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**ORIGINAL ARTICLE**

# Histopathological Correlates of NAFLD in PCOS: Correlation with Serum Creatinine, eGFR, and Urinary Albumin Levels

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## ABSTRACT

**Background:** Non-alcoholic fatty liver disease (NAFLD) is increasingly recognized as a major metabolic complication in women with polycystic ovary syndrome (PCOS), yet its association with early renal dysfunction remains underexplored in South Asian populations.

**Objective:** This study aimed to evaluate the histopathological severity of NAFLD in PCOS and determine its correlation with serum creatinine, estimated glomerular filtration rate (eGFR), and urinary albumin levels.

**Methods:** A cross-sectional analytical study was conducted from March 2022 to February 2023 at Aziz Bhatti Shaheed Teaching Hospital, Gujrat, and the Department of Gynaecology & Obstetrics, KRL Hospital Islamabad, enrolling 100 women with PCOS diagnosed by Rotterdam criteria. All participants underwent clinical assessment, biochemical testing, ultrasonography, and liver histopathology (in consenting cases). Renal function was evaluated through serum creatinine, eGFR (CKD-EPI), and early-morning urinary albumin measurements.

**Results:** NAFLD was detected in 85% of participants, with Grade I being most common. Increasing NAFLD severity showed a significant rise in serum creatinine and urinary albumin, along with a notable decline in eGFR. Histopathological grading demonstrated strong positive correlations with serum creatinine (r = 0.59) and urinary albumin (r = 0.71), and a negative correlation with eGFR (r = –0.64).

**Conclusion:** NAFLD severity in PCOS is strongly associated with early renal impairment, indicating that renal dysfunction may begin long before overt chronic kidney disease develops. Integrating hepatic and renal screening could improve early detection and risk stratification in this high-risk population.

**Keywords:** NAFLD; Polycystic Ovary Syndrome; PCOS; Serum Creatinine; eGFR; Urinary Albumin; Hepatic Steatosis; Renal Dysfunction; Metabolic Syndrome; Histopathology

## INTRODUCTION

Polycystic ovary syndrome (PCOS) is a complex endocrine–metabolic disorder affecting 6–20% of reproductive-aged women worldwide[1]. Traditionally recognized for its reproductive manifestations such as anovulation, menstrual irregularities, and hyperandrogenism PCOS is now widely accepted as a multisystem disorder with profound metabolic implications. Insulin resistance, central obesity, dyslipidemia, chronic low-grade inflammation, and oxidative stress form the core metabolic disturbances that contribute to long-term complications extending far beyond the reproductive axis. Among these, non-alcoholic fatty liver disease (NAFLD) has emerged as one of the most significant yet underdiagnosed comorbidities in women with PCOS[2,3].

NAFLD represents a spectrum of hepatic pathology ranging from simple steatosis to steatohepatitis, fibrosis, cirrhosis, and hepatocellular carcinoma. Women with PCOS have a two- to four-fold higher risk of developing NAFLD compared with non-PCOS women of the same age group[4]. Hyperinsulinemia, adipose tissue dysfunction, androgen excess, and altered adipokine signaling accelerate hepatic fat deposition and fibrotic progression even in young, non-obese PCOS patients. This association is of particular relevance in South Asian populations, who exhibit higher visceral adiposity, earlier onset of insulin resistance, and increased susceptibility to metabolic syndrome[5].

While the hepatic consequences of PCOS-related metabolic dysfunction are increasingly recognized, far less attention has been given to the renal axis in these patients. Emerging evidence suggests that early alterations in renal function may occur long before the development of clinically overt chronic kidney disease[6]. Serum creatinine, estimated glomerular filtration rate (eGFR), and urinary albumin levels serve as sensitive indicators of glomerular function and microvascular injury. Microalbuminuria, in particular, reflects endothelial dysfunction and is considered a strong marker of early renal involvement and cardiovascular risk[7].

The interplay between liver and kidney dysfunction in PCOS may be mediated by shared mechanisms, including systemic inflammation, insulin resistance, oxidative stress, and endothelial injury[8]. However, the extent to which histopathological severity of NAFLD correlates with early renal biomarkers remains poorly understood, especially within Pakistani and other South Asian female populations, where both metabolic disorders and PCOS are highly prevalent[9].

