syndrome, Non-Alcoholic Fatty Liver Disease, Renal Disease.*

Introduction

NAFLD is a chronic hepatic state ranging from steatosis of the liver to cirrhosis, is defined as the accumulation of fat in the liver without the presence of other conditions such as viral hepatitis or significant drinking of alcohol [1–4]. Initially NAFLD is associated with metabolic abnormalities such as insulin resistance and metabolic syndrome (MetS), and it is becoming more common as obesity and type 2 diabetes mellitus (T2DM) [5]. According to epidemiological studies, NAFLD affects approximately 30% of the USA population, 27% in Asia and 24% in Europe [6–8]. Its prevalence rises as people with obesity and T2DM age [9].

Non-alcoholic fatty liver disease can lead to the development of progressive liver diseases, including cirrhosis, non-alcoholic steatohepatitis (NASH), hepatocellular carcinoma (HCC) and end-stage liver disease [10]. Interestingly, NAFLD is a leading reason for HCC even in absence of cirrhotic development, and those with T2DM and obesity have a minimum of a two-fold increased risk of developing HCC [11].

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Beyond its effects on the liver, NAFLD is linked to a number of systemic prolonged conditions, including cardiovascular disease, diabetes mellitus, osteoporosis, also sarcopenia, underscoring its systemic character and link to higher risks of mortality and cardiometabolic disorders [12–15].

The advancement of chronic renal disease and cardiovascular disease are both known to be predicted by albuminuria [16]. Urine albumin levels of 30-300 mg/day or urinary albumin/creatinine ratios (UACR) of 30-300 mg/g are the conventional measures used to diagnose microalbuminuria. Nevertheless, because single threshold values have their limitations, researchers have highlighted the importance of high albuminuria levels below 30 mg/day (or 30 mg/g), which is known as "low-grade albuminuria" (LGA) [17]. Research has demonstrated a link between LGA and a number of cardiometabolic conditions. Particularly, Tanaka et al. have connected LGA to higher death rates [18]. In people with diabetes mellitus or hypertension, microalbuminuria has been found to be a distinct indicator of death [19]. It is associated with a higher risk of cardiovascular disease in individuals with diabetes and acts as a potential indicator of diabetic nephropathy. According to Kim et al., microalbuminuria is linked to a worse clinical result and an increased risk of coronary artery disease in individuals with type 2 diabetes who are asymptomatic [20]. Additionally, obesity is associated with microalbuminuria, with higher visceral adipose tissue correlating with its prevalence, even in non-diabetic individuals [21]. Conversely, studies have also noted a connection between obesity and microalbuminuria. Research indicates that increased levels of visceral adipose tissue are significantly related to a higher prevalence of microalbuminuria, even at non-diabetic individuals [22].

Microalbuminuria has been linked to coronary artery disease in NAFLD patients, however there hasn't been much clinical research on the subject despite these correlations. As a result, the present investigation attempts to determine the level of urine microalbumin in patients with NAFLD.

Materials and Methods

Patients having a confirmed diagnosis of NAFLD participated in this cross-sectional study, which was carried out at the Tertiary Care Hospital. After a brief explanation of the study process, patient consent was obtained with ethical approval from the hospital ethics committee. The period of this study's execution was January 2023–March 2024. For the purpose of comparing the results, patients were divided into two groups: those with NAFLD and those without NAFLD. Patients who exhibit symptoms of NAFLD, have not smoked, are hospitalized with cirrhosis, jaundice, or infection, and have given their informed agreement to be part of the study are eligible to be included. A history of significant alcohol consumption (more than 30g for male and 20g for femlae per day), a BMI (body mass index) of more than 30 kg/m^2, positive results for anti-HCV or HBsAg, Wilson's disease, autoimmune hepatitis, any known chronic liver disease, hemochromatosis, cancer, hypertension, thyroid disease, diabetes mellitus, renal disease and atherosclerotic heart disease are among the exclusion criteria for this study [23,24].

