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# Evaluation of The Connection Between the Intensity of Non-Alcoholic Fatty Liver Disease (Nafld) And Respiratory Performance Among a Cohort of Individuals Gathered from The Adiwaniyah Region, Iraq: A Cross-Sectional Exploration

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## ABSTRACT

**Background:** Non-alcoholic fatty liver disease (NAFLD) stands as a prevalent culprit of chronic liver ailments across the globe. In the realm of NASH, the accumulation of fat in the liver is intertwined with inflammatory responses and cell death, potentially paving the way to fibrosis and cirrhosis. The delicate balance of pulmonary function can be swayed by a myriad of inherent (age, sex, ethnicity) and external (air pollution, smoking, biomass) influences. Moreover, its capability is compromised in diseases that affect areas beyond the lungs, such as cardiovascular disorders and chronic kidney issues. Notably, diminished pulmonary function has also been linked to the presence of nonalcoholic fatty liver disease (NAFLD).

**Aim of the study:** The aim of this study is to assess the severity of non-alcoholic fatty liver disease (NAFLD) in a sample of Iraqi patients using fibrsocan and correlate the severity to pulmonary function.

**Patients and methods:** The present investigation is a cross-sectional design that encompassed 124 individuals exhibiting clinical, laboratory, and imaging signs indicative of NAFLD, all of whom were enlisted from the gastroenterology hub at Al-Diwaniyah Teaching Hospital in Al-Diwaniyah, Iraq, during the timeframe spanning from February 2023 to April 2024. A Fibro scan (Fibroscan 530 compact, Echosense, Paris, France) was employed, with a skilled gastroenterologist overseeing the assessment of liver fibrosis and steatosis. For every participant enrolled in the research, spirometry was conducted utilizing the Cardio Touch - 3000 (Korea). The subsequent parameters were recorded: Forced Vital Capacity (FVC) and Forced Expiratory Volume in the first second (FEV1).

**Results:** The patients were categorized as follows: 26 individuals exhibited Normal (Fibrosis score 0), representing 21.0 %; 44 individuals showed Mild (Fibrosis score 1), comprising 35.5 %; 23 individuals were classified as Moderate (Fibrosis score 2), accounting for 18.5 %, while 31 individuals fell into the Severe category (Fibrosis score 3), making up 25.0 %. The interplay between pulmonary function tests and non-alcoholic fatty liver disease (NAFLD) was assessed according to fibroscan outcomes, revealing that 90 patients demonstrated normal function, while 34 patients exhibited a restrictive pattern, with a notable correlation between the escalating severity of liver fibrosis and the prevalence of restrictive patterns among patients ($p = 0.003$).

**Conclusion:** A significant proportion of patients with NAFLD have in addition impaired pulmonary function mostly in the form of restrictive changes and these changes are more frequently seen with increasing degree of liver fibrosis as indicated by fibroscan technique.

***Keywords:*** *non-alcoholic fatty liver disease, pulmonary function*

## 1. INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) stands as a prevalent instigator of chronic liver ailments across the globe. NAFLD embodies a continuum of the condition defined by the accumulation of fat in the liver, with no discernible alternative reasons for this surplus fat deposition (e.g., excessive consumption of alcohol) (1). The NAFLD continuum spans from the relatively harmless state of non-alcoholic fatty liver (NAFL) to the more serious manifestation known as non-alcoholic steatohepatitis (NASH), which occupies the more critical end of the spectrum. NAFLD has the potential to evolve into fibrosis and cirrhosis (2, 3). In the case of NAFLD, hepatic steatosis exists devoid of any signs of inflammation, while in NASH, this fat accumulation is coupled with lobular inflammation and cell death, setting the stage for fibrosis and cirrhosis (4, 5). The incidence of liver disease (NAFLD) has surged dramatically on a global scale, boasting a worldwide prevalence of 25%. NAFLD is increasingly establishing itself as a common chronic liver disorder, especially among individuals grappling with central obesity, T2DM, dyslipidaemia, and metabolic syndrome (6).

