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Original Article

Clinical Spectrum of Nonalcoholic Fatty Liver Disease in Patients with Chronic Obstructive Pulmonary Disease

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Abstract

OBJECTIVE: The purpose of this study was to determine the prevalence of nonalcoholic fatty liver disease in a group of chronic obstructive pulmonary disease patients.

MATERIAL AND METHODS: This study comprised 48 stable chronic obstructive pulmonary disease patients who were diagnosed and categorized using the Global Initiative for Chronic Obstructive Lung Disease 2017 criteria. The prevalence of nonalcoholic fatty liver disease in chronic obstructive pulmonary disease patients was determined using noninvasive biomarkers and imaging methods. Steatosis was detected using magnetic resonance mDIXON-Quant sequence imaging, while fibrosis was detected using the acoustic radiation force impulse and FIB-4 index.

RESULTS: A total of 58.3% of the patients investigated had a fat level of 5%, and nearly a quarter of them had a fat content of 10% or more, and 45.8% of the patients studied had severe hepatic fibrosis. The Fibrosis-4 (FIB-4) index revealed advanced fibrosis in 18.75% of them. No statistically significant association was found between chronic obstructive pulmonary disease groups of studied patients and the presence of steatosis and fibrosis (≥F2) using acoustic radiation force impulse. The presence of fibrosis, however, was statistically significant linked with chronic obstructive pulmonary disease groups of examined patients using the FIB-4 index. γ-Glutamyl transferase and alkaline phosphatase levels were greater in Global Initiative for Chronic Obstructive Lung Disease 3/4 and C/D groups.

CONCLUSION: Nonalcoholic fatty liver disease is a common comorbidity in chronic obstructive pulmonary disease and should be included in the list of chronic obstructive pulmonary disease comorbidities.

KEYWORDS: NAFLD, NASH, COPD
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INTRODUCTION

Nonalcoholic fatty liver disease (NAFLD) is a broad term that includes several disorders ranging from disorders with any hepatic fat deposition to the more progressing steatosis with concomitant hepatitis, fibrosis, cirrhosis, and in rare, reported patient's hepatocellular carcinoma (HCC). Nonalcoholic fatty liver (NAFL) and nonalcoholic steatohepatitis (NASH) are the main components of NAFLD. Nonalcoholic fatty liver is recognized by liver steatosis affecting more than 5% of the parenchyma without any signs of hepatocyte damage. Nonalcoholic steatohepatitis, on the other hand, is characterized histologically as a necro inflammatory process in which the liver cells become damaged in the context of steatosis.[2] Nonalcoholic fatty liver disease is associated with metabolic complications, such as obesity, type 2 diabetes, hyperlipidemia, and hypertension,[3] and it may also be a precursor to metabolic syndrome.[4]

Metabolic syndrome is frequent in individuals with chronic obstructive pulmonary disease (COPD). Furthermore, there is mounting evidence that inflammatory visceral fat depots in COPD patients contribute significantly to COPD-related systemic inflammation and metabolic comorbidities.[5]

Despite the presence of a solid explanation endorsing the idea of higher NAFLD frequency in COPD patients, NAFLD has received less attention in these patients. In addition, the "spill-over" mechanism, which proposes that oxidative stress and systemic inflammation may contribute to the generation of hepatic reactive oxygen species and inflammation in COPD, is currently being debated.[6] As a result, the purpose of this study was to employ noninvasive tests to detect the prevalence of steatosis, NASH, and fibrosis in a group of COPD patients, as well as to assess the association between steatosis, NASH, and fibrosis and COPD severity.

MATERIAL AND METHODS

From 60 COPD patients, 10 were excluded due to inadequate images (inadequate breath hold during magnetic resonance mDIXON-Quant sequence imaging), and 2 female patients refused to participate, so a total of 48 male patients completed

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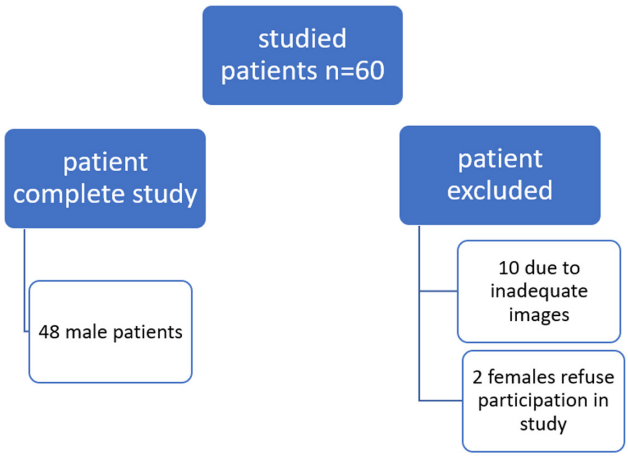

