The Prevalence of Liver Diseases among Chronic Obstructive Pulmonary Disease Patients: Statistics from Riyadh, Saudi Arabia

Majed Alghamdi [a], Bussma Ahmed Bugis [b], Alaa Bugis [c*], Nader Alharbi [d], Saleh Mohammed Alotaibi [e], Ziyad Hamdan Alanzi [e], Yazeed Yousef Almutairi [e], Rakan Abdullah Elamro [e], Fahad Abdulaziz Aloqayfi [e] and Omar Abdulaziz Alsalem [e]

[a] *National Guard Hospital, Riyadh, Saudi Arabia.*
[b] *Department of Public Health, College of Health Sciences, Saudi Electronic University, Dammam, Saudi Arabia.*
[c] *Department of Respiratory Therapy, College of Applied Medical Sciences, King Saud Bin Abdulaziz University for Health Sciences, Jeddah, Saudi Arabia.*
[d] *College of Science and Health Professions, King Saud bin Abdulaziz University for Health Sciences, King Abdullah International Medical Research Center, Riyadh, Saudi Arabia.*
[e] *Department of Respiratory Therapy, College of Applied Medical Sciences, King Saud Bin Abdulaziz University for Health Sciences, Riyadh, Saudi Arabia.*

Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

Article Information

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ABSTRACT

Background: Alpha-1 antitrypsin is an important protein produced by the liver, and deficiency in this protein will cause many liver diseases. A deficiency in this protein can cause congenital emphysema, characterized by damaged and stretched air sacs of the lungs. To our knowledge, limited studies have been performed on liver disease prevalence among chronic obstructive pulmonary disease (COPD) patients in Saudi Arabia.
Methods: This study was a secondary data analysis of existing clinical records and aimed at

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Corresponding author: E-mail: bugisa@ksau-hs.edu.sa;

determining the prevalence and association of liver diseases among COPD patients from 2016 to 2020. A total of 1579 clinical records were collected. In this study we analyzed one hundred fifty-five records.

Results: Senior patients who were aged 65 or older represented most patients (61.29%). In addition, 81% of the selected COPD patients were diagnosed with cirrhosis, while only one patient was diagnosed with fibrosis. Senior COPD patients aged 65 years or older were more likely to be diagnosed clinically with any type of liver disease (61.75%) than those from younger age groups.

Conclusions: Screening and expression tests for patients showing liver and lung diseases are the procedures to determine whether symptoms are due to alpha-1 antitrypsin deficiency. However, this is challenging in patients with COPD.

Keywords: Chronic obstructive pulmonary disease; emphysema; liver disease; liver failure; cirrhosis; AAT alpha-1 antitrypsin.

ABBREVIATIONS

COPD   :Chronic obstructive pulmonary disease
FEV1   : Forced expiratory volume one
AAT   : alpha-1-antitrypsin
AATD α1   : Antitrypsin deficiency
Pi   : Protease inhibitor

1. INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a disease that causes obstructed airflow from the lungs. In recent years, a dramatic increase in mortality and morbidity rates has been observed for COPD. Air pollution, long-term exposure to particulate matter, aggravating gases (particularly tobacco smoke), inherited conditions that influence the initial forced expiratory volume one in second (FEV1), and alpha-1-antitrypsin (AAT) deficiency are common COPD risk factors. COPD includes chronic bronchitis and emphysema, characterized by air trapping, progressive airflow limitations, and a chronic inflammatory response in the lung [1].

Currently, more than 11 million people are diagnosed with COPD, and it is estimated that this number will increase up to 24 million. In addition, COPD can result from a congenital deficiency in the protease inhibitor (Pi) of the proteolytic enzyme elastase known as alpha-1 antitrypsin, belonging to the class of serine protease inhibitors (serpins) [2]. Alpha-1-antitrypsin (AAT) is a glycoprotein (molecular weight 55,000) AAT (alpha-1 antitrypsin) is a glycoprotein (molecular weight 55,000) secreted primarily by hepatocytes but also by monocytes, neutrophils, and epithelial cells of the gut and lung. The AAT molecule includes galactose, mannose, N-acetyl glucosamine, and sialic acid. It is the most common serine protease inhibitor in human plasma, AAT normally acts to inhibit neutrophil elastase and other related proteases. In addition, AAT has immunomodulatory and anti-inflammatory properties. The carbohydrate content is approximately 12%. This glycoprotein forms 90% of the alpha-1 globulin in serum and is present at a concentration of 2 g/liter or more in healthy individuals. Very high serum levels of AAT may be found in conditions of stress, such as fibrinogen, an acute phase reactant protein [3].

