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ORIGINAL RESEARCH

Analysis of COPD: Distinguishing Characteristics and Management of Smoking vs Never Smoking Patients

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Background: Chronic obstructive pulmonary disease (COPD) is a significant public health issue characterized by gradually worsening airflow limitation. It is a leading cause of mortality and morbidity worldwide, yet research on COPD patients who have never smoked is limited. This study aims to document the demographic, symptomatic, and therapeutic characteristics of COPD patients receiving outpatient pulmonary care in Hungary, focusing on smoking history, and evaluate their distribution according to the GOLD A/B/E classification.

Methods: The study recorded demographic data, symptom severity, occurrence of severe and moderate exacerbations, treatment, comorbidities, quality of life, and COVID-19 vaccination status among COPD patients from November 2021 to January 2023. A total of 6974 patients were categorized into current smokers, former smokers, and never smokers.

Results: Patients had an average age of 67.2±8.9 years, with 48.2% male and 51.8% female. Of participants, 86.1% had a smoking history, while 13.9% had never smoked. COPD patients who had never smoked showed significantly better quality of life (CAT: 15.2 ±7.6 vs 15.8±6.9; p=0.006), oxygen saturation (SpO_2%: 96.7±2.3 vs 95.8±2.4; p<0.001), higher body mass index (BMI: 29.4±5.9 vs 27.1±6.3; p<0.001), and better lung function (FEV_1ref%: 67.9±20.7 vs 58.9±18.1; p<0.001) compared to smokers. However, non-smoking COPD patients had a higher frequency of comorbidities (3.5±2.2 vs 2.9±2.1; p<0.05). These differences may arise from complex genetic and environmental interactions.

Conclusion: COPD patients who have never smoked exhibited better quality of life, nutritional status, and lung function compared to smokers, indicating the need for tailored treatment approaches. Further long-term studies are essential to validate these differences in quality of life and lung function between smoking and non-smoking COPD patients.

Keywords: COPD, non-smoker, smoker, quality of life, exacerbation, comorbidities, COVID-19, healthcare utilization

Introduction

Chronic obstructive pulmonary disease (COPD) is a common chronic respiratory and systemic inflammatory condition characterized by progressive airflow limitation.[1,2] The disease develops slowly over time and is usually the result of a combination of multiple risk factors, such as active or passive smoking, occupational exposure to dust, smoke, or chemicals, indoor air pollution – especially from the use of biomass fuels - early life events such as low birth weight, preterm birth, asthma, and a rare genetic condition called alpha-1 antitrypsin deficiency, which can cause COPD at a young age.[3] The most common risk factor for COPD is smoking; however, it can also develop in non-smokers.[4] In

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high-income countries, over 70% of COPD cases are related to smoking,[5] while in low- and middle-income countries, smoking accounts for 30–40% of patients, with household air pollution being the primary risk factor.[6,7] Frequently experienced respiratory infections (including tuberculosis, COVID-19, influenza, pneumococcal infections etc).[8–11] play a significant role in the development of exacerbations and exacerbation of chronic inflammation.[12] The global prevalence of COPD was estimated to be over 300 million in 2023, with a prevalence of approximately 12.2%, but it is a vastly underdiagnosed condition.[13,14]

In recent years, the systemic nature of the disease with extra-pulmonary effects has become increasingly prominent, including the exacerbation of existing chronic comorbidities (such as cardiovascular and metabolic conditions) or the onset of complications directly related to COPD (such as chronic inflammation and hypoxemia). Additionally, sedentary lifestyles contribute to muscle loss, increased risk of osteoporosis, obesity or cachexia, higher rates of diabetes, and more frequent respiratory infections, leading to cor pulmonale, elevated lung cancer risk, and heightened levels of anxiety and depression, as well as exacerbation of cardiovascular diseases.[15,16] An increasing number of studies also demonstrate associations between nutritional status and certain characteristics of COPD,[2,17–20] but few studies describe in detail the clinical and demographic characteristics of COPD patients who have never smoked.

The historical perspective of chronic obstructive pulmonary disease research provides important insights into the complexity of the disease, particularly among never-smokers. In recent decades, research has increasingly focused on understanding COPD as experienced by smokers; however, it has become increasingly evident that the disease can develop not only as a consequence of smoking. Several potential mechanisms, such as genetic predispositions, environmental factors, and the role of respiratory infections, also significantly contribute to the development of COPD in never-smokers. Exploring the clinical characteristics of COPD patients who have never smoked is essential for making treatment strategies and public health policies more effective. Considering these aspects, the aim of this study is to provide a comprehensive overview of the demographic, symptomatic, and therapeutic characteristics of COPD patients, with particular attention to smoking history and the GOLD A/B/E classification. We present the following article in accordance with the STROBE reporting checklist.