Measurement Procedure and Diagnosis Criteria

Each participant had their height and weight measured. The weight (kg) was divided by the square of the height (m) to get the BMI. Indicators of the condition were a self-reported diagnosis of diabetes treated with specific medication or a fasting plasma glucose (FPG) level of greater than 125 mg/dL. If the patient's 2-hour post-load glucose (75 g) was 140 mg/dL and their fasting plasma glucose (FPG) was between 110 and 125 mg/dL, impaired

fasting glucose (IFG) was diagnosed if they had never been diagnosed with diabetes before. The study excluded participants diagnosed with diabetes mellitus or with a BMI of more than 30 kg/m². Standing with the subject upright, a lone examiner measured the subject's waist circumference (in centimetres) at the level of the umbilicus. Participants rested for at least five minutes before being seated with their feet on the floor and their arms at heart level. Their blood pressure was measured using a mercury sphygmomanometer. Accuracy was ensured by using a fitting cuff. The first Korotkoff sound (phase 1) was detected to determine the systolic blood pressure, and the last phase (phase 5) was identified as the point at which the sounds stopped occurring [23].

Laboratory Assessment

After an eight-hour overnight fast, all individuals underwent laboratory tests. Liver function tests, such as aspartate aminotransferase (AST), gamma-glutamyl transferase (GGT) and alanine aminotransferase (ALT), also creatinine, urea, insulin levels, and fasting blood glucose (FBG) were performed using conventional techniques specified by the manufacturer [25]. Insulin resistance was measured using the homeostatic model assessment of insulin resistance (HOMA-IR), which was calculated using the following formula [26]:

HOMA: fasting plasma insulin (μU/mL) × fasting plasma glucose (mmol/L)/22.5

The glomerular filtration rate was determined using the Modification of Diet in Renal Disease (MDRD) equation. (GFR) [27]:

$GFR_{MDRD186} = 186 \times [Scr\ (mg/dL)]^{-1.154} \times [age(years)]^{-0.203} \times 0.742$ (if female) × 0.180 (if black).

Urinary albumin excretion was measured using an early-morning urine sample, and the albumin-to-creatinine ratio was determined using an immunonephelometric approach. Microalbuminuria was defined as a urine albumin excretion rate between 30 and 299 mg/mg creatinine.

NAFLD Grading

Every participant had hepatic ultrasonography, wherein an experienced radiologist, who was not privy to the subjects' test findings, evaluated the prevalence and severity of fatty liver. On a scale ranging from 0 to 3, the degree of liver steatosis was categorized as follows: 0 denoted no steatosis, 1 mild steatosis, 2 moderate steatosis, and 3 severe steatosis. The criteria for grading steatosis were defined by Saverymuttu et al. [28]. These criteria took into account various factors, including hepatic parenchymal echoes that were abnormally intense, variations in the amplitude of echo between the liver and kidney, the depth at which echo penetrated the liver, and the clarity of the blood vessel structure within the liver.

Data Collection and Statistical Analysis

All analyses were performed using the Statistical Package for Social Sciences (SPSS) for Windows, version 17.0 (Chicago, IL). The demographic features of the groups were compared using Fisher's exact test and Pearson's chi-square ($\chi 2$) test. A two-tailed Student's t-test was employed to compare groups to groups, and an ANOVA test was utilized to determine whether there was a significant difference between the groups. The results were shown as mean ± SD. The odds ratio (OR) and 95% confidence interval (CI) for microalbuminuria were calculated using logistic regression models that included relevant covariates. It was determined that a p-value of less than 0.05 was statistically significant.

Patient demographic information, including gender, age, NAFLD grade, microalbumin levels and body mass index was recorded in MS Excel 2021. The ANOVA test was utilized to determine significant differences, and the Student's t-test was employed to compare

patients with NAFLD to those without the condition. The criterion for statistical significance was set at $p < 0.05$.

Results

The distribution of NAFLD and NON-NAFLD in relation to gender, body mass index and age was examined in our study [Figure 1 & Table 1 illustrates the demographic profile (Age, Gender, BMI) of both NAFLD & NON-NAFLD patients].

Age Distribution

In the under 40 age range, 3 cases of NAFLD (12.0%) were found, while 1 case of NON-NAFLD (4.0%) was identified. Although the younger age group had a higher prevalence of NAFLD, the difference was not statistically significant (P = 0.753). In 41-50 age individuals, there were 9 cases of NAFLD (36.0%) and 11 cases of non-NAFLD (44.0%). The 51-60 age group was equally divided, with 11 cases of NAFLD (44.0%) and 11 cases of NON-NAFLD (44.0%). For individuals above the age of 61, NAFLD and NON-NAFLD each had 2 cases, accounting for 8.0% of the total. These findings demonstrate that the prevalence of NAFLD does not show a considerable change across different age groups, and statistical insignificance implies no apparent age-related trend in NAFLD prevalence.