Vibration-controlled transient elastography stands as the premier and most trusted technique among the noninvasive methods for gauging liver stiffness. The FibroScan device, renowned for its extensive research and validation, reigns as the most utilized and examined VCTE apparatus (7). The European Union and the Food and Drug Administration (FDA) granted approval for FibroScan's application in 2003 and 2013, respectively, for assessing liver stiffness. In an enlightening revelation by Yoneda in 2007, it was first unveiled that this innovative system could effectively ascertain the extent of fibrosis in NAFLD (8).

Pulmonary performance can be influenced by a medley of innate (age, sex, ethnicity) and external (air pollution, smoking, biomass) elements (9). Furthermore, it faces challenges in extrapulmonary ailments like cardiovascular disease (10) and chronic kidney disease (11). It has also been observed that diminished pulmonary performance correlates with nonalcoholic fatty liver disease (NAFLD) (12). Both forced vital capacity (FVC) and forced expiratory volume in one second (FEV1) tend to decline progressively alongside the advancement of hepatic steatosis (13, 14) or the severity of fibrosis (15), as evaluated through noninvasive diagnostic tools. These negative correlations between the severity of NAFLD and pulmonary function can be partially elucidated by various metabolic and inflammatory syndromes (16). Individuals grappling with metabolic syndrome and abdominal obesity tend to exhibit compromised pulmonary performance (16). Insulin resistance coupled with diabetes brings about a noteworthy decrease in FEV1 and FVC (17). Additionally, low-grade systemic inflammation bears a connection to weakened pulmonary function (18). There is scant Iraqi literature that delves into the issues surrounding pulmonary function in NAFLD patients. Hence, this study aims to evaluate the severity of non-alcoholic fatty liver disease (NAFLD) among a cohort of Iraqi patients using fibroscan and to draw parallels between the severity of the condition and pulmonary function.

## 2. PATIENTS AND METHODS

### *Patients*

The present investigation adopts a cross-sectional approach, encompassing 124 individuals exhibiting clinical, laboratory, and imaging indicators of NAFLD, all gathered from the gastroenterology center at Al-Diwaniyah teaching hospital in Al-Diwaniyah, Iraq, during the timeframe stretching from February 2023 to April 2024. This research received the green light from the Ethical Approval Committee at Kufa College of Medicine, affiliated with the University of Al Kufa, as well as from the medical research ethical committee of the Al-Diwaniyah department of health. Every participant provided their informed consent following a detailed discussion regarding their involvement in this inquiry. The patients selected were seeking routine medical evaluations. The criteria for inclusion were defined as follows: Adult individuals, regardless of gender, diagnosed with NAFLD were eligible for participation in the study. However, pregnant women, smokers, individuals who consume alcohol, and those with other underlying health conditions were excluded from this research endeavor.

### *Methods*

For every individual, we meticulously recorded anthropometric metrics [the waist circumference (WC) gauged at the precise midpoint between the rib cage and hip bones, to compute body mass index (BMI) by dividing weight in kilograms (kg) by the square of height (m) (19)], conducted biochemical blood tests, performed an abdominal ultrasound (US), and executed a fibroscan. The Fibroscan (Fibroscan 530 compact, Echosense, Paris, France) was utilized under the expert supervision of a skilled gastroenterologist, responsible for assessing liver fibrosis and steatosis. The threshold values for steatosis and fibrosis were adapted from Kamali et al.'s research (20) as illustrated in table 1.

**Table 1: grading of steatosis & fibrosis according to fibroscan measurements (20)**

| Steatosis score | Cut off value | Fibrostatic score | Cut off value |
|---|---|---|---|
| S0 (No) | < 237 dB/m | F0 (no) | Less than 5.5 |
| S1 (mild) | 237– 259 dB/m | F1 (mild fibrosis ) | 5.5 to 8.0 |
| S2 (moderate) | 259 – 291 dB/m | F2 (moderate fibrosis) | 8.1 to 10.0 |
| S3 (sever) | 291 – 400 dB/m | F3 (severe fibrosis) | 10.1 to 16.0 |