Therefore, this study aims to investigate the histopathological correlates of NAFLD in women with PCOS and evaluate their association with serum creatinine, eGFR, and urinary albumin levels. Understanding this interrelationship may provide critical insights for early risk stratification and integrated metabolic management in this vulnerable population[10].

## MATERIALS AND METHODS

**Study Design and Duration:** This research was conducted as a cross-sectional analytical study spanning one year, from March 2022 to February 2023. The study was carried out at two major tertiary-care centers: Aziz Bhatti Shaheed Teaching Hospital, Gujrat, Pakistan, and the Department of Gynaecology and Obstetrics, KRL Hospital, Islamabad. Both institutions cater to a diverse patient population and serve as referral centers for metabolic, endocrine, and reproductive disorders, ensuring adequate representation of women diagnosed with polycystic ovary syndrome (PCOS). The study design enabled simultaneous evaluation of hepatic and renal parameters to establish their correlation within the same clinical encounter.

**Study Population and Sampling:** The study included 100 women diagnosed with PCOS based on the Rotterdam 2003 criteria. Women aged 18 to 45 years presenting to the outpatient departments of the participating hospitals were recruited consecutively after fulfilling the diagnostic criteria for PCOS. Only those who provided informed written consent were enrolled. Patients with known chronic liver diseases such as viral hepatitis,

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autoimmune liver disorders, Wilson's disease, or any history of alcohol intake were excluded. Additional exclusion criteria included pregnancy, previously diagnosed chronic kidney disease, the use of hepatotoxic medications, and endocrine disorders such as thyroid dysfunction or Cushing's syndrome. These measures ensured that hepatic and renal findings could be attributed specifically to PCOS-associated metabolic dysfunction rather than confounding medical conditions.

**Clinical and Anthropometric Assessment:** All participants underwent a detailed clinical evaluation at the time of enrollment. Their demographic information, menstrual history, symptomatic duration, and comorbidities were documented comprehensively. Anthropometric measurements were obtained using standardized methods and included height, weight, body mass index (BMI), and waist circumference. Blood pressure was measured after adequate rest. Clinical evidence of hyperandrogenism, including hirsutism, acne, and androgenic alopecia, was assessed by trained clinicians. This multidimensional evaluation provided a complete metabolic and reproductive profile for each participant and allowed for the identification of risk factors associated with NAFLD severity.

**Biochemical and Renal Investigations:** Venous blood samples were collected from each participant after an overnight fast of 8 to 10 hours. Serum creatinine was measured using the enzymatic method, while fasting plasma glucose and insulin levels were obtained to calculate the Homeostatic Model Assessment for Insulin Resistance (HOMA-IR). Lipid profile parameters, including total cholesterol, triglycerides, LDL, and HDL, were analyzed alongside liver enzymes such as alanine aminotransferase (ALT) and aspartate aminotransferase (AST). Renal function was assessed using the estimated glomerular filtration rate (eGFR), calculated using the CKD-EPI equation, which provides a reliable indicator of glomerular filtration efficiency. Early-morning spot urine samples were collected to determine urinary albumin levels, which were quantified to detect early renal involvement. Albumin excretion was interpreted in terms of normal values, microalbuminuria, and macroalbuminuria, enabling early detection of glomerular damage.

**Radiological and Histopathological Evaluation of NAFLD:** All participants underwent abdominal ultrasonography performed by experienced radiologists to classify non-alcoholic fatty liver disease. Liver echogenicity, hepato-renal contrast, and visualization of intrahepatic vessels were assessed to categorize fatty liver into Grade 0 (normal), Grade I (mild), Grade II (moderate), or Grade III (severe). Women who consented to further evaluation underwent liver biopsy, and the tissue samples were processed in the histopathology laboratory. Histopathological assessment included the degree of steatosis, lobular inflammation, ballooning degeneration, and fibrosis stage, evaluated using the Nonalcoholic Steatohepatitis Clinical Research Network (NASH-CRN) scoring system. These detailed assessments allowed accurate classification of NAFLD severity and provided the basis for correlating histopathological findings with renal biomarkers.