Gender Distribution

In terms of gender, females accounted for 8 NAFLD (32.0%) and 7 NON-NAFLD (28.0%) cases, with a non-significant P value of 0.758. Males exhibited a higher prevalence of NAFLD, with 17 cases (68.0%), as compared to 18 cases of NON-NAFLD (72.0%). Although males are more prevalent in both groups, the lack of a significant statistical difference indicates that gender has not much impact on NAFLD prevalence in this study.

BMI Distribution

Among individuals with normal weight, the examination of BMI categories revealed 10 cases of NAFLD (40.0%) and 9 cases of NON-NAFLD (36.0%). NAFLD and NON-NAFLD were found in 14 (56.0%) and 14 (56.0%) of the overweight individuals. There were 2 cases of NON-NAFLD (8.0%) and 1 case of NAFLD (4.0%) in the obese category. The non-significant P value of 0.824 suggests that the prevalence of NAFLD in this sample is not significantly influenced by BMI. The relatively low frequency in the obese category may be due to certain features of the study population or possible sample limitations, even though those who are normal weight and overweight have increased rates of NAFLD.

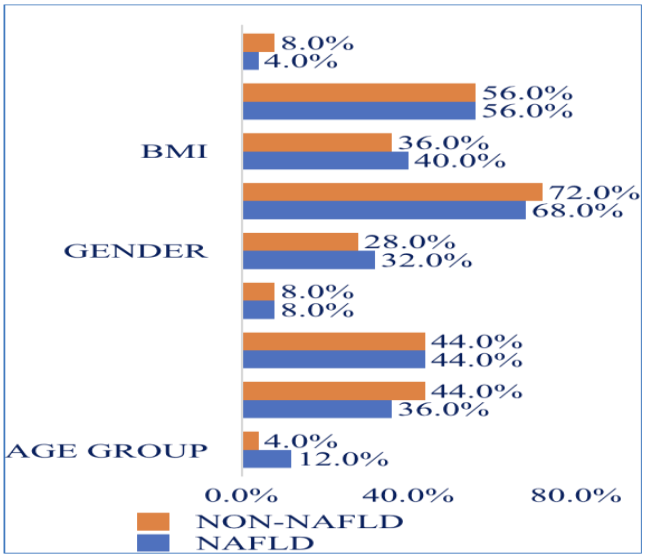

Figure 1. Demographic Profile (Age, Gender, BMI) of Both NAFLD & NON-NAFLD Patients

Table 1. Demographic Presentation of Both Group

Demographic profile		GROUP				P value
		NAFLD		NON-NAFLD		
		Count	Column N %	Count	Column N %	
AGE GROUP	<40	3	12.0%	1	4.0%	0.753
	41-50	9	36.0%	11	44.0%	
	51-60	11	44.0%	11	44.0%	
	>61	2	8.0%	2	8.0%	
GENDER	Female	8	32.0%	7	28.0%	0.758
	Male	17	68.0%	18	72.0%	
BMI	Normal weight	10	40.0%	9	36.0%	0.824
	Overweight	14	56.0%	14	56.0%	
	Obese	1	4.0%	2	8.0%	

Among the patients, 13 individuals were classified as Grade 1 NAFLD, constituting 52.0% of the total cohort. Grade 2 NAFLD encompassed 8 patients, representing 32.0% of the cohort, while Grade 3 NAFLD comprised 4 patients, accounting for 16.0% of the cohort [Figure 2 & Table 2 demonstrates the grading of NAFLD in patients].

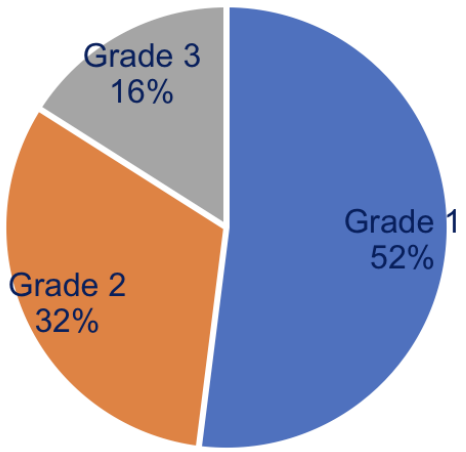

Figure 2. Grading of Non-Alcoholic Fatty Liver Disease in Patients

Table 2. NAFLD Grading of Patients

NAFLD Grade	Number of patients	Percentage
Grade 1	13	52.0%

Grade 2	8	32.0%
Grade 3	4	16.0%

The evaluation and comparison of microalbuminuria in both groups revealed that microalbuminuria was prevalent in the NAFLD group consisting of 19 patients (76.0%). However, no incidence of microalbuminuria was reported in the non-NAFLD group. A fundamental association was reported between microalbuminuria and NAFLD patients (p < 0.0001) [Figure 3 & Table 3 significantly shows the comparative analysis of Microalbuminuria between both groups].

