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RELATIONSHIP BETWEEN NON-ALCOHOLIC FATTY LIVER DISEASE AND PULMONARY FUNCTION

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Abstract
Non-alcoholic fatty liver disease (NAFLD) is increasingly recognized as a multisystem disorder with extrahepatic manifestations, including potential effects on pulmonary function. This cross-sectional observational study evaluated 110 treatment-naïve patients with ultrasound-confirmed NAFLD to analyse the connection between hepatic steatosis severity and pulmonary function parameters, and to explore the mediating role of systemic inflammation. Hepatic fat was graded semi-quantitatively, and pulmonary function was evaluated by spirometry. Participants were stratified as lean or obese based on BMI index. Increased steatosis grade was associated with significantly lower FVC, FEV_1, all $p < 0.001$. Obese NAFLD patients had more severe pulmonary impairment than lean individuals. These findings highlight hepatic steatosis as an independent determinant of pulmonary dysfunction in NAFLD, warranting routine respiratory evaluation.

Keywords: Non-alcoholic fatty liver disease, Hepatic steatosis, Respiratory function, Restrictive lung impairment

Introduction

Non-alcoholic fatty liver disease (NAFLD) has developed as the leading cause of persistent hepatic condition, impacting around 25–30% of adults.[1] Once considered a benign hepatic condition, it is now recognized as a complex multisystem disease with implications that extend far beyond the liver.[2] The condition spans a continuum from isolated hepatic fat accumulation, known as liver steatosis, to the more severe non-alcoholic steatohepatitis, which can further advance to liver fibrosis, scarring, and potentially liver cancer. The growing burden of this condition parallels the worldwide epidemics of overweight, metabolic syndrome, and Diabetes mellitus type 2, particularly in middle-income countries undergoing rapid lifestyle transitions.[3] Its rising prevalence poses a growing public health challenge, given its contribution to disease burden, increased medical expenditures, and reduced quality of life.[4]

Beyond liver-related complications, it is increasingly recognized as a systemic condition associated with various extrahepatic disorders, including cardiovascular disease, chronic kidney disease, and

select endocrine abnormalities. Recent attention has turned to the respiratory system, as evidence suggests a possible link between NAFLD and impaired pulmonary function.[5] This association may be mediated through shared pathophysiological pathways, particularly systemic inflammation, oxidative stress, insulin resistance, and ectopic fat deposition. These mechanisms are hypothesized to alter pulmonary mechanics, gas exchange, and vascular tone, potentially leading to measurable decrements in lung function without overt respiratory disease.

Pulmonary function, primarily assessed through spirometric measures such as forced vital capacity (FVC) and forced expiratory volume in one second (FEV_1), provides valuable insight into both restrictive and obstructive lung patterns.[6] Emerging studies have reported reduced FVC, FEV_1, values in individuals with NAFLD compared to controls, suggesting the liver–lung interaction may be clinically significant.[7] The precise mechanisms underlying this relationship remain incompletely understood.

Another important dimension in the NAFLD–pulmonary function relationship is the phenotypic heterogeneity within NAFLD populations. While obesity has long been associated with both hepatic steatosis and reduced lung volumes, a growing body of literature underscores the clinical significance of lean NAFLD, a subtype characterized by hepatic fat accumulation in persons with a body mass index (BMI) below the traditional obesity threshold (<25 kg/m^2).[8] These patients may still harbor metabolic risk factors and exhibit histologically significant liver damage. The question arises as to whether lean and obese NAFLD phenotypes demonstrate differential pulmonary profiles, and whether body composition plays a modifying role in the liver–lung interaction.[9] Investigating these phenotypic differences could offer a more sophisticated comprehension of the pathogenesis and help tailor clinical screening strategies.

Despite the biological plausibility and emerging data, the existing literature on the NAFLD–pulmonary function axis remains limited by small sample sizes, heterogeneous diagnostic criteria, and inconsistent adjustment for perplexing factors such as smoking status, physical activity, and comorbid conditions. Most studies have relied on biochemical or indirect surrogate markers for hepatic fat content rather than imaging-based confirmation, thereby limiting diagnostic precision.[10] Advanced imaging modalities provide highly accurate quantification of liver fat but are costly and not widely available, particularly in low-resource settings.[11] There is a critical need for studies that utilize accessible but reliable diagnostic tools such as ultrasonography to bridge this evidence gap in real-world clinical environments.