### *Pulmonary function*

For every individual participating in the investigation, spirometry was conducted utilizing the cardio Touch - 3000 (Korea), accompanied by a detailed elucidation of the process for each participant. The ensuing metrics were acquired: Forced Vital Capacity (FVC) and Forced Expiratory Volume in the first second (FEV1). The spirometry results are deemed typical when FVC is between (4.8 to 5.5) liters in males and (3.25 to 3.75) liters in females, whereas FEV1 ranges from (3.5 to 4.5) liters in males and (2.5 to 3.25) liters in females, with an FEV1/FVC ratio of ≥70% (21). In cases of a restrictive pulmonary pattern, the FVC diminishes and FEV1 also decreases proportionately, resulting in a normal or even heightened FEV1/FVC ratio (22, 23).

### *Statistical analysis*

The data were subjected to statistical analysis utilizing SPSS version 20.0. The data were ultimately presented as the mean value ±the standard deviation (SD). The relationship between parameters was evaluated using analysis of variance (ANOVA), followed by post-hoc testing to compare variables between each group of patients. In this investigation, a significance level of 0.05 or less was used as the threshold for determining statistical significance.

## 3. RESULTS

The overarching traits of the participants in this investigation are illustrated in table 2. Participants' ages spanned from 26 to 60 years, averaging a captivating 47.06 ±9.71 years. The cohort comprised 74 (59.7 %) males and 50 (40.3 %) females. The body mass index (BMI) fluctuated between 22.66 -34.5 kg/m2, with a delightful mean of 31.81 ±3.47 kg/m2. Waist circumference varied from 90 -127 cm, with a striking average of 107.73 ±10.89 cm. In terms of liver function, the AST level ranged from 15 -67 IU/L, boasting a mean of 47.81 ±12.34 IU/L, while the ALT level stretched from 10 -116, yielding a mean of 52.56 ±27.06 IU/L; the TSB level danced between 0.7 -4.7 mg/dl, revealing a mean of 2.20 ±1.15 mg/dl. Regarding the pulmonary function test, FEV1 spanned from 1.21 -4.4, with an average of 3.14 ±0.65. The mean FVC reached 3.96 ±0.90, with a range from 1.64 -5.3, while the mean FEV/FVC% stood at 79.82 ±7.66, encompassing a range between 58.59 -98.32.

The outcomes of the fibroscan are illustrated in figure 1 and table 3. The distribution of patients is as follows: 26 individuals exhibited Normal (Fibrosis score 0), representing 21.0%; 44 individuals displayed Mild (Fibrosis score 1), constituting 35.5%; 23 individuals were classified as Moderate (Fibrosis score 2), making up 18.5%, while 31 individuals were categorized as Severe (Fibrosis score 3), accounting for 25.0%.

The correlation between pulmonary function tests and non-alcoholic fatty liver disease (NAFLD) in accordance with fibroscan outcomes is depicted in table 4. According to pulmonary function results, we identified 90 patients with normal function and 34 patients demonstrating a restrictive pattern, revealing a significant relationship between the escalating severity of liver fibrosis and the prevalence of patients exhibiting a restrictive pattern ($p = 0.003$).

**Table 2: The general characteristics of patients enrolled in this study**

| Characteristic | | Result |
|---|---|---|
| Number of cases | n (%) | 124 (100.0 %) |
| Age (years) | Mean± SD | 47.06 ±9.71 |
| | Range | 26 -60 |
| Sex | Male, n (%) | 74 (59.7 %) |
| | Female, n (%) | 50 (40.3 %) |
| BMI (kg/m$^2$) | Mean± SD | 31.81 ±3.47 |
| | Range | 22.66 -34.5 |
| WC (cm) | Mean± SD | 107.73 ±10.89 |
| | Range | 90 -127 |
| AST (IU/L) | Mean± SD | 47.81 ±12.34 |
| | Range | 15 -67 |
| ALT (IU/L) | Mean± SD | 52.56 ±27.06 |
| | Range | 10 -116 |
| TSB (mg/dl) | Mean± SD | 2.20 ±1.15 |
| | Range | 0.7 -4.7 |
| FEV1 | Mean± SD | 3.14 ±0.65 |
| | Range | 1.21 -4.4 |
| FVC | Mean± SD | 3.96 ±0.90 |

| | | |
|---|---|---|
| | Range | 1.64 -5.3 |
| FEV/FVC% | Mean± SD | 79.82 ±7.66 |
| | Range | 58.59 -98.32 |