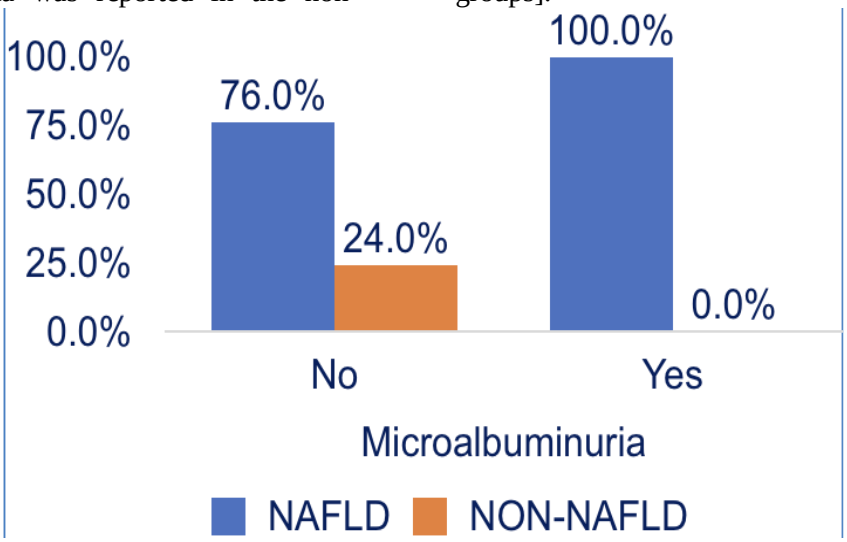

Figure 3. Comparative Analysis of Microalbuminuria between Both NAFLD and non-NAFLD Groups

Table 3. Comparison of NAFLD with NON-NAFLD Group for Microalbuminuria

Microalbuminuria		**GROUP**				
		NAFLD		**NON-NAFLD**		
		Count	Column N %	Count	Column N %	**P value**
Microalbuminuria	No	19	76.0%	25	100.0%	
	Yes	6	24.0%	0	0.0%	<0.0001

The demographic distribution and clinical characteristic of patients with NAFLD in comparison to those without the disease (NON-NAFLD) are highlighted in our report. By age, gender, or BMI categories, we discovered that there were no significant differences in the prevalence of NAFLD; the age groups with the highest prevalence were 41–50 and 51–60. Interestingly, our research revealed a strong correlation between microalbuminuria and NAFLD, with microalbuminuria being more common in NAFLD individuals (P < 0.0001). This is by studies revealing a high frequency of microalbuminuria in NAFLD patients, especially those with Type II diabetes, and research integrating NAFLD to elevated cardiovascular and renal risks [29]. Because NAFLD and renal impairment have been found to be correlated, it is important to closely evaluate kidney function in NAFLD patients in order to address possible renal complications.

Discussion

The findings from our study shed light on the demographic distribution and clinical features of individuals with Non-Alcoholic Fatty Liver Disease compared to those without (NON-NAFLD). Our analysis across different age groups revealed varying proportions of NAFLD cases, with the highest prevalence observed in the 41-50 and 51-60 age groups. However, the differences in NAFLD prevalence among age groups were not statistically significant. Similarly, gender distribution showed a higher percentage of NAFLD cases among males compared to females, although the P value did not reach significance. Gender differences in individuals with NAFLD were examined by Carulli et al. Their findings revealed a noteworthy age difference between men and women diagnosed with NAFLD, with men being approximately 10 years younger on average than women with the same condition. The authors posited a potential protective role of physiological estrogen levels in women against the development of NAFLD. They proposed that this protective effect might be attributed to improvements in insulin sensitivity, dyslipidemia, and the accumulation of visceral fat associated with estrogen levels. These insights suggest a nuanced interplay between gender, hormonal factors, and the pathogenesis of NAFLD, warranting further exploration and consideration in clinical management strategies [30].