**Data Processing and Statistical Analysis:** All collected data were compiled and analyzed using SPSS software version 25. Continuous variables such as serum creatinine, eGFR, urinary albumin, liver enzymes, and metabolic markers were expressed as mean ± standard deviation, while categorical variables were presented as frequencies and percentages. The association between NAFLD grades and renal function markers was assessed using one-way ANOVA, enabling comparison across multiple groups. Pearson correlation analysis was applied to determine the strength and direction of correlation between histopathological severity and renal biomarker levels. Statistical significance was defined as a p-value of less than 0.05. This analytical approach ensured that all correlations were evaluated with appropriate statistical rigor.

**Ethical Considerations:** Ethical approval for the study was obtained from the institutional review boards of both participating hospitals. All procedures were performed in accordance with the ethical standards of the Helsinki Declaration. Confidentiality of patient data was strictly maintained, and participants were included only after providing informed written consent. The ethical framework ensured that the study was conducted with respect for patient autonomy, safety, and privacy.

## RESULTS

A total of 100 women with polycystic ovary syndrome were included in the study from Aziz Bhatti Shaheed Teaching Hospital and KRL Hospital over the one-year study duration. The mean age of participants was 29.7 ± 6.1 years, and the majority exhibited central obesity, elevated BMI, and biochemical evidence of insulin resistance. NAFLD was detected on ultrasonography in 85% of participants, with varying grades of severity. Liver biopsy, performed in consenting patients, confirmed corresponding histopathological stages.

The distribution of NAFLD grades demonstrated that Grade I steatosis was the most common pattern, followed by Grade II and Grade III disease. Table 1 presents the frequency distribution of NAFLD grades. Increasing grades were associated with progressively higher BMI, fasting insulin, ALT, and HOMA-IR values, although the current study focused on hepatic–renal associations rather than metabolic predictors.

A clear and significant pattern emerged when renal biomarkers were analyzed across NAFLD severity groups. Women without hepatic steatosis demonstrated the lowest serum creatinine levels and highest eGFR values. In contrast, those with Grade II and Grade III steatosis showed a marked elevation in serum creatinine alongside a substantial decline in eGFR. Urinary albumin excretion increased sharply with disease progression and shifted from normal to microalbuminuric levels in many Grade II patients, while several Grade III patients approached or exceeded the macroalbuminuria range. These findings are summarized in Table 2.

Correlation analysis further confirmed that histopathological severity bore a strong positive association with serum creatinine and urinary albumin levels, while showing a significant negative correlation with eGFR. The correlation coefficients demonstrated that worsening steatosis and fibrosis were directly linked with early renal injury indicators. These results collectively suggest that NAFLD severity in PCOS is not merely a hepatic manifestation but also reflects early renal involvement, even in the absence of overt chronic kidney disease. Table 3 summarizes the correlation matrix for key renal biomarkers in relation to NAFLD grades.

Table 1. Distribution of NAFLD Grades Among Study Participants (n = 100)

| NAFLD Grade | Frequency | Percentage (%) |
|---|---|---|
| Grade 0 (Normal) | 15 | 15% |
| Grade I (Mild) | 38 | 38% |
| Grade II (Moderate) | 32 | 32% |
| Grade III (Severe) | 15 | 15% |

Table 2. Renal Function Parameters Across NAFLD Severity

| Parameter | Grade 0 | Grade I | Grade II | Grade III | p-value |
|---|---|---|---|---|---|
| Serum Creatinine (mg/dL) | 0.67 ± 0.09 | 0.72 ± 0.11 | 0.83 ± 0.14 | 0.94 ± 0.17 | <0.001 |
| eGFR (mL/min/1.73 m²) | 119 ± 10 | 111 ± 13 | 97 ± 15 | 86 ± 19 | <0.001 |
| Urinary Albumin (mg/g) | 11.8 ± 3.5 | 19.6 ± 4.9 | 35.4 ± 6.1 | 62.7 ± 7.9 | <0.001 |

Table 3. Correlation of NAFLD Histopathology with Renal Biomarkers

| Parameter | Correlation Coefficient (r) | Direction |
|---|---|---|
| Serum Creatinine | +0.59 | Positive |
| eGFR | –0.64 | Negative |
| Urinary Albumin | +0.71 | Strong Positive |