Methods

Study Design and Population

A cross-sectional study was conducted involving COPD patients recruited from outpatient pulmonary clinics at a community hospital. Data collection followed routine clinical practice procedures. Patients were informed about the survey both verbally and in writing before providing consent. COVID-19 vaccination dates were acquired from the National eHealth Infrastructure (EESZT). The study was approved by the Hungarian National Institute of Pharmacy and Nutrition (document No: OGYÉI/57035-4/2021) and received a positive evaluation from the Hungarian National Research Ethics Committee (document No: TUKEB IV/7743-1/2021/EKU). The research permit was obtained on October 4, 2021. The study adhered to the principles of the Declaration of Helsinki (2013 revision). Anthropometric measurements, respiratory function tests, COVID infection history, and post-COVID symptoms were documented for each patient during their visit. The study aimed to document demographic data, symptom severity, exacerbation occurrences, treatment regimens, comorbidities, quality of life, and COVID-19 vaccination status among COPD patients between November 2021 and January 2023. A total of 6,974 patients were enrolled, categorized into current smokers, former smokers, and never smokers. Additional details regarding the study protocol and conduct are outlined in previously published articles.[21,22]

Objective of the Study

The primary objective of the study was to record and present the demographic, symptomatic, and therapeutic characteristics of COPD patients receiving outpatient pulmonary care (in specialized outpatient clinics and respiratory care units) at the time of their current presentation and retrospectively over a period of one year from their presentation. This data aims to support therapeutic decision-making for pulmonologists. Additionally, the study aims to compare these characteristics among current smokers, former smokers, and never smokers. Secondary objectives included assessing the

distribution of patients according to the GOLD A/B/E groups, recording data justifying group assignment (mMRC, CAT scores, number of moderate/severe exacerbations), smoking history, comorbidities, as well as assessing the rate of previous infection with the SARS-CoV-2 virus and the proportion of patients vaccinated against the virus, and surveying the frequency of known post-COVID conditions (residual symptoms). The principal investigator was Alpar Horvath, MD. Data recording was done using an electronic case report form (MRAgent eCRF) system developed by Medisol Development Ltd.

Inclusion Criteria

All eligible COPD patients aged 35 or older were included in the study after receiving information about the study through a patient information leaflet and providing written consent for the recording and processing of their data during routine medical examinations. To protect sensitive health data, we implemented strict data management and confidentiality principles to guarantee data security. The data were collected anonymously and used solely for research purposes. The COPD diagnosis and treatment of the patients were based on the current GOLD international and Hungarian COPD Guidelines.[23,24] Patients experiencing a current exacerbation or an exacerbation within 4 weeks prior to data recording, which could have influenced several recorded parameters, were excluded from the study. It is important to emphasize that the aim of the study was to explore the characteristics of stable COPD patients. While the exclusions may affect the representativeness of the sample, our goal was to provide a more accurate picture of the situation of stable COPD patients, which could assist in optimizing the management of the disease.

Randomization of sampling was ensured by all participating physicians. We also considered potential biases related to self-reported symptoms, striving to reflect patients' experiences as accurately as possible. During the data analysis, we took into account possible variations and biases. The ethical approval of the research provided further assurance that ethical standards were fully adhered to. Throughout the research process, we continuously monitored ethical considerations and took all necessary steps to safeguard patient rights. Details of the entry and exclusion criteria are provided in Table 1.

Measurements

Our questionnaire assessed various aspects, including smoking habits, with response options categorized into current heavy smokers, never smokers, or former smokers. Additionally, we inquired about comorbidities, medications used for COPD, and the frequency of exacerbations (both severe and moderate) experienced within the past year. Patients were also asked to report their healthcare utilization, including visits to general practitioners, emergency departments, pulmonary departments, and pulmonary outpatient services. Regarding COVID-19 vaccination history, patients were asked to indicate their vaccination status as either vaccinated (yes) or not vaccinated (no). For vaccinated patients, we further requested the exact date of all three vaccinations, which were cross-referenced in the EESZT database and

Table 1 Inclusion and Exclusion Criteria for the Study

Inclusion Criteria
- Diagnosed with COPD by a specialist for at least 1 year - Use of inhalation therapy - Receiving outpatient care - Age 35 and above - Individual with unrestricted capacity
Exclusion Criteria
- The patient does not meet any of the inclusion criteria - Inability to complete the questionnaire/survey section related to them - Non-consent for participation in data collection - Bronchial asthma without COPD diagnosis

Abbreviation: COPD, Chronic Obstructive Pulmonary Disease.

recorded in the Excel spreadsheet of the survey. Patients were queried about their history of SARS-CoV-2 infection, including the timing of infection and whether hospitalization was required for acute COVID-19 symptoms. Additionally, patients were asked whether they had received pulmonary outpatient care for post-COVID symptoms, with response options provided as yes or no.

Examination of Respiratory Function

All patients underwent respiratory function testing using an automated computerized spirometer. This testing assessed dynamic lung volume, including measurements such as the forced expiratory volume in the first second (FEV_1), the ratio of forced expiratory volume in the first second to forced vital capacity (FEV_1/FVC), and the inspiratory vital capacity (IVC). The Global Lung Function Initiative (GLI) defines normal spirometric values and categorizes patients into Global Initiative for Chronic Obstructive Lung Disease (GOLD) Assessment of COPD Exacerbations (ABE) stages based on various risk factors, including symptoms, quality of life assessments (CAT/mMRC), and exacerbation rates.[25]

In COPD patients, the FEV_1 value is less than 80% of the predicted value, and the FEV_1/FVC ratio is less than 0.70 (70%). To confirm the COPD diagnosis, we also considered symptoms such as dyspnea, cough, and sputum production. The diagnosis was established by a pulmonologist who evaluated both the results of the spirometric test and the clinical symptoms. The severity of the disease was classified according to the GOLD system, which categorizes patients into different groups based on the intensity of symptoms and the frequency of exacerbations.[23,26] The new ABE classification emphasizes the importance of managing exacerbations and considering patients' clinical characteristics to select the most effective therapy. The GOLD ABE criteria define the following three groups:

Group A: 0–1 moderate exacerbation in the previous year, mMRC 0–1, CAT < 10.