One notable aspect of our study was the analysis based on Body Mass Index (BMI) categories, which showed a trend of increasing NAFLD prevalence with higher BMI. Notably, the overweight BMI category had the highest percentage of NAFLD cases. However, the differences in NAFLD prevalence among BMI categories were not statistically significant.

In terms of NAFLD grading, our study revealed a distribution of NAFLD cases across different severity grades, with Grade 1 being the most common, followed by Grade 2 and Grade 3. This highlights the spectrum of NAFLD severity within our study population.

Furthermore, our analysis of microalbuminuria in both groups showed a significant relationship between microalbuminuria and also in NAFLD patients. With a P value of less than 0.0001, microalbuminuria was significantly more common in the NAFLD group than in the NON-NAFLD group, indicating a strong relationship between these two factors. El Azeem et al.'s findings highlight significant associations between NAFLD and adverse renal and cardiovascular outcomes. In comparison to controls, their study showed that individuals with NAFLD had a significantly increased frequency of cardiovascular events and renal impairment. They found that the prevalence of microalbuminuria in NAFLD patients was 32.8% throughout a 3-year follow-up period. This was noticeably higher than the 18.4% prevalence in control cases. El Azeem et al. also found that NAFLD patients had a considerably reduced mean estimated glomerular filtration rate (eGFR), which is indicative of impaired kidney function. They concluded that NAFLD could serve as a reliable predictor of renal and cardiovascular conditions, emphasizing the clinical significance of monitoring and managing NAFLD to mitigate associated cardiovascular and renal risks [31]. Hwang et al.'s study provides additional insights into the relationship between diseases of the fatty liver and microalbuminuria in different populations, particularly among Type 2 diabetics. Their analysis of 1361 subjects with an abnormal oral glucose tolerance test revealed higher prevalence rates of microalbuminuria in patients with NAFLD. Specifically, they reported microalbuminuria rates of 19% in pre-diabetics and 32.6% in diabetics with NAFLD, indicating a significant correlation between these conditions [32].

The potential link between kidney disease and NAFLD is indeed intriguing, although establishing a cause-and-effect relationship remains challenging due to the complexity of their interactions. Both kidney disease and NAFLD share common complications, including inflammation and metabolic disturbances. Previous research has proposed various pathways through which NAFLD may contribute to the progression or development of chronic renal conditions [33]. These pathways include mechanisms such as hypertension, dyslipidemia, chronic inflammation, oxidative stress and insulin resistance all of which can have harmful effects on kidney function long time. Hence, it's important to consider that many studies assessing this association have primarily relied on markers like urine dipstick tests or estimated glomerular filtration rate (eGFR) for overt proteinuria to define chronic kidney disease. This limitation in defining and diagnosing kidney disease could contribute to the complexity and inconclusiveness of the cause-effect relationship between NAFLD and kidney disease [34].

We determined a crucial association between microalbuminuria prevalence and NAFLD, highlighting the potential impact of hepatic steatosis on renal function. Notably, NAFLD patients with microalbuminuria exhibited lower mean eGFR values, indicative of compromised kidney function. These results emphasize the importance of monitoring kidney health in NAFLD patients, particularly those with concurrent microalbuminuria. Future research should focus on elucidating the underlying mechanisms linking NAFLD, microalbuminuria, and renal impairment to facilitate the development of targeted interventions aimed at mitigating adverse outcomes in this patient population.

Conclusion

Finally, our research concludes with several important discoveries about Non-Alcoholic Fatty Liver Disease (NAFLD). We found that NAFLD was more common in men and in the 41–50 and 51–60 age ranges, which may indicate that these individuals are more susceptible to the disease. Furthermore, a strong correlation between NAFLD and microalbuminuria was discovered by our research, suggesting that individuals with NAFLD are more susceptible to show early indicators of kidney dysfunction. This conclusion highlights the greater impact of this disease on general health and is consistent with previous research correlating NAFLD with adverse cardiovascular and renal outcomes. In addition, NAFLD and microalbuminuria have been shown to be related, it is even more important to manage NAFLD proactively and with routine monitoring to reduce associated risks and enhance patient outcomes. Reduced long-term health impacts from nonalcoholic fatty liver disease (NAFLD) can be achieved by managing cardiovascular risks and closely monitoring renal function.

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Conflict of Interest

The authors hereby declare that there is no conflict of interest in this study.

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