Figure 1. Flowchart of included patients.

all the examinations (Figure 1). So, this observational cross-sectional study comprised 48 stable COPD patients, diagnosed in accordance with the Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2017,[7] who attended the outpatient clinic of the chest medicine department at our hospital from November 2017 to December 2019. Patients with malignancy, viral hepatitis, autoimmune hepatitis, diabetes, obstructive sleep apnea, BMI more than 30, patients on steatogenic medicines, and COPD patients with respiratory failure were excluded. This study was carried out in accordance with our university institutional research board ethics committee's necessary ethical requirements (code number; MD.18.04.28).

Modified medical research council (m-MRC) dyspnea scale, COPD assessment test (CAT), and exacerbation history were assessed to classify the enrolled patients according to GOLD 2017[7] into: *COPD group A*, *COPD group B, COPD group C*, and *COPD group D.*

Air flow limitation severity of included patients was classified into: GOLD 1, GOLD 2, GOLD 3, and GOLD 4 according to forced expiratory volume in first second value.[7]

Evaluation of Hepatic Steatosis by Using Magnetic Resonance mDIXON-Quant Sequence Imaging

An experienced radiologist used a 1.5-T MR scanner (Ingenia, Philips, Healthcare, Best, Netherlands) to perform mDIXON-Quant MR imaging of the liver on all patients. In mDIXON-Quant, 3D-FFE with multiple acquired echoes was utilized to create water, fat, T2*, R2* pictures, as well as in-phase and opposed-phase images synthesized from the water-fat images. Following MRI collection, we calculated the hepatic fat percentage and R2* value from the 6 ROIs in the transverse sections via the right hepatic portal vein and below the second portal vein. The average fat content and R2* value of 6 ROIs, each with a 1.28-cm^2 region, were recorded. The radiologist who examined the MRI scans was unaware of the severity of COPD. A liver fat level of 50 mg/g (5% by wet weight) is indicative with hepatic steatosis.[8]

Evaluation of Hepatic Fibrosis

1. FIB-4:

It is determined by dividing the product of age (years) and aspartate aminotransferase (AST, U/L) by the product of platelet count and the square root of alanine aminotransferase (ALT, U/L).

Hepatic fibrosis was divided into 3 categories: nonsignificant fibrosis (FIB-4 <1.45) , advanced fibrosis (FIB-4 >3.25) and moderate degree of liver fibrosis (FIB-4 >1.45 and <3.25).[9]

2. Acoustic radiation force impulse:

The measurements of ARFI were performed after 8 hours of fasting using a curved array transducer of the ultrasound system (I-U22, Philips, Healthcare, Best, Netherlands). An area of interest in the liver parenchyma was chosen during real-time B-mode imaging to avoid major vessels, and an average amount of 12 measurements were collected in the right hepatic lobe utilizing an intercostal approach during relaxed breath-holding and discarding the highest and the lowest Measurements. After that, the mean and standard deviation of the remaining measurements were obtained. The radiologist who evaluated the ARFI was completely unaware of the severity of COPD. Significant fibrosis was defined as ≥F2.[10]

Assessment of Biological Markers

The enzymes (ALT and AST), γ-glutamyl transferase (GT), and alkaline phosphatase (ALP) were all tested.

Statistical Analysis

The Statistical Package for Social Sciences version 26.0 software (IBM Corp.; Armonk, NY, USA) was used to analyze the data. According to the findings of Shapiro–Wilk tests for the assumptions of normal distributions of data, continuous data were shown as mean (SD) or median (min-max). Frequencies and percentages were used to show categorical data. For continuous data, statistical significance was determined using Welch's t-test, t test, or Mann-Whitney U-test. (with respect to presence or absence of normal distribution of data). For categorical data, use Fisher's exact test or the chi square test (with respect to the minimal expected values in the contingencies tables). The significance threshold was chosen at $P = .05$. The threshold of significance was fixed at 0.05.

RESULTS

A total of 48 male patients completed all the examinations in this study (mean age was 56 years old). Most of studied patients had group C COPD (17 patients, 35.4%) while group D was reported in 14 patients (29.2%). In addition, 31 patients (64.6 %) of them had GOLD 3 and 4 in airflow limitation severity assessment Table 1.