Alpha 1-antitrypsin deficiency (AATD) is a genetic disorder that characterized by a low serum level of AAT. AATD is associated with a risk of developing liver disease and pulmonary emphysema, and other chronic respiratory disorders such as bronchiectasis and asthma. It is thought that individuals with AATD develop early-stage emphysema and chronic obstructive respiratory illness determining AAT concentration in plasma or serum and identifying allelic variants by genotyping or phenotyping are fundamental in the diagnosis of AATD. Initial evaluation measurement and annual follow-up of pulmonary function test PFT, including post-bronchodilator FEV1 and gas transfer inform on disease progression. The most sensitive measure of emphysema progression is lung densitometry but should not be use in the follow-up routine of patients in clinical practice. The only approved specific treatment for AATD is the exogenous administration of purified human serum-derived AAT. AAT augmentation therapy is not recommended in current smokers of any protein phenotype, or in patients with liver disease. Endoscopic bronchial valve placement and lung volume reduction are useful in selected patients, whereas the survival benefit of lung transplant is unclear [4]. It is critical to examine COPD patients to determine whether the disease is associated with AATD [1]. For patients showing

both liver and lung disease symptoms, screening and expression tests are the standard procedures to determine whether the symptoms are due to AATD. This is even more challenging in patients with COPD because COPD due to alpha-1 antitrypsin deficiency is difficult to distinguish from regular COPD because both conditions manifest similar symptoms [5].

More than 90% of the population has an ordinary allele called PI*M. The most common insufficient allelic variations are PI*S and PI*Z, which are responsible for the creation of anomalous proteins that polymerize inside hepatocytes; in this manner, the plasma levels of these proteins are extraordinarily decreased in individuals who are bearers of at least one, and particularly two, Z alleles. The protein Pi*ZZ is the most common genotype related to poor respiratory and hepatic function, and AAT deficiency is the primary hereditary factor leading to the development of respiratory emphysema in adults, as the deficiency in alpha-1 antitrypsin causes an imbalance of proteases activity, which causes tissue damage [6]. Alpha-1 antitrypsin can protect the tissues against neutrophil elastase and other serine proteases. These proteins are associated with emphysema and bronchial mischievous. It is responsible for approximately 90% of the protection against elastolytic behavior in the small airways caused by elastase released from neutrophils. If the neutrophils' elastases are not opposed, panacinar lung tissue is injured and increases the risk of developing COPD [7].

The deficit of anti-proteolytic and anti-inflammatory functions, together with pro-inflammatory effects of polymerized AAT contribute to increased inflammation and protein degradation resulting in an increased risk of developing emphysema and COPD, peculiarly in smokers. AATD is a subtle disease (5-15% of homozygous individuals have been identified) that is significantly underdiagnosed. Moreover, the diagnostic delay commonly exceeds 5 years, resulting in an average age of about 45 years at diagnosis. Despite the American Thoracic Society/European Respiratory Society recommendations state that all symptomatic adults with persistent airway obstruction should be screened, this guidance are not being followed. Potential reasons for that include the appropriate tests and missing knowledge about the disorder, and the low awareness of physicians about the disease. A screening test such as AAT serum level or other should be performed. Further diagnostic evaluations are based on the following techniques: isoelectric focusing (IEF) with or without immunoblotting, polymerase chain reaction (PCR) for persistent and clinically important mutations, and sequencing of the gene locus coding for AAT. Current laboratory methods like the use of serum separator cards, a lateral flow assay to detect the Z-protein, and a broader existing of next-generation sequencing are recent advances, likely to revise available algorithms [8].

Gene sequencing is important for AATD diagnosis, as it can be sued to identify uncommon alleles and obtain a precise diagnosis. AAT augmentation is a treatment for alpha-1 antitrypsin insufficiency at present and includes weekly intravenous infusions of cleansed, pooled human plasma with alpha-1 antitrypsin. However, doctors regularly disregard AAT treatment. mRNA treatment might target both the liver and lungs patients with AAT deficiency (pending current tests). In the RED AAT trial in 2016, 650 patients with AAT deficiency were enrolled and comparted to a control group of 10% of the patient population, with a minimum age of 18. People with a follow-up time of 8 years or a greater had a mean age of 61.6 (16.2) years, 76 (58.5%) were men, and 8 (6.2%) were present smokers. The mean age at diagnosis was 54.2 (11.2) years, and the age at symptom onset was 38.6 years (SD=12.2). The most widely recognized clinical manifestation was emphysema (83.1%, n=108), and the mean FEV1 % was 60.8% (SD=30.6%) [6].