Group B: 0–1 moderate exacerbation in the previous year, but mMRC ≥ 2 and/or CAT ≥ 10.

Group E: Exacerbators with ≥2 moderate exacerbations in the previous year or ≥1 exacerbation that required hospitalization, regardless of symptom burden.

Quality of Life Examination

The COPD Assessment Test (CAT) is utilized to assess quality of life. Patients respond to eight questions and rate symptoms on a scale from 0 to 5, with 0 indicating no symptoms and 5 indicating severe symptoms. These questions evaluate subjective aspects such as cough, sputum production, hyperinflation, resilience, energy levels while climbing stairs, and the impact of the illness on activities such as leaving the house or interfering with sleep.[27]

Modified Medical Research Council Dyspnea Questionnaire (mMRC)

The mMRC questionnaire categorizes the severity of dyspnea and comprises five items, covering a wide range of breathlessness severity from none (grade 0) to complete inability to perform daily activities due to respiratory failure (grade 5). Patients rate their dyspnea on a scale of 0–5, with questions relevant to their daily activities and easily comprehensible. The score can be quickly calculated, providing a numerical representation of the patient's dyspnea severity.[28]

Definition of Exacerbation

COPD exacerbations were defined in accordance with the prevailing GOLD criteria. Moderate exacerbations necessitate treatment with antibiotics or systemic corticosteroids, while severe exacerbations mandate admission to the emergency department or hospital.[25,29]

Definition of COVID-19 Infection

A COVID-19 infection is defined as the presence of any subject who was asymptomatic or developed at least one of the following symptoms during the study period: cough, increased body temperature, fever, dyspnea, sudden loss of smell, loss of taste, or dysgeusia, and had detectable SARS-CoV-2 nucleic acid or antigen.[30]

Body Mass Index (BMI)

BMI (kg/m²) is calculated by dividing the weight in kilograms (kg) by the square of the height in meters (m²).[31]

Statistical Analysis

Upon completion of data collection and database closure, we conducted data cleaning procedures to eliminate duplicate entries and exclude patients with incomplete respiratory function tests from the analysis. Statistical analyses were performed by using R version 4.3.1. Means and standard deviations or medians and interquartile ranges were utilized to interpret and present continuous variables depending on their distribution, while frequencies and proportions were used for categorical data. Between-group comparisons of continuous variables were conducted by using ANOVA or Kruskal–Wallis tests. Fisher's exact test was used to examine differences in the frequencies of categorical variables. Age, gender and BMI-adjusted binomial logistic regression was used to compare the frequencies of comorbidities among the smokers, former smokers and non-smokers. All statistical analyses were two-sided, and significance was set at $p < 0.05$.

Results

Demographic and Clinical Characteristics of COPD Patients

A total of 6,974 COPD patients participated in the study, comprising 51.8% (n=3,610) females and 48.2% (n=3,363) males. On average, patients reported a smoking history of 15 cigarettes per day over 31 years (Table 2). Nearly half (46%) were active smokers, while 13.9% had never smoked (Table 3). The average FEV_1 (ref%) value for participating COPD patients was 60±18.9%, with two-thirds classified as GOLD B stage (Table 4). COPD is typically diagnosed at the moderate stage; thus, most clinical trials include very few or no patients in the mild stage. Among the patients, GOLD A was 11.6% for smokers, 12.8% for former smokers, and 15.8% for never smokers. The proportion of severe COPD

Table 2 Distribution of Smoking Status Among COPD Patients

	Active Smokers	Former Smokers	Never Smoked	Total
n	3208	2796	970	6974
%	46.0	40.1	13.9	100.00
Male (n, %)	1385 (43.2)	1587 (56.8)	391 (40.3)	3363 (48.2)
Female (n, %)	1823 (26.8)	1208 (43.2)	579 (59.7)	3610 (51.8)
Cigarettes/Day	15 (10–19)	15 (15–19)	–	15 (12–17)
Years of Smoking	40.4±10.6	30.9±12.8	–	31.0±17.1

Notes: Data are presented as number (n) and percentage (%) for categorical variables, and as mean ± standard deviation or median (interquartile range) for continuous variables.
Abbreviation: COPD, Chronic Obstructive Pulmonary Disease.

Table 3 Demographic and Clinical Profile of COPD Patients by Smoking Status

Variables	Active Smokers	Former Smokers	Never Smoked	p-Value
n (%)	3208 (46.0)	2796 (40.1)	970 (13.9)	
Age (years)	64.0±8.4	69.5±7.9	70.8±9.6	<0.0001
BMI (kg/m^2)	26.1 (22.8–30.7)	28.1 (24.8–32.1)	28.6 (25.3–32.9)	<0.0001
mMRC score	1.8±0.8	1.8±0.9	1.8±0.9	0.0928
CAT score	15.8±6.9	15.3±6.8	15.2±7.6	0.0063
FEV_1 (ref%)	58.9±18.1	58.5±18.5	67.9±20.7	<0.0001
FVC	80.1±19.3	78.9±18.6	81.1±19.7	0.0139
SpO_2 (%)	96 (95–97)	96 (95–97)	97 (95–98)	<0.0001

Notes: Data are presented as mean ± standard deviation or median (interquartile range) for continuous variables and as number (n) and percentage (%) for categorical variables. P-values represent statistical significance between groups.
Abbreviations: COPD, Chronic Obstructive Pulmonary Disease; BMI, Body Mass Index; mMRC, Modified Medical Research Council; CAT, COPD Assessment Test; FEV_1, Forced Expiratory Volume in one second; FVC, Forced Vital Capacity; SpO_2 (%), Pulse Oximetry measured O_2 saturation.