By using magnetic resonance mDIXON-Quant sequence for evaluation of liver fat in studied patients, hepatic fat content varied from 1.25% to 27.8% and 41.7% of studied patients had fat content < 5%. Accordingly, the remaining 58.3% of studied patients had fat content ≥ 5% and about a quarter of them had fat content >10% Figure 2.

Through using ARFI, 45.8% of studied patients had significant hepatic fibrosis (F2, F3, and F4 stages was discovered in 29.2%, 12.5%, and 4.25% of them, respectively). Accordingly, the remaining 54.2% of studied patients had nonsignificant hepatic fibrosis (stage F0–F1). Also, nonsignificant fibrosis was found in 70.84% of studied patients by

Table 1. Characteristics of Studied Patient

	n = 48	%
Age/years (mean ± SD)	56 ± 9.14	
FEV1 (mean ± SD)	48.1 ± 15.7	
COPD group		
A	9	18.8%
B	8	16.7%
C	17	35.4%
D	14	29.2%
GOLD		
2	17	35.4%
3-4	31	64.6%
Serum cholesterol level (mean ± SD)	178.8 ± 37.4	
Serum triglyceride level (mean ± SD)	117.3 ± 32.2	
Serum bilirubin (mean ± SD)	1 ± 0.2	

COPD, chronic obstructive pulmonary disease; GOLD, Global Initiative for Chronic Obstructive Lung Disease.

using FIB-4 index (FIB-4 index <1.45) and advanced fibrosis has been detected in 18.75% of them (FIB-4 index >3.25). In addition, 10.4% of studied patients had moderate fibrosis (FIB-4 index 1.45-3.25) Table 2.

The results of this study demonstrated that the existence of fibrosis using ARFI and FIB-4 index was significantly associated with age of studied patients (*P* = .04, .001 respectively). However, no statistical significance association was found between the presence of steatosis and age (*P* = .3).

No statistical significance association was found between COPD groups of studied patients and the presence of steatosis and fibrosis (≥F2) using ARFI (*P* = .1). However, by using FIB-4 index, the presence of fibrosis was statistically significant associated with COPD groups of studied patients (*P* = .04). As regard serum levels of biological markers in studied patients, levels of γ-GT and ALP were higher in COPD groups C and D in comparison to groups A and B (*P* = 0.001). However, no statistical differences were found between COPD groups as regard ALT and AST (*P* = .7 and .1 respectively, Table 3).

Also, no statistically significant association has been identified between the severity of airflow limitation and the presence of steatosis and fibrosis (*P* = .5, .4, respectively). However, levels of γ-GT and ALP were higher in GOLD 3/4 (*P* = .04, .001, respectively, Table 4).

DISCUSSION

In this study, we evaluated the use of noninvasive tests to detect the prevalence of steatosis, NASH, and fibrosis in a group of COPD patients, as well as to assess the association between steatosis, NASH, and fibrosis and COPD severity. We found that steatosis by mDIXON-Quant MR and fibrosis by ARFI were seen in about half of studied patients. Using FIB4, fibrosis was found only in about one-third of studied patients (most of them had advanced fibrosis). The presence of fibrosis was significantly associated with age of studied patients.

In this study, the presence of steatosis and fibrosis utilizing ARFI not associated with COPD groups. However, the presence of fibrosis using the FIB-4 index was statistically significantly linked with COPD groups. In addition, the existence of steatosis and fibrosis is not related to the degree of airflow limitation. γ-glutamyl transferase and ALP were higher in advanced COPD groups and severe airflow limitations.

According to Viglino et al.[5] the prevalence of steatosis, NASH, and fibrosis in COPD patients was 41.4%, 36.9%, and 61.3%, respectively, and SteatoTest was strongly related with COPD GOLD stage.