To address these limitations and further elucidate the interplay between hepatic steatosis and pulmonary physiology, the current study was intended to be a transverse and observational investigation involving treatment-naïve NAFLD patients. Hepatic steatosis was quantified using standard abdominal ultrasonography, while pulmonary function was assessed via spirometry testing per American Thoracic Society (ATS) guidelines. Participants were further stratified into lean and obese NAFLD phenotypes to measure the modifying impact of body composition on respiratory function outcomes.

The objective of the study includes:

1. To measure the link between hepatic fat accumulation and specific pulmonary function parameters (FVC, FEV_1) in treatment-naïve NAFLD patients.
2. To compare pulmonary function profiles between lean and obese NAFLD phenotypes to determine whether body composition modifies the liver–lung interaction.

In light of the escalating prevalence of NAFLD and its systemic consequences, the identification of impaired pulmonary function as a potential extrahepatic manifestation carries significant clinical implications. Early detection of subclinical respiratory compromise in NAFLD patients, particularly among those without overt obesity, may prompt timely intervention, thereby reducing long-term morbidity. The integration of simple, non-invasive tools such as ultrasound and spirometry into standard care pathways can enhance diagnostic yield in resource-constrained settings. The

investigation intends to contribute meaningful insights to the existing literature on NAFLD's systemic reach and inform future preventive and therapeutic strategies.

2. Methodology

The study employed a cross-sectional observational design. Investigation aimed at assessing the connection between non-alcohol-induced hepatic steatosis and pulmonary function, and exploring the potential mediating role of systemic inflammation. Data collection is taking place at the outpatient hepatology and endocrinology departments.

2.1 Study Population

Individuals between 18 and 65 years of age with a confirmed diagnosis of non-alcohol-induced hepatic steatosis were included in the study. Detection of hepatic steatosis was established using ultrasonographic criteria during routine abdominal imaging. Eligible participants were treatment-naïve, with no history of pharmacological, surgical, or lifestyle interventions for NAFLD.

Patients were excluded with signs and symptoms of persistent respiratory conditions such as asthma, COPD, or interstitial lung disease. Other exclusion criteria included significant alcohol intake (>20g/day in women and >30g/day in men), viral hepatitis, autoimmune hepatitis, decompensated systemic illness, or any other known liver pathology unrelated to liver steatosis. Based on their BMI, participants were categorized into lean (BMI < 25 kg/m^2) and obese (BMI 30 kg/m^2) NAFLD subgroups to examine the impact of body composition on pulmonary parameters.

2.2 Assessment of Hepatic Steatosis

The extent of hepatic fat accumulation was assessed using abdominal ultrasonography, a validated, non-invasive, and cost-effective imaging technique suitable for population-level studies. All sonographic evaluations were performed by experienced radiologists using high-frequency convex transducers (3.5–5 MHz). Fatty liver was diagnosed based on characteristic features, including increased hepatic echogenicity relative to the renal cortex, blurring of intrahepatic vascular margins, and posterior beam attenuation.

Steatosis was classified semi-quantitatively into 3 grading metrics:

- Grade I (mild): Minor upsurge in echogenicity with clear picturing of hepatic vessels and diaphragm
- Grade II (moderate): Modest increase in echogenicity with partial obscuration of intrahepatic vessels
- Grade III (severe): Marked rise in echogenicity with poor visualization of hepatic architecture

2.3 Pulmonary Function Testing

Respiratory performance was evaluated through spirometry and diffusion capacity testing, following the standardized procedures recommended by the American Thoracic Society. All tests were conducted by certified respiratory technicians who were blinded to the participants' hepatic status.

Spirometric parameters included:

- Forced Vital Capacity or FVC
- Forced Expiratory Volume in one second or FEV_1
- FEV_1/FVC ratio

All values were recorded both in absolute terms and as percentages of predicted values standardized for age, gender, height, and ethnicity.

2.4 Anthropometric and Clinical Data Collection

Standardized procedures were used to measure height, weight, waist circumference, and calculate BMI. Body composition outcomes, including fat mass and lean mass, were evaluated using bioelectrical impedance analysis. Each participant underwent a structured interview using a validated

questionnaire to collect information on demographics, comorbidities (e.g., type 2 diabetes, hypertension), medication history, smoking habits, and physical activity levels.