Patients with AAT deficiency are inclined to have obstructive respiratory conditions and liver ailments such as hepatocellular carcinoma [9]. Babies with ZZ-related AAT deficiency can have cholestasis, leading to dark urine. Children can show unexplained increases in the levels of aminotransferases, hepatomegaly, and in server cases, cirrhosis or serious liver dysfunction in early adolescence. Such patients customarily show AAT deficiency in early examinations; however, in some unrecognized cases, AAT-deficient infants do not eat or grow well, manifesting as a failure to prosper. Emphysema related to AAT deficiency develops over a very long period of time, so it is not seen in youngsters. However, youngsters with AAT deficiency have an increased possibility of developing asthma [10]. Overall, the goal of this study is to determine the association of liver diseases with COPD to improve the wellbeing of these patients. This study aimed to describe the

prevalence and association of liver diseases among COPD patients from 2016 to 2020.

2. MATERIALS AND METHODS

This is a secondary data analysis of existing clinical records aiming to describe the prevalence and association of liver diseases among COPD patients from 2016 to 2020. The dataset was extracted from the clinical records of COPD patients who had liver diseases between 2016 and 2020 at a specific hospital in Riyadh. The data were collected from the ICUs, wards, and outpatient clinics of the hospital. The patient data related to this study are not publicly available, and the researchers have obtained the required approvals to have access to the COPD patient records for research purposes. Although using existing clinical records has supplemented and supported the purposes of this study, there is still a possibility of missing or incomplete clinical records, which may limit the significance of some statistics.

A total of 1579 clinical records of patients who had COPD at any time from 2016 to 2020 were collected. A data cleaning process was performed on the collected clinical records by removing duplicate patient clinical records. The data cleaning process led to a total of 985 clinical records of COPD patients. Furthermore, of the 985 records, patients who were not diagnosed with any type of liver disease were excluded from this study. The five liver disease types that were included in this study were liver inflammation, fibrosis, cirrhosis, liver cancer, and liver failure. As a result, 155 clinical records of COPD patients who had liver diseases any time between 2016 and 2020, were analyzed for this study (Fig. 1).

The data analysis was carried out by using an online calculator mathisfun.com to calculate prevalence statistics, and chi-square tests of significance. The resulting statistics were verified by another online calculator socscistatistics.com to ensure reliability. A frequency table was used to describe the available demographic characteristics of the included patients. Two-sided p-values were used for significance: $p<0.10$ and $p<0.05$.

3. RESULTS

A total of 155 COPD patient clinical records were selected for inclusion in this study. The selected patients were diagnosed clinically with both COPD and liver diseases at any time between 2016 and 2020. Table 1 shows the available demographic characteristics and BMI. Senior patients aged 65 or older represented most patients (61.29%). In addition, most (66.45%) selected patients were overweight.

In this study, five specific types of liver disease were identified among the data available in patient clinical records. Some of the selected patients were diagnosed with more than one type of liver disease, which led to a total of 183 diagnosed cases of liver diseases. Approximately 81% of selected COPD patients were diagnosed with cirrhosis, while only one patient was diagnosed with fibrosis. Fig. 2 shows the number of diagnosed liver disease cases among the selected COPD patients and prevalence percentages.

Statistics on the association of the COPD patients who were diagnosed with any type of liver disease from 2016 to 2020, including age, gender, and BMI, are presented in Table 2. There were 183 diagnosed liver disease cases among the 155 selected COPD patients. Male and female patients were diagnosed with liver disease in similar with no significant difference between the genders ($p = 0.754$).

The number of liver disease cases was associated with patient age ($p \leq 0.05$). Senior COPD patients aged 65 years or older were more likely to be clinically diagnosed with any type of liver disease (61.75%) than those from younger age groups. Furthermore, a weak association was identified between liver disease cases among COPD patients and patient BMI ($p \leq 0.10$). Diagnosed liver disease cases were more likely to occur in overweight COPD patients than in normal-weight or underweight COPD patients.

4. DISCUSSION

Most of our data were represented by senior patients who were aged 65 or older (61.29%). A total of 81 selected COPD patients were diagnosed with cirrhosis, while only one patient was diagnosed with fibrosis. The number of liver disease cases was associated with patient age ($p \leq 0.05$). Senior COPD patients aged 65 years or older were more likely to be clinically diagnosed with any type of liver disease (61.75%) than those from younger age groups. A similar result was documented by other researchers that age over 50 years is highly associated with the risk of developing liver disease.