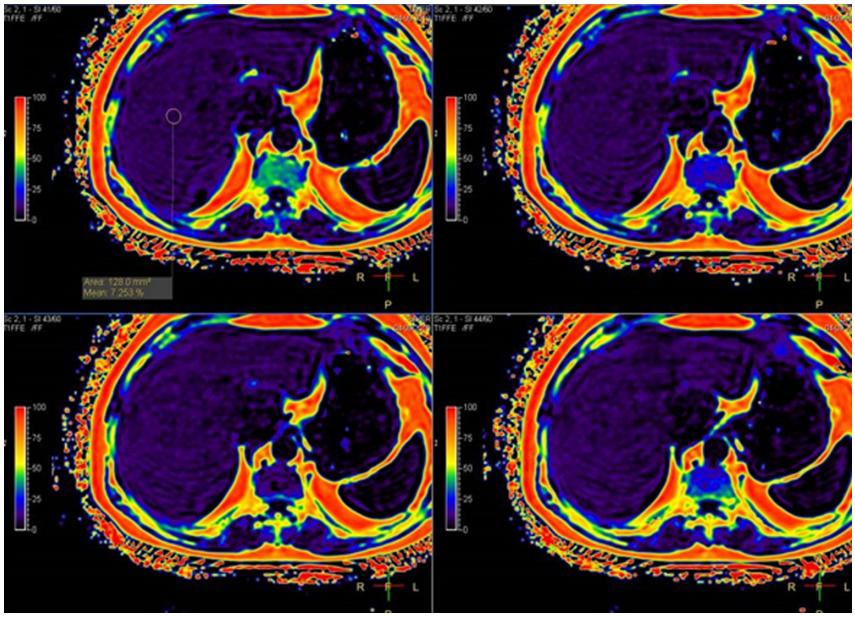

Figure 2. Magnetic resonance mDIXON-Quant sequence in 52-year-old COPD patient shows a 7.253% hepatic fat content. COPD, chronic obstructive pulmonary disease.

Table 2. Assessment of Degree of Hepatic Fibrosis Using ARFI and FIB-4 Index in Studied Patients

	***n* = 48**	**%**
ARFI median (minimum-maximum)	6.51 (0-19.9)	
FIB-4 index median (minimum-maximum)	1.75 (0.41-6.5)	
Grade of fibrosis (ARFI)		
F0–F1	26	54.2%
F2	14	29.2%
F3	6	12.5%
F4	2	4.2%
FIB-4 index <1.45	34	70.84%
FIB-4 index 1.45-3.25	5	10.41%
FIB-4 index >3.25	9	18.75%

ARFI, acoustic radiation force impulse.

In the study by Viglino et al.[5] many inflammatory markers were examined. Patients diagnosed with steatosis showed greater Tumor necrosis factor-∞ (TNF-∞) levels than those without liver illness, and those with a positive NASH Test had considerably higher leptin levels than those without hepatic impairment. However, blood levels of biological markers (γ-GT and ALP) were utilized in this study, and greater levels were identified in COPD groups C and D, as well as GOLD 3/4.

Divo et al[11] followed more than 1600 COPD patients for a median of about 4 years. A total of 2.5% of patients had hepatic cirrhosis and its presence was linked with higher deaths. Although, hepatic cirrhosis has been linked to alcohol and smoking, it could also be the result of steatosis progression which represent a part of the COPD-related metabolic comorbidities.

Table 3. The Association between COPD Severity and the Presence of NAFLD in Studied Patients

Parameter		**COPD A/B (17) *n* (%)**	**COPD C/D (31) *n* (%)**	**Significance**
Steatosis	No steatosis Steatosis	5 (29.4) 12 (70.6)	15 (48.4) 16 (51.6)	X^2= 2.21 *P* = .1*
ARFI	No fibrosis (26) Fibrosis (≥F2) (22)	12 (70.58) (29.42) 5	(45.17) 14 17 (54.83)	X^2 = 1.81 *P* = .17*
FIB-4	No fibrosis Fibrosis	15 (88.2) (11.8) 2	(61.3) 19 (38.7) 12	X^2 = 4.13 *P* = .04*
γ-GT	Mean ± SD	29.8 ± 10.2	44.1 ± 10.4	*t* = −3.4, *P* = .001**
ALP	Median (min-max)	201 (99-247)	260 (109-300)	*Z*= −3.7, 0.001***
ALT	Median (min-max)	24 (21-110)	26 (18-110)	*Z*= −0.26, 0.7***
AST	Median (min-max)	22 (18-55)	26 (16-92)	*Z* = β1.3, 0.1***

COPD, chronic obstructive pulmonary disease; NAFLD, nonalcoholic fatty liver disease; AST, aspartate aminotransferase; ALT, alanine aminotransferase; γ-GT, γ-glutamyl tranferase.
*Chi-square tests, **Independent t test, ***Mann–Whitney U-test.