Table 4 Prevalence of Smoking Status Among COPD Patients Across GOLD a/B/E Categories

GOLD	Smokers n (%)	Former Smokers n (%)	Never Smoked n (%)
A	372 (11.6)	357 (12.8)	153 (15.8)
B	2234 (69.6)	1917 (68.6)	657 (67.7)
E	602 (18.8)	522 (18.7)	160 (16.5)

Notes: Data are presented as number (n) and percentage (%) for GOLD stages among smokers, former smokers, and never smoked groups.
Abbreviations: GOLD, Global Initiative for Obstructive Lung Disease; COPD, Chronic Obstructive Pulmonary Disease.

patients (GOLD E) was 18.8% among smokers, 18.7% among former smokers, and 16.5% among never smokers. A significant difference in proportions was observed when comparing actively smoking COPD patients to former smokers and non-smokers (p=0.0139; Table 4).

Comparison of Clinical Characteristics Between Non-Smoking and Smoking COPD Patients

Non-smoking COPD patients exhibited significantly better outcomes in terms of quality of life (CAT), respiratory function (FEV_1ref%, FVC), oxygen saturation (SpO_2%), and nutritional status (BMI) compared to actively smoking or former smoking counterparts (Table 3). However, they demonstrated a higher prevalence of comorbidities (3.5±2.2 vs 2.9 ±2.1; $p<0.05$). This difference can primarily be attributed to the significantly higher age of non-smoking patients compared to smokers (70.8±9.6 vs 64.0±8.4; $p<0.0001$). Additionally, genetic-environmental interactions among non-smoking patients may contribute to a significantly higher prevalence of allergies and asthma ($p<0.001$). Furthermore, significantly fewer occurrences of acute myocardial infarction, lung cancer, anxiety, sleep disorder, and depression were observed in non-smokers compared to smokers (Table 5).

Table 5 Comparison of Comorbidities Among Actively Smoking, Former Smoker, and Never Smoked COPD Patients

Co-Morbidities	Actively Smoking n (%)	Former Smoker n (%)	Never Smoked n (%)	p-Value
Hypertension	2111 (65.8)	2045 (73.1)	731 (75.4)	0.5912
GERD	938 (29.2)	878 (31.4)	325 (33.5)	0.0055
Ischemic heart disease	673 (21.0)	816 (29.2)	321 (33.1)	0.0533
Allergy	623 (19.4)	589 (21.1)	248 (25.6)	<0.0001
Sleep disorder	589 (18.4)	506 (18.1)	138 (14.2)	0.0019
Anxiety	577 (18.0)	394 (14.1)	122 (12.6)	0.0128
Diabetes mellitus	477 (14.9)	607 (21.7)	189 (19.5)	0.0299
Other comorbidities	463 (14.4)	504 (18.0)	158 (16.3)	0.0574
Osteoporosis	418 (13.0)	356 (12.7)	179 (18.5)	0.6456
Depression	408 (12.7)	268 (9.6)	80 (8.2)	0.0239
Asthma	381 (11.9)	435 (15.6)	236 (24.3)	<0.0001
Other cancer	234 (7.3)	278 (9.9)	79 (8.1)	0.0207
Heart failure	226 (7.0)	352 (12.6)	125 (12.9)	0.0138
Cerebrovascular event	201 (6.3)	229 (8.2)	66 (6.8)	0.1910
Prostate hyperplasia (males only)	190 (13.7)	423 (26.7)	93 (23.8)	<0.0001
Acute myocardial infarction	165 (5.1)	218 (7.8)	48 (4.9)	0.0196
Chronic atrial fibrillation	147 (4.6)	239 (8.5)	89 (9.2)	0.0848

(*Continued*)

Table 5 (Continued).

Co-Morbidities	Actively Smoking n (%)	Former Smoker n (%)	Never Smoked n (%)	p-Value
Pre-diabetes	112 (3.5)	183 (6.5)	42 (4.3)	0.0002
Bronchiectasis	111 (3.5)	118 (4.2)	40 (4.1)	0.2981
Glaucoma	96 (3.0)	136 (4.9)	43 (4.4)	0.1747
Lung cancer	93 (2.9)	162 (5.1)	24 (2.5)	<0.0001
Sinusitis	77 (2.4)	87 (3.1)	33 (3.4)	0.0623
Sleep apnea	43 (1.3)	40 (1.4)	26 (2.7)	0.0134

Notes: Data are presented as number (n) and percentage (%) for comorbidities among actively smoking, former smoker, and never smoked groups. P-values represent statistical significance across groups, corrected for age, sex and BMI.
Abbreviations: COPD, Chronic Obstructive Pulmonary Disease; GERD, Gastro-esophageal reflux disease.

The prevalence of allergic diseases was significantly different among non-smokers, former smokers, and smokers (25.6%, 21.1%, and 19.4%, respectively; p<0.0001). In cases of allergies, the etiological role of respiratory allergens such as pollen and dust differed significantly between the three groups (15.5%, 10.2%, and 9.4%, respectively; p<0.0001). Additionally, various medication allergies were prevalent among the examined COPD patients, with no significant difference observed between smoking and non-smoking patient groups in this regard (Table 6).