Diagnosed liver disease cases were more likely to be identified in overweight COPD patients than in normal-weight or underweight COPD patients. We identified two important factors among the 155 patients: patient age and BMI. In a previous study that discussed alpha-1 antitrypsin deficiency as a risk factor for COPD, the authors found that among 1123 individuals, the prevalence of any liver disease was 10% (n = 155). Liver cirrhosis was found in 7% of the individuals (n = 116), and hepatocellular carcinoma was found in 2% (n = 29) [11]. In our study, some of the selected patients were diagnosed with more than one type of liver disease. which led to a total of 183 diagnosed cases of liver diseases, so there were 183 diagnosed liver disease cases among the 155 COPD selected patients. Other researchers found that 10.5% of adults were reported to develop liver cirrhosis [12].
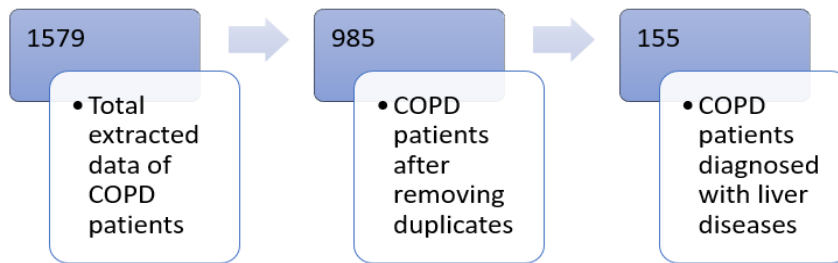

Fig. 1. Clinical records selection process

Table 1. Descriptive statistics of COPD patients with liver diseases

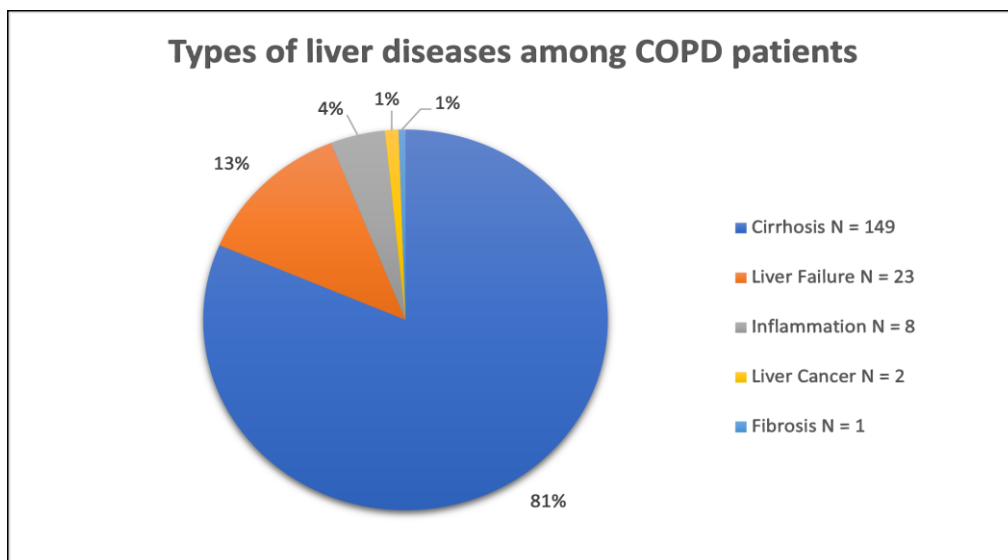| Characteristics	Categories	N = 155	Percentage
Age	≤ 18	1	0.65
	18-44	9	5.81
	45-64	50	32.26
	65 ≤	95	61.29
Gender	Male	79	50.97
	Female	76	49.03
BMI	< 18.5	12	7.74
	18.5-24.9	39	25.16
	> 30	103	66.45
	Not Reported	1	0.65

Fig. 2. Types of liver diseases among the selected COPD patients (N = 183)

Table 2. Association statistics of liver disease cases among COPD patients with age, gender, and BMI (N =183)