2.6 Statistical Analysis

Data were entered into a secure platform and examined using SPSS version 22.0. The Kolmogorov–Smirnov test was used to assess the distribution of continuous variables. The results were presented as a median with interquartile range or as a mean with standard deviation, depending on the distribution. Categorical variables were described using counts and percentages. The independent t-test or Mann-Whitney U test was utilized for continuous variables in group comparisons between lean and obese NAFLD participants, and chi-square tests were employed for categorical data. Correlation between liver fat and pulmonary parameters was assessed using Pearson or Spearman coefficients, depending on data normality. The study employed multivariate linear regression to account for confounding variables like smoking, age, sex, and BMI. Mediation analysis followed the Baron and Kenny approach, with the indirect effect tested using bootstrapping (5000 resamples).

2.7 Ethical Considerations

The Institutional Ethics Committee provided ethical approval [Jhalawar Medical College, Jhalawar (Rajasthan)] (Approval No.: [EC/NEW/INST/2022/RJ/0134]). All protocols followed the Declaration of Helsinki. Informed consent was obtained from every patient following explanation of the study, and withdrawal was permitted at any stage without affecting clinical care.

3. Results

3.1 Demographic and Clinical Profile of Participants at Enrollment

110 treatment-naive patients with ultrasound-confirmed NAFLD were enrolled in the study. These 48 participants (43.6%) were classified as lean NAFLD, and 62 participants (56.4%) were obese NAFLD. The population's average age was 44.3 ± 10.6 years, and 62.7% were male. Obese NAFLD participants exhibited significantly higher BMI, waist circumference, and body fat percentage. The prevalence of comorbidities was also greater in this group, with higher rates of Diabetes mellitus type 2 (51.6% vs. 25.0%, p = 0.004) and hypertension (38.7% vs. 16.7%, p = 0.014) than in the lean NAFLD group, as shown in Table 1.

Table 1. Baseline Characteristics of Study Participants

Variable	**Total (n = 110)**		**Obese NAFLD (n = 62)**	**p-value**
Age (years)	44.3 ± 10.6	45.1 ± 10.2	43.7 ± 10.9	0.282
Male sex, n (%)	69 (62.7%)	31 (64.6%)	38 (61.3%)	0.715
BMI (kg/m^2)	28.4 ± 5.1	23.4 ± 1.6	33.2 ± 2.8	<0.001***
Waist circumference (cm)	91.2 ± 10.4	82.5 ± 7.8	98.4 ± 8.3	<0.001***
Body fat (%), mean ± SD	27.6 ± 5.9	21.8 ± 4.2	32.3 ± 5.1	<0.001***
Type 2 diabetes, n (%)	45 (40.9%)	12 (25.0%)	32 (51.6%)	0.004**
Hypertension, n (%)	33 (30.0%)	8 (16.7%)	24 (38.7%)	0.014*

*p < 0.05, **p < 0.01, ***p < 0.001.

3.2 Hepatic Steatosis Severity

Ultrasonographic grading revealed that 42 participants (38.2%) had Grade I steatosis, 46 (41.8%) had Grade II, and 22 (20.0%) had Grade III. Moderate to severe steatosis (Grades II and III) was more common among obese NAFLD participants (p < 0.001), suggesting greater hepatic fat burden in this phenotype.

3.3 Pulmonary Function by Phenotype

Across the cohort, pulmonary function measures were lower in obese NAFLD compared to lean NAFLD. The mean predicted values for FVC, FEV_1 were 91.7 ± 13.0%, 88.6 ± 12.2% respectively, in the lean group, versus 83.5 ± 11.3%, 81.3 ± 12.9% in the obese group, respectively ($p < 0.01$ for all). The FEV_1/FVC ratio remained preserved in both groups, consistent with a restrictive ventilatory pattern, as shown in Table 2.