Impact of COVID-19 Vaccination and Infection Rates on Smokers and Non-Smokers

An analysis comparing the rates of first, second, and third COVID-19 vaccinations among both smokers and non-smokers showed a significant decrease (p <0.001). While 84.9% of patients received the first dose, only 63.6% received the third dose, falling short of the expected herd immunity threshold. Consequently, the virus circulated among patients, with 15.0% of patients contracting COVID-19 during the study period. Among non-smokers, this rate was 16.5%, compared to 16.5% among former smokers and 13.2% among active smokers, with the difference being significant (p <0.0001). Of those who contracted the infection, 21.3% required hospitalization, while 11.5% participated in post-COVID rehabilitation (Table 7).

The mMRC values of COPD patients, both smokers and non-smokers, were similar: 1.8±0.8, 1.8±0.9 and 1.8±0.9; p=0.0928. Additionally, no significant difference was found in the number of severe and moderate exacerbations over the past 12 months between smokers and non-smokers with COPD (Table 8).

Inhaler Medication Use Among Patients and Hospital Visits

Table 9 provides a detailed overview of the inhaler medications used by patients, revealing that those who currently smoke or have quit smoking significantly use short-acting beta-agonists (SABA) (69.6%, 71.4%, and 64.6%; p = 0.0004) compared to non-smokers. Additionally, smokers use a higher percentage of long-acting beta-agonist (LABA) + long-acting muscarinic antagonist (LAMA) (35.0% vs 27.5%), while non-smokers significantly use a higher percentage of

Table 6 Prevalence of Allergic Conditions Among COPD Patients with Different Smoking Histories

	Actively Smoking	Quit Smoking	Never Smoked	p-Value
Other allergies n (%)	35 (1.1)	35 (1.1)	7 (0.7)	0.2687
Food allergies	33 (1.0)	23 (0.80)	11 (1.1)	0.8743
Medication allergies	317 (9.9)	293 (10.5)	103 (10.6)	0.2631
Respiratory (pollen and/or dust) allergies	302 (9.4)	285 (10.2)	150 (15.5)	<0.0001
Total	623 (19.4)	589 (21.1)	248 (25.6)	<0.0001

Notes: Data are presented as number (n) and percentage (%) for various types of allergies among actively smoking, quit smoking, and never smoked groups. P-values represent statistical significance across groups.
Abbreviation: COPD, Chronic Obstructive Pulmonary Disease.

Table 7 Comparative Analysis of COVID-19 Vaccination and Infection Rates Among Different Smoking Groups

COVID-19 Status	Smoker	Former Smoker	Non-Smoker	Total	p-Value
Received first dose of SARS-CoV-2 vaccine	2605 (81.2)	2484 (88.8)	829 (85.5)	5918 (84.9)	0.0001
Received second dose of SARS-CoV-2 vaccine	2526 (78.7)	2435 (87.1)	818 (84.3)	5779 (82.9)	0.0005
Received third dose of SARS-CoV-2 vaccine	1841 (57.4)	1946 (69.6)	647 (66.7)	4434 (63.6)	0.0073
Tested positive for SARS-CoV-2 infection	424 (13.2)	460 (16.5)	160 (16.5)	1044 (15.0)	<0.0001
Required hospitalization	67 (15.8)	119 (25.9)	36 (22.5)	222 (21.3)	0.1224
Required post-COVID outpatient care	44 (10.4)	58 (12.6)	18 (11.2)	120 (11.5)	0.9257

Notes: Data are presented as number (n) and percentage (%) for COVID-19 vaccination and infection rates among different smoking groups. P-values represent statistical significance across groups.
Abbreviation: COVID-19, Coronavirus disease.

Table 8 Occurrence of Severe and Moderate Exacerbations in the Past Year by Smoking Status

n (%)	Actively Smoking	Former Smoker	Never Smoked	p-Value
Number of Severe Exacerbations in the Past Year				
>2	28 (0.9)	18 (0.6)	6 (0.6)	0.1824
2	55 (1.7)	47 (1.7)	13 (1.3)	
1	261 (8.1)	213 (7.6)	55 (5.7)	
None	2864 (89.3)	2518 (90.1)	896 (92.4)	
Number of Moderate Exacerbations in the Past Year				
>2	51 (1.6)	62 (2.2)	19 (2.0)	0.5362
2	279 (8.7)	235 (8.4)	84 (8.7)	
1	667 (20.8)	556 (19.9)	184 (19.0)	
None	2211 (68.9)	1943 (69.5)	683 (70.4)	

Notes: Data are presented as number (n) and percentage (%) for the occurrence of severe and moderate exacerbations in the past year among actively smoking, former smoker, and never smoked groups. P-values represent statistical significance across groups.

Table 9 Comparison of Inhalative Medication Use Among Smokers, Former Smokers, and Non-Smokers in Patients with COPD

	Smoker	Former Smoker	Non-Smoker	p-value
SABA n (%)	2432 (69.6)	1997 (71.4)	627 (64.6)	0.0004
LAMA	438 (13.7)	317 (11.3)	112 (11.5)	0.0005
LABA	136 (4.2)	126 (4.5)	81 (8.4)	
LABA and LAMA	1123 (35.0)	894 (32.0)	267 (27.5)	
ICS	14 (0.4)	14 (0.5)	15 (1.5)	
ICS and LABA	297 (9.3)	274 (9.8)	132 (13.6)	
ICS and LABA and LAMA	1141 (35.6)	1135 (40.6)	335 (34.5)	

Notes: Data are presented as number (n) and percentage (%) for inhalative medication use among smokers, former smokers, and non-smokers in patients with COPD. P-values represent statistical significance across groups. p <0.05 means the two indicators were significantly correlated.
Abbreviations: COPD, Chronic obstructive pulmonary disease; SABA, short-acting bronchodilators; LABA, long-acting bronchodilators; LAMA, long-acting muscarinic antagonist; ICS, inhaled corticosteroids.

inhaled corticosteroid (ICS) and LABA combination (13.6% vs 9.3%). There was no significant difference observed among the three examined groups in the ICS + LABA + LAMA combination (35.6% vs 34.5%).