*n*: number of cases; SD: standard deviation; BMI: body mass index; WC: waist circumference; AST: aspartate transaminase; ALT: alanine transaminase; TSB: total serum bilirubin; FEV1: forced expiratory volume; FVC: forced vital capacity

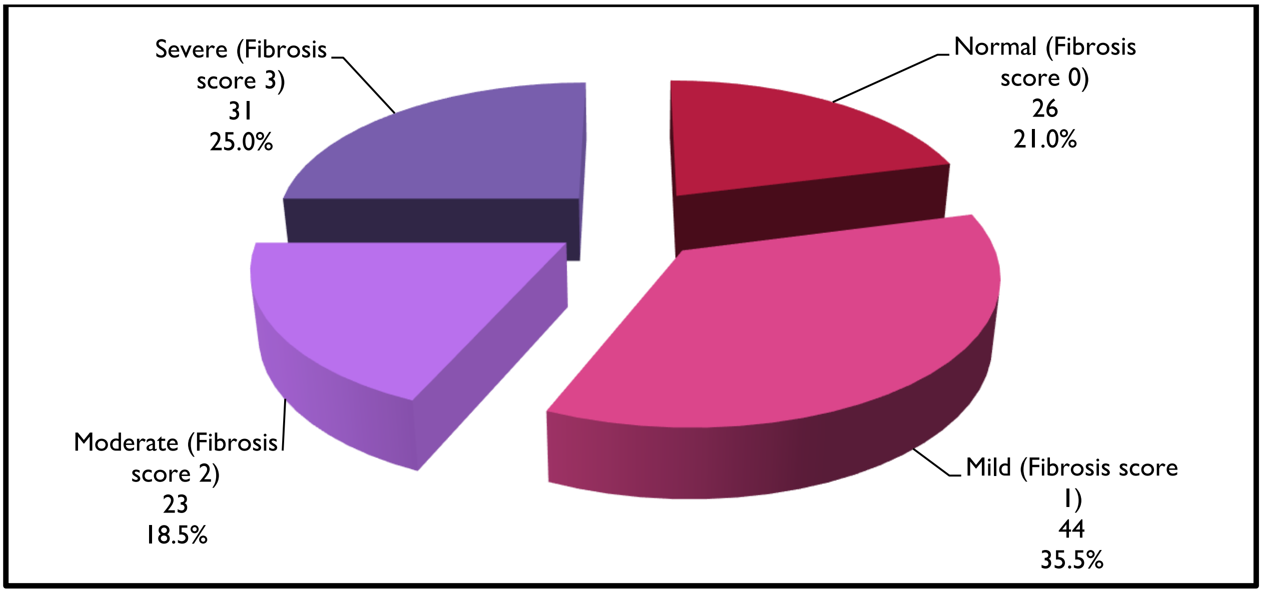


**Figure 1: Pie chart showing the frequency distribution of enrolled patients according to results of fibroscan**

**Table 3: The results of fibroscan**

| Fibrosis score | Number of cases | Mean ±SD | Range |
|---|---|---|---|
| Normal (Fibrosis score 0) | 26 | 4.21 ±0.63 | 3.2 -5 |
| Mild (Fibrosis score 1) | 44 | 6.91 ±0.67 | 5.8 -7.8 |
| Moderate (Fibrosis score 2) | 23 | 8.72 ±0.36 | 8.2 -9.2 |
| Severe (Fibrosis score 3) | 31 | 11.56 ±0.80 | 10.6 -12.8 |
| Total | 124 | 7.84 ±2.67 | 3.2 -12.8 |