Table 2. Pulmonary Function Parameters by NAFLD Phenotype

Parameter	Lean NAFLD (n = 48)	Obese NAFLD (n = 62)	p-value
FVC (% predicted)	91.7 ± 13.0	83.5 ± 11.3	0.003**
FEV_1 (% predicted)	88.6 ± 12.2	81.3 ± 12.9	0.006**
FEV_1/FVC ratio	0.81 ± 0.05	0.79 ± 0.06	0.114

3.5 Correlation Between Steatosis and Pulmonary Function

Spearman correlation analyses demonstrated significant inverse associations between hepatic steatosis grade and pulmonary function indices: FVC ($r = –0.45$), FEV_1 ($r = –0.38$), all $p < 0.001$ mentioned in Table 4. These results indicate a clear decline in lung function as steatosis severity increases.

Table 4. Correlation Between Steatosis Grade and Pulmonary Function

Variable	FVC	FEV_1
Steatosis Grade	–0.45***	–0.38***

Spearman's correlation; ***$p < 0.001$.

These associations are also shown in Figure 1, which presents scatterplots of steatosis grade versus pulmonary function metrics.

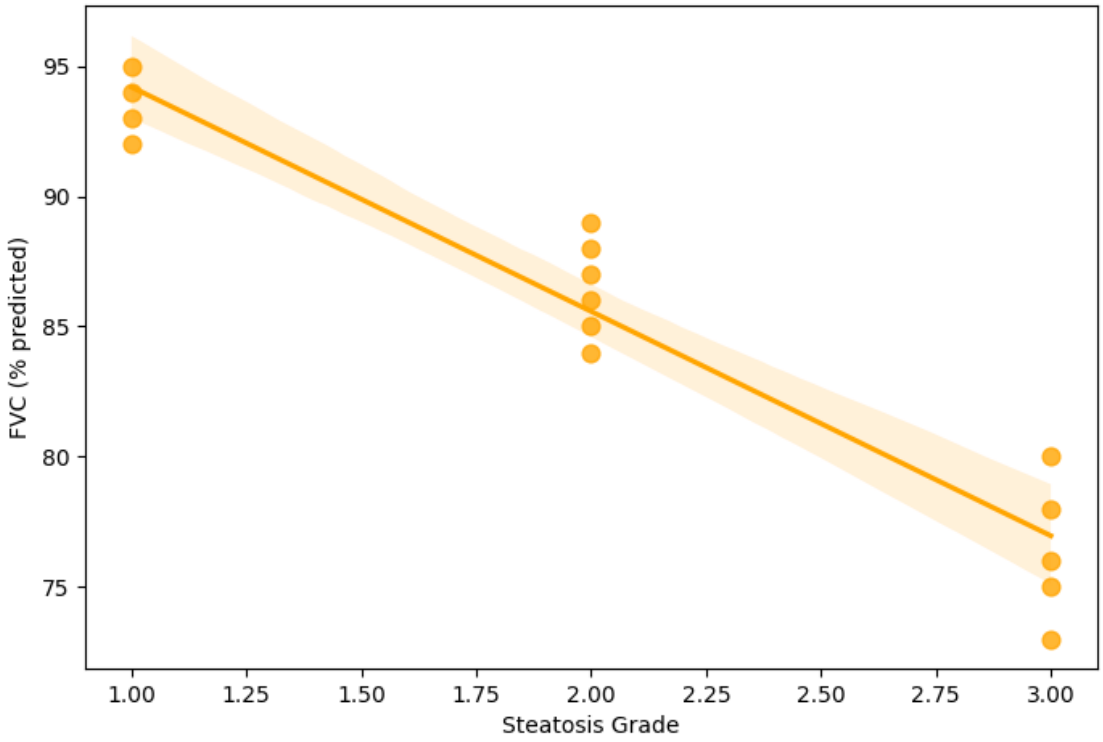

Figure 1. Scatterplots showing the associations between steatosis severity and FVC

Scatterplot showing a negative correlation between hepatic steatosis grade and forced vital capacity (FVC, % predicted).

Linear regression lines with 95% confidence intervals are overlaid. Each point represents an individual participant. Steatosis grades were determined by ultrasonography.

3.6 Multivariate Regression Analysis

Adjusting multivariable linear regression models for age, sex, BMI, smoking, diabetes, and physical activity confirmed that hepatic steatosis was an autonomous interpreter of decreased pulmonary function. Steatosis was significantly associated with lower FVC ($\beta = -2.81$, $p = 0.005$), FEV_1 ($\beta = -2.43$, $p = 0.011$), as shown in Table 5.