COPD patients with liver diseases		Type of liver disease[a]; N (%)					
		Inflammation	Fibrosis	Cirrhosis	Liver Cancer	Liver Failure	Total Cases
Age	≤ 18	0.00	0.00	0.00	0.00	1 (4.35)	1(0.55)
	18-44	2(25.00)	1 (100.00)	9 (6.04)	0.00	1 (4.35)	13 (7.10)
	45-64	3(37.50)	0.00	49 (32.89)	0.00	4 (17.39)	56 (30.60)
	65 ≤	3(37.50)	0.00	91 (61.07)	2 (100.00)	17 (73.91)	113 (61.75)
	Overall fit	$X^2 = 28.36, df = 12, p = 0.005**$					
Gender	Male	3(37.50)	0.00	76 (51.01)	1 (50.00)	13 (56.52)	93 (50.82)
	Female	5(62.50)	1 (100.00)	73 (48.99)	1 (50.00)	10 (43.48)	90 (49.18)
	Overall fit	$X^2 = 1.90, df = 4, p = 0.754$					
BMI	< 18.5	1(12.50)	1 (100.00)	11 (7.38)	0.00	2 (8.70)	15 (8.20)
	18.5-24.9	1(12.50)	0.00	38 (25.50)	2 (100.00)	3 (13.04)	44 (24.04)
	> 30	6(75.00)	0.00	99 (66.44)	0.00	18 (78.26)	123 (67.21)
	Not Reported	0.00	0.00	1 (0.67)	0.00	0.00	1 (0.55)
	Overall fit	$X^2 = 20.27, df = 12, p = 0.062*$					

[a] *Percentage of column total*
*The result is significant at *p ≤ 0.10; **p ≤ 0.05 level*

In our study, which included only adults, we found that approximately 81% of selected COPD patients were diagnosed with cirrhosis, while only one patient was diagnosed with fibrosis. According to previous studies, cirrhosis is the most prevalent type of chronic liver disease in Saudi Arabia [13]. The most common causes of cirrhosis are hepatitis B and C infections, which are one of the most common types of liver infection [14]. Alcohol abuse is a huge problem worldwide. Other results have been reported. A cohort study of 111 COPD patients found that 25%of patients had no liver disease and 75% had at least one type of liver disease [15]. In our study, we found that the gender distribution of patients with both COPD and liver diseases was nearly equal. Diagnosed liver disease cases were more likely to be identified in overweight COPD patients than in normal-weight or underweight COPD patients.

Most selected patients (66.45%) were overweight, and obesity is commonly associated with nonalcoholic fatty liver (NAFL), a benign condition characterized by hepatic lipid accumulation. However, NAFL can progress in some patients to nonalcoholic steatohepatitis (NASH) and then to severe liver lesions including extensive fibrosis, cirrhosis and hepatocellular carcinoma [16]. From a clinical point of view, obesity has increased morbidity and mortality when combined with NAFLD [17]. Senior COPD patients aged 65 years or older were more likely to be diagnosed clinically with any type of liver disease (61.75%) than younger patients. According to a Saudi study, the prevalence of COPD in Saudi Arabia is 4.2% due to lifestyle factors and immune system weakness. Furthermore, increasing age and smoking were the main risk factors for COPD [18]. According to the Saudi General Authority of Statistics, the population in the Kingdom of Saudi Arabia exceeds 35 million people, with a total of 35,013,414 people, and the number of males reached 20,231,425 (57.78% of the total population), and the number of females reached 14,781,989 people (42.2% of the total population) [19]. A similar result was documented by other researchers that age over 50 years was highly associated with the risk of developing liver disease. We found similar results for age and BMI, regarding gender distribution, they found that there were more male patients than female patients, which did not match our results.

5. CONCLUSION

In conclusion, among 985 COPD patients, 155 COPD patients had liver disease. We found that there was no relationship between COPD and liver disease. Our results match those of previous studies, in which there was also no relationship between COPD and liver disease [11,12,15]. Thus, the occurrence of the liver disease seems to be independent of COPD.

Patient records are frequently incomplete, which is a key drawback to using existing healthcare records. Researchers cannot assume that a lack of data equals a negative answer. For example, researchers cannot conclude that a lack of information concerning a symptom indicates that the patient did not have the symptom. Patients may have experienced the symptoms but failed to inform practitioners. Perhaps the practitioners did not precisely ask whether the symptom was present. Perhaps the patients mentioned the symptom, but the practitioners did not note it since it did not seem particularly important. Likewise, even if patients' records at one clinical site may not indicate that they were taking a certain drug, the patients may have been prescribed the drug by other physicians at other facilities. A primary study design may be required when data must be collected in a certain manner to be useful to researchers.

AVAILABILITY OF DATA AND MATERIALS

The dataset analyzed during the current study are available from the corresponding author on reasonable request.

CONSENT

It is not applicable.

ETHICAL APPROVAL

The study protocol has been reviewed and approved by the Institutional Review Board (IRB) at the King Abdullah International Medical Research Center (KAIMRC) as study # SP20/130/R. The procedures used in this study adhere to the tenets of the Declaration of Helsinki.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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