SD: standard deviation

**Table 5: The association between results of fibroscan and results of pulmonary function test**

| Fibrosis score | Normal *n* = 90 | | Restrictive *n* = 34 | | *p* |
|---|---|---|---|---|---|
| | *n* | % | *n* | % | |
| Fibrosis score 0 | 24 | 26.7 | 2 | 5.9 | 0.003 C ** |
| Fibrosis score 1 | 35 | 38.9 | 9 | 26.5 | |
| Fibrosis score 2 | 15 | 16.7 | 8 | 23.5 | |
| Fibrosis score 3 | 16 | 17.8 | 15 | 44.1 | |

C: chi-square test; NS: not significant; **: significant at $p \leq 0.01$

## 4. DISCUSSION

In this investigation, fibroscan was employed to assess the liver condition in individuals battling NAFLD, thanks to its superior benefits when juxtaposed with traditional ultrasound evaluations. Despite its affordability and widespread accessibility, abdominal ultrasonography continues to reign as the most commonly utilized imaging technique for uncovering hepatic steatosis in patients suffering from MAFLD (24). Nevertheless, its effectiveness in identifying mild-to-moderate steatosis (<30%) is constrained, necessitating the use of more precise techniques – such as the controlled attenuation parameter derived from FibroScan – which should be advocated (25). Additionally, a key benefit of FibroScan over abdominal ultrasonography is its ability to provide insights into both steatosis and fibrosis concurrently. Ultimately, the data produced by FibroScan exhibit a high degree of concordance with liver biopsy results across various stages of fibrosis (26, 27).

It has been revealed that a reduction in FEV1 and FVC is independently linked to an approximately 15% heightened risk of developing NAFLD (28). A multitude of observational studies has delved into the relationship between NAFLD and lung function metrics (predominantly within the normal range) among community-based adult cohorts and extensive groups of Asian participants engaged in health screening initiatives (29-32). In fact, the meta-analysis conducted by Mantovani et al. uncovered notable disparities in FEV1, FVC, and the FEV1/FVC ratio between those afflicted with NAFLD and those who are not, confirming that the correlation between NAFLD and lung capacity remained statistically significant even after adjustments for variables such as age, sex, smoking history, measures of adiposity (BMI or waist circumference), dyslipidemia, hypertension, or diabetes (28).

In this investigation, concerning the average figures of FEV1, FVC, and FEV/FVC%, a decline was observed with the escalation of fibrosis, and a notable number of patients exhibited restrictive lung disease; furthermore, the intensity of fibrosis displayed a positive correlation with an increased prevalence of restrictive lung disease. Echoing our findings, Kim et al. (33) identified a significant link between NAFLD and deteriorating pulmonary function, particularly within the restrictive pattern, and their findings imply that the NAFLD index may serve as a predictive marker for restrictive lung ailments. Additionally, reinforcing our research conclusions, the data released by Shen et al. (34) indicated that diminished lung function, particularly FEV1, is intricately tied to the risk of NAFLD; while the underlying mechanisms remain elusive, FEV1 may be a crucial factor in evaluating NAFLD risk and could emerge as a promising target for NAFLD prevention.

Lee et al. (35) conducted a research investigation aimed at elucidating the relationship between the histological severity of non-alcoholic fatty liver disease (NAFLD) and pulmonary function, with the findings of their research delineated as follows: Among a cohort of 420 individuals possessing biopsy-confirmed NAFLD, the pre-/post-bronchodilator forced vital capacities (FVCs; expressed as a percentage of the predictive value) exhibited an inverse correlation with the histological severity of NAFLD. Specifically, the post-bronchodilator FVC (%) demonstrated a linear decrement concomitant with the exacerbation of histological severity of NAFLD. Notably, the fibrosis stage emerged as a significant independent predictor of reduced post-bronchodilator FVC (%); consequently, the authors inferred that pulmonary function declines with the progression of histological severity of NAFLD, particularly at the fibrosis stage. Indeed, these results bear substantial resemblance to the outcomes observed in our own study, notwithstanding the divergent methodologies employed in assessing the severity of liver fibrosis across the two investigations.

## 5. CONCLUSION

A significant proportion of patients with NAFLD have in addition impaired pulmonary function mostly in the form of restrictive changes and these changes are more frequently seen with increasing degree of liver fibrosis as indicated by fibroscan technique.

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