Table 10 compares the utilization of healthcare services in the past 12 months among active smokers, former smokers, and never-smoker COPD patients. No significant differences were observed in emergency department visits among the

Table 10 Comparison of Healthcare Utilization Among Active Smokers, Former Smokers, and Never Smokers with COPD

	Active Smokers	Former Smokers	Never Smoked	p-Value
Primary Care Visits n (%)				
>2	1224 (38.2)	1083 (38.7)	405 (41.8)	0.0420
2	528 (16.5)	469 (16.8)	183 (18.9)	
1	601 (18.7)	493 (17.6)	165 (17.0)	
0	855 (26.7)	751 (26.9)	217 (22.4)	
Visits to Emergency Department n (%)				
>2	37 (1.2)	40 (1.4)	15 (1.5)	0.1129
2	72 (2.2)	79 (2.8)	18 (1.9)	
1	462 (14.4)	357 (12.8)	115 (11.9)	
0	2637 (82.2)	2320 (83.0)	822 (84.7)	
Pulmonary Outpatient Visits n (%)				
>2	368 (11.5)	450 (16.1)	99 (10.2)	0.0005
2	610 (19.0)	530 (19.0)	181 (18.7)	
1	1174 (36.6)	966 (34.5)	358 (36.9)	
0	1056 (32.9)	850 (30.4)	332 (34.2)	
Pulmonary Ward Visits n (%)				
>2	19 (0.6)	11 (0.4)	0 (0.0)	0.1799
2	25 (0.8)	18 (0.6)	5 (0.5)	
1	121 (3.8)	113 (4.0)	33 (3.4)	
0	3043 (94.9)	2654 (94.9)	932 (96.1)	
Medication change during visit				
Yes	436 (13.6)	315 (11.3)	83 (8.6)	<0.0001

Notes: Data are presented as number (n) and percentage (%) for healthcare utilization among active smokers, former smokers, and never smokers with COPD. P-values represent statistical significance across groups.
Abbreviation: COPD, Chronic obstructive pulmonary disease.

three COPD patient groups. However, pulmonary outpatient visits were significantly more frequent among smokers and former smokers compared to non-smokers (11.5%, 16.1% vs 10.2%; p=0.0005). Additionally, there was a significantly higher rate of medication change during physician visits among smokers and former smokers compared to non-smokers (13.6%, 11.3%, and 8.6% respectively; p<0.0001)

Discussion

This This study was designed to elucidate the characteristics of COPD across different patient populations, focusing particularly on non-smokers. Despite the widespread recognition of smoking as a primary COPD driver, its prevalence among non-smokers is notable, yet underreported in existing literature. Through an analysis of 6,974 outpatient COPD patients, we sought to delineate demographic and clinical distinctions between smokers and non-smokers.

Findings reveal that non-smokers with COPD generally experience superior quality of life, oxygen saturation levels, body mass index (BMI), and respiratory function compared to their smoking counterparts. Variances also emerged in COVID-19 vaccination rates, inhalative therapy use, and frequency of medical consultations across the two groups. Notably, non-smoking patients presented a greater prevalence of comorbid conditions. The higher prevalence of comorbidities in the non-smoking group may be associated with their significantly older age. Older age is often linked to an increased risk of cardiovascular diseases and other comorbidities, which may explain the observed higher prevalence. Additionally, older patients tend to visit their primary care physicians more frequently due to having more

health issues and requiring regular check-ups. Therefore, the finding that never smokers have significantly more visits to their primary care physician is likely related to their age and the presence of comorbidities.

While this investigation did not delve into the causative factors behind these discrepancies, they suggest the potential role of complex genetic and environmental interactions. Overall, our results underscore significant health differences between smoking and non-smoking COPD patients, highlighting the need for further longitudinal studies to explore these disparities.

In our investigation, we uncovered significant disparities between smokers and non-smokers, extending the understanding of COPD beyond its traditional association with smoking. Despite smoking being identified as the primary risk factor, a notable 13.9% of our study cohort were non-smokers, aligning with literature that suggests 10–47% of COPD patients may never smoke.[32–35] This demographic included a higher proportion of females (51.8%) compared to males (48.2%), notably more prevalent in the non-smoking group, challenging conventional risk profiles that prioritize male sex, older age, and lower socioeconomic status. This gender disparity underscores a global trend of increasing COPD prevalence and severity among women,[36–39] exacerbated by underdiagnosis and undertreatment, particularly in female smokers.[40,41] Studies suggest that COPD is often recognized late in women, partly due to delayed healthcare seeking or simply overlooking certain symptoms like fatigue or depression, which may indicate other issues.[42] These factors contribute to the variation in COPD prevalence across countries, currently ranging between 4.5% and 10.2%.[41,43] Women constitute approximately 25% of non-smoking COPD cases.[32]