## DISCUSSION

The findings of this study demonstrate a significant association between the histopathological severity of non-alcoholic fatty liver disease (NAFLD) and early renal dysfunction in women with polycystic ovary syndrome (PCOS)[10]. As NAFLD progressed from mild to severe grades, there was a consistent rise in serum creatinine, a decline in estimated glomerular filtration rate (eGFR),

and a marked increase in urinary albumin excretion. These results highlight a growing body of evidence suggesting that PCOS is not solely an endocrine or reproductive disorder but a systemic metabolic condition capable of influencing multiple organ systems simultaneously[11].

Several mechanisms may explain the link between worsening hepatic pathology and renal impairment in PCOS. Insulin resistance, a hallmark of both PCOS and NAFLD, contributes to glomerular hyperfiltration, endothelial dysfunction, and eventual microalbuminuria[12]. Hyperinsulinemia promotes lipotoxicity, oxidative stress, and chronic inflammation, all of which exert detrimental effects on hepatic and renal tissues. The strong positive correlation between urinary albumin and NAFLD histopathology observed in this study supports the concept of early glomerular injury occurring concurrently with hepatic fat accumulation. Elevated albuminuria, even at microalbuminuric levels, indicates systemic endothelial dysfunction, which is a precursor to both cardiovascular and renal morbidity[13].

The decline in eGFR among women with Grade II and Grade III steatosis further reinforces the hypothesis that renal impairment begins much earlier than previously recognized in PCOS[14]. Although the absolute eGFR values did not fall into chronic kidney disease ranges, the downward trend suggests progressive glomerular compromise that warrants early clinical attention. These observations align with international studies reporting reduced renal perfusion and higher microalbuminuria rates in women with metabolic syndrome and NAFLD. However, the present study contributes novel evidence specific to South Asian women with PCOS, a population characterized by higher visceral adiposity and increased susceptibility to metabolic dysfunction[15].

Another important implication of this study is the recognition of NAFLD as a potential clinical marker for systemic metabolic deterioration in PCOS. Liver histopathology may reflect the cumulative burden of metabolic abnormalities, and identifying worsening grades of steatosis could enable clinicians to promptly evaluate renal function, particularly urinary albumin excretion, as an early detection strategy. Integrating hepatic and renal assessments may therefore improve long-term monitoring and reduce the risk of chronic kidney disease development[16,17].

The strengths of this study include its multi-institutional data collection, histopathological confirmation of NAFLD severity, and simultaneous evaluation of key renal biomarkers. However, certain limitations must be acknowledged[18]. The cross-sectional design limits the ability to determine causal relationships. Liver biopsy, although the gold standard, was not performed in all participants, potentially affecting the interpretation of advanced fibrosis. Additionally, the study did not evaluate long-term renal outcomes or the effect of therapeutic interventions such as weight reduction, insulin-sensitizing agents, or lifestyle modifications[19].

Despite these limitations, the study provides important insights into the hepatic–renal axis in PCOS and emphasizes the need for integrated metabolic evaluation. Future longitudinal studies with larger sample sizes and follow-up assessments are required to determine whether early detection and intervention for NAFLD can prevent the progression of renal injury in this high-risk group[20].

## CONCLUSION

This study demonstrates a strong and progressive association between the histopathological severity of NAFLD and early renal dysfunction in women with PCOS. Increasing grades of hepatic steatosis correlate with rising serum creatinine levels, declining eGFR, and significantly elevated urinary albumin excretion. These findings support the concept that NAFLD in PCOS is a systemic metabolic manifestation rather than an isolated hepatic condition. Early renal involvement may occur even before clinically evident chronic kidney disease develops. Routine evaluation of serum creatinine, eGFR, and urinary albumin should therefore be integrated into the management of PCOS patients diagnosed with NAFLD, particularly those with Grade II and Grade III steatosis. Early detection provides a crucial opportunity for timely metabolic intervention, lifestyle modification, and prevention of future renal and cardiovascular complications. Overall, this study underscores the importance of multidisciplinary care in PCOS, recognizing its far-reaching metabolic consequences across multiple organ systems.

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