Table 4. The Association between Airflow Limitation Severity and the Presence of NAFLD in Studied Patients

Parameter		**GOLD 2 (17) *n* (%)**	**GOLD 3/4 (31) *n* (%)**	**Significance**
Steatosis	No steatosis Steatosis	(47.06) 8 (52.94) 9	(38.7) 12 (61.3) 19	X^2 = 0.315 *P* = .5*
ARFI	No fibrosis (26) Fibrosis (≥F2) (22)	(47.06) 8 (52.94) 9	(58.06) 18 (41.94) 13	X^2 = 0.53 *P* = .4*
FIB-4	No fibrosis Fibrosis	(76.5) 13 (23.5) 4	(67.7) 21 10 (32.3)	X^2 = 0.45 *P* = .5*
γ-GT	Mean ± SD	32.5 ± 9.2	41.1 ± 8.5	*t* = −2.08, *P* = .04**
ALP	Median (min-max)	125 (99-300)	260 (143-300)	*Z*= −4.14, 0.001***
ALT	Median (min-max)	22 (18-110)	25 (18-110)	*Z* = −.08, 0.9***
AST	Median (min-max)	22 (16-92)	24 (18-92)	*Z* = −0.6, 0.5***

COPD, chronic obstructive pulmonary disease; NAFLD, nonalcoholic fatty liver disease; AST, aspartate aminotransferase; ALT, alanine aminotransferase; γ-GT, γ-glutamyl tranferase.
*Chi-square tests, **independent *t* test, ***Mann-Whitney U-test.

According to Moon et al.[12] patients in the NAFLD group were more likely to have COPD than those who are in the non-NAFLD group (8.5% vs 10.0%, respectively), and COPD patients were more likely to have NAFLD than non-COPD patients (30.0% vs. 33.7%, respectively, $P = .060$). The lack of a control group, however, restricted this study's ability to compare the prevalence rate among the general population and COPD patients.

Using the hepatic steatosis score, Hong et al[13] discovered NAFLD in 124 (14.6 %) of 850 COPD patients. They concluded that sarcopenia was linked to NAFLD in COPD patients.

Patients with COPD with elevated biomarkers of liver disease and fibrosis had an elevated risk of cardiovascular insults and mortality in a prospective cohort study done by Viglino et al.[14] although this had no effect on the occurrence of COPD exacerbations.

Most of the imaging techniques perform inadequately in the detection of NASH and may not be reliable for the recognition of NASH by themselves. However, considerable progress has been made in quantitative imaging-based biomarkers for detection and quantification of liver fibrosis in patients with NAFLD.[15] Palmeri et al[16] studied 172 patients with NAFLD and found that the diagnostic accuracy of ARFI for the detection of advanced fibrosis was 0.90.

The gold standard for quantification of triglyceride (liver fat) content in the liver is magnetic resonance spectroscopy.[15] Thus, when utilized in an proper clinical context MRS can produce an accurate diagnosis of NAFLD when hepatic steatosis is present as defined by a liver fat content of 5% or higher, and also help quantify the liver fat content away from the presence of hepatic steatosis.[17]

The small number of individuals examined limited our research, and we did not conduct a liver biopsy, which is a gold standard for verifying NAFLD diagnosis. However, it is an invasive and expensive technique that may result in mild side effects such as discomfort or more serious problems. As a result, many benefits of these noninvasive tests should be highlighted: they are less expensive, repeatable, and result in less interobserver variability, severe adverse consequences, rejection, and bias as compared to biopsy.

From our study, NAFLD is a common comorbidity in COPD (regardless of COPD group or airflow limitation severity) and should be included in the list of COPD comorbidities. Chronic obstructive pulmonary disease- associated chronic illnesses and systemic comorbidities pose a significant problem in the risk assessment and affect the integrated treatment plans. Liver disorders are part of these comorbidities that are vastly underestimated and probably underreported. Noninvasive tools could be helpful in detection of steatosis, NASH, and fibrosis in COPD patients.

Ethics Committee Approval: This study was approved by Ethics committee of Mansoura University, (Approval No: MD.18.4.28).

Informed Consent: Written informed consent was obtained from the patients who agreed to take part in the study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – S.W.S., W.E.; Design – S.W.S., M.A., W.E.; Supervision – M.A., A.A., A.M.Y.; Materials – A.A., A.M.Y., S.W.S.; Data Collection and/or Processing – S.W.S.; Analysis and/or Interpretation – W.E., M.A.; Literature Review – S.W.S.; Writing – S.W.S.; Critical Review – M.A.

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