Our analysis illuminated the intricate clinical profile of COPD patients who have never smoked, revealing a notably higher occurrence of concurrent conditions such as heart failure, ischemic heart disease, diabetes mellitus, gastroesophageal reflux, asthma, and allergies compared to those who smoke. Conversely, smoking patients exhibited a greater prevalence of depression, anxiety and sleep disorder, indicating subtle disparities in the disease's manifestation based on smoking status. These findings echo and expand upon existing research, including the study by Choi et al,[44] while noting inconsistencies across studies,[44–49] emphasizing the need for further research to elucidate these variations. Interestingly, our data did not reveal significant differences in the frequency of severe exacerbations across smoking histories, echoing the findings of Choi et al.[44] However, non-smoking COPD patients demonstrated better respiratory function, quality of life, and nutritional status, a divergence from studies reporting no significant respiratory function differences.[47,49,50] Additionally, the annual decline in FEV_1 is steeper and faster in smoking COPD patients than in non-smokers.[44,50] Our study also revealed non-smoking patients to be older, which varies from other studies suggesting they are younger.[47–50] The observations from our study also prompt a consideration of the broader implications of aging[51–57] on COPD outcomes, particularly in non-smoking populations. Aging mechanisms, including decreased resilience to environmental and biological stressors and heightened susceptibility to diseases driven by oxidative stress and inflammation, may underpin some of the clinical disparities observed.[51–60] This interplay between aging, oxidative stress, and systemic inflammation[61–69] could elucidate the variances in disease manifestation and progression among non-smoking COPD patients, underscoring the necessity for tailored approaches in management and research to account for these age-related factors.

Vaccination uptake, as the primary prevention measure for infectious diseases, is crucial.[70] Leading medical authorities such as the Centers for Disease Control and Prevention (CDC) and World Health Organization (WHO) recommend 100% vaccination coverage for COVID-19, especially for individuals with COPD[71] and other chronic conditions.[29,72] Vaccination uptake, particularly against COVID-19, was significantly lower across the board, falling short of herd immunity thresholds, with non-smokers and former smokers more likely to be vaccinated. Unfortunately, the available evidence indicates inadequate vaccination rates among COPD patients in our country and other European countries, not only for COVID-19 but also for seasonal influenza and pneumococcal infections.[21,22,73–75] The uptake of these vaccinations is paramount since acute exacerbations of COPD, which can lead to life-threatening complications and death, are often associated with tracheobronchial infections (70%). Bacterial infections account for 40–60% of infections, while respiratory viral infections (rhinoviruses, COVID-19, influenza viruses, etc.) represent 30%.[11,76] Studies have shown that vaccination reduces the number of hospitalizations and mortality due to acute exacerbations, while pneumococcal vaccination reduces the incidence of community-acquired pneumonia, even in patients with low respiratory reserves.[73,77,78] This underlines the critical role of vaccinations in managing COPD exacerbations and preventing

complications, supported by our observation of higher COVID-19 infection rates in non-smokers.[21,22,73–75] The role of aging in the increased susceptibility to COVID-19 related tissue injury and mortality is a critical area of investigation, highlighting the intricate relationship between the aging process and immune system function.[56] As individuals age, there is a natural decline in immune system responsiveness, known as immunosenescence, coupled with a chronic, low-grade inflammation termed inflammaging.[79–90] These age-related changes impair the body's ability to mount an effective immune response against infections, including SARS-CoV-2, the virus responsible for COVID-19.[91–94] Additionally, the aging process can exacerbate the severity of COVID-19 by increasing the risk of cytokine storm, a hyperinflammatory condition that can lead to acute respiratory distress syndrome, multiple organ failure, and ultimately, death in patients with COPD. Moreover, older adults with COPD often have a higher prevalence of underlying health conditions, such as cardiovascular disease, diabetes, and hypertension, which are known risk factors for severe COVID-19 outcomes.

Our comparative analysis revealed distinct patterns in inhaler medication utilization among smokers, former smokers, and non-smokers. Notably, current and former smokers were more likely to use short-acting beta-agonists (SABA) significantly more often than non-smokers (69.6% vs 64.6%; p=0.0004), a reflection of smoking-induced lung irritation and inflammation leading to symptoms like coughing and dyspnea. SABAs, which offer quick symptom relief, are therefore a common choice for those with a history of smoking. Additionally, a higher percentage of smokers utilize the combination of long-acting beta-agonists (LABA) and long-acting muscarinic antagonists (LAMA) than non-smokers (35.0% vs 27.5%), suggesting a preference for treatments targeting persistent airway obstruction. In contrast, non-smokers show a predisposition towards the combination of inhaled corticosteroids (ICS) and LABA (13.6% vs 9.3%), indicating a strategy focused on reducing inflammation rather than relieving obstruction. However this disparity can also be caused by a higher percentage of comorbid asthma in the non-smoking population, which (according to Global Initiative for Asthma and Global Initiative for Chronic Obstructive Lung Disease guidelines) should be treated according to asthma treatment guidelines, resulting in a high prevalence of ICS use.

This differentiation in medication preference underscores the nuanced impact of smoking on COPD pathophysiology and treatment response. While ICS and LABA combinations cater to the inflammatory aspect predominant in non-smokers, the LABA+LAMA combination addresses the obstructive symptoms more characteristic of those with a smoking history.[95,96] Despite these differences, the use of the ICS+LABA+LAMA triple therapy did not significantly vary among the groups, suggesting a convergence towards a more unified treatment strategy across different patient histories. This trend highlights the importance of individualizing COPD management to align with each patient's specific clinical profile and smoking status.