Table 5. Multivariate Regression Analysis Predicting Pulmonary Impairment

Pulmonary Variable	β Coefficient	95% CI	p-value
FVC (% predicted)	–2.81	–-4.65 to –0.97	0.005**
FEV_1 (% predicted)	–2.43	–-4.29 to –0.58	0.011*

Discussion

The study found a strong link between fatty liver severity and respiratory function decline in treatment-naïve patients with NAFLD. Higher grades of hepatic fat accumulation were correlated with lower values of forced vital capacity (FVC), forced expiratory volume in one second (FEV_1), indicating restrictive lung impairment and compromised alveolar-capillary gas exchange.[12] These observations emphasize the systemic nature of NAFLD and suggest that pulmonary dysfunction may represent an important extrahepatic manifestation of this increasingly prevalent metabolic condition.

The observed inverse correlation between hepatic steatosis and lung function aligns with previous studies that have reported spirometric abnormalities in NAFLD populations.[13] Prior epidemiological analyses, including large cohort-based studies from East Asia, have indicated that individuals with NAFLD exhibit a higher prevalence of restrictive ventilatory defects, even in the absence of overt respiratory disease. Existing literature has relied on surrogate biochemical indicators or non-specific fatty liver indices, limiting diagnostic precision.[14] The current findings are based on direct imaging-based classification of hepatic steatosis, adding strength to the validity of the hepatic phenotype categorization and offering a more reliable basis for interpreting hepatic-pulmonary interactions.[15]

The relationship between hepatic steatosis and pulmonary impairment was evident across both lean and obese NAFLD phenotypes. Although obese patients exhibited greater degrees of hepatic fat and more pronounced lung function decline, lean individuals with steatosis also demonstrated significant reductions in FVC with increasing fat grades.[16] This finding underscores the metabolic complexity of NAFLD, particularly in regions with high prevalence of lean NAFLD, such as South Asia. Lean individuals, though not obese by BMI, harbor visceral adiposity, insulin resistance, or genetic predispositions that promote hepatic inflammation and systemic cytokine activation.[17]

The clinical implications of these findings are substantial. Pulmonary function decline in NAFLD, even in its early stages, could contribute to fatigue, reduced exercise tolerance, and diminished quality of life, symptoms often attributed solely to metabolic dysfunction.[18] Routine spirometric screening may be warranted in individuals with moderate to severe steatosis, especially in the presence of comorbidities such as diabetes or hypertension.[19]

The study design precludes definitive conclusions regarding causality, and the possibility of reverse causation or confounding by unmeasured variables cannot be excluded. The absence of detailed pulmonary imaging, such as high-resolution computed tomography or functional assessments, such as exercise capacity testing, limits anatomical correlation with physiological findings. Lung function impairments were evaluated at rest and may underestimate exertional deficits. The sample size, while adequate for primary analysis, was insufficient for extensive subgroup evaluation based on sex, fibrosis stage, or duration of NAFLD.[20]

Future investigation should rely on longitudinal studies to determine whether progressive hepatic fat accumulation predicts decline in pulmonary function over time, or whether improvement in liver status through lifestyle or pharmacologic therapy leads to measurable respiratory gains. Investigating

the role of other inflammatory and metabolic mediators, including leptin, adiponectin, endotoxins, and gut microbiota, may help elucidate the multifaceted pathways of liver-lung interaction.[21]

Conclusion

In this study clear inverse association was identified between the severity of fatty liver and respiratory function parameters in treatment-naïve individuals with NAFLD. Higher steatosis grades were associated with progressively lower pulmonary indices, including FVC (% predicted: Grade I = 91.2, Grade III = 78.4), FEV_1 (Grade I = 89.5, Grade III = 76.2, suggesting ventilatory restriction. These findings reinforce the conceptualization of NAFLD as a systemic disorder with extrahepatic manifestations, including subclinical pulmonary dysfunction. Both lean and obese NAFLD phenotypes demonstrated pulmonary compromise, highlighting the need for comprehensive evaluation beyond anthropometric criteria alone. Pulmonary screening helps in the early identification of systemic progression in individuals with moderate to severe hepatic steatosis. Integrating pulmonary function assessment into NAFLD care algorithms may facilitate timely interventions, improve quality of life, and reduce multi-organ morbidity associated with metabolic liver disease.

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