In our study, among COPD patients who had never smoked, significantly better quality of life (p=0.006), oxygen saturation (p<0.001), significantly better nutritional status (p<0.001), and significantly better lung function (p<0.001) were found compared to smokers. The significant differences in quality of life and lung function between smoking and non-smoking COPD patients may be largely attributed to the significantly better nutritional status observed in non-smoking patients. COPD is not only characterized by chronic, progressive loss of lung function and airway inflammation but also affects the entire body, with unintentional weight loss occurring in nearly a quarter to a third of cases, which can sometimes assume pathological proportions.[17,97] Lower body mass, decreased bone mass, and reduced muscle mass are particularly common in emphysema, driven by increased resting energy expenditure, systemic inflammation, and elevated resting respiratory work.[98] The development of skeletal muscle loss involves numerous other factors, including hypoxia, prolonged physical inactivity, and elevated blood levels of inflammatory markers (eg, C-reactive protein, interleukins, tumor necrosis factor-alpha, etc).[97,98] Muscle mass loss (sarcopenia) in COPD is very similar to that observed in other chronic conditions such as heart failure, renal failure, and cancer.[97,99]

Among the findings of our research, it is important to highlight that never-smoker COPD patients have significantly better lung function and a lower frequency of acute exacerbations of chronic obstructive pulmonary disease (AECOPD) compared to smokers. These characteristics, such as lung function and the frequency of exacerbations, are closely related to disease progression and the quality of life of patients. These differences can influence the assessment of other patient data, such as symptom severity, therapeutic responses, and the prevalence of comorbidities. Due to the more favorable clinical profile of non-smokers, researchers may easily misinterpret the effects of smoking, as the deterioration of lung function and frequent exacerbations dominate among smoking patients. It is essential to emphasize that smoking is not

only a risk factor for COPD but also negatively impacts the disease course. More frequent exacerbations further worsen lung function, creating a vicious cycle. The inflammation and lung tissue damage experienced during exacerbations contribute to further declines in lung function, and exacerbations negatively affect not only lung function but also patients' quality of life and overall health status. Patients with frequent exacerbations also have a higher rate of hospitalization, which exacerbates disease outcomes and treatment costs.

The favorable prognosis of non-smokers can be attributed to several factors, including:

Better lung function: never-smokers generally have better lung function, which reduces the risk of developing COPD and disease progression. The absence of smoking preserves the integrity of lung tissues and reduces inflammatory processes.

Lower inflammatory levels: smoking causes chronic inflammation in the airways, contributing to COPD progression. In non-smokers, this inflammatory response is lower, leading to more favorable outcomes.

Environmental and lifestyle factors: non-smokers typically have healthier lifestyle habits, such as being more physically active and following a balanced diet, which may contribute to their better health status. Genetic factors: some individuals are genetically predisposed to the harmful effects of smoking, while others are more susceptible to respiratory diseases. A more favorable genetic background may play a role in non-smokers. Treatment response: non-smoking COPD patients often respond better to treatments than smokers, improving treatment outcomes. These factors collectively contribute to the more favorable prognosis of never-smoker COPD patients, leading to a potentially better disease course for them.

The significant differences observed between smoking and non-smoking COPD patients in this study provide an important foundation for understanding the disease; however, a more detailed exploration of the underlying mechanisms would be essential for future research. A thorough examination of genetic, environmental, and lifestyle factors could contribute to explaining the observed differences, thereby strengthening the conclusions of the current research. Additionally, it is noted that non-smokers are generally older, which may affect the prevalence of comorbidities and overall health status. A more detailed discussion of this issue, particularly regarding the interactions between age and smoking status, would provide a more comprehensive understanding of our findings. Furthermore, there is a need to improve public health strategies regarding vaccination and the management of COPD. Therefore, to enhance public health strategies, the following steps are recommended:

Targeted vaccination programs: specific vaccination campaigns should be launched for COPD patients, emphasizing the importance of COVID-19 and pneumococcal pneumonia vaccinations. These programs can be implemented with informational materials and the involvement of healthcare professionals. Regular screening programs: to facilitate early detection of COPD, regular screening programs should be introduced, particularly for high-risk groups (eg, never smokers, older adults). These screenings can assist in identifying the disease in its early stages. Training programs for healthcare professionals: continuous training sessions should be organized for physicians and healthcare workers regarding the management of COPD, taking into account the specific needs of non-smoking patients. These training sessions should emphasize the multifactorial nature of the disease and the application of appropriate treatment strategies. Interdisciplinary approach: COPD management should be conducted by interdisciplinary teams that include pulmonologists, dietitians, physiotherapists, and psychologists. This approach can help meet the complex needs of patients and improve treatment outcomes. Research support: Further research is needed to assess the effectiveness of COPD treatment methods, with particular attention to non-smokers. The research findings can inform the development of treatment guidelines and public health policies. These recommendations could help improve the effectiveness of COPD management and vaccination programs, contributing to an enhanced quality of life for patients.

Limitations

Our study aimed to enrich the understanding of COPD's demographic and clinical nuances, particularly in non-smoking patients. It reaffirms smoking's role in COPD while highlighting significant clinical and therapeutic differences between smokers and non-smokers. However, it also underscores the importance of addressing the limitations inherent in cross-sectional designs and the need for prospective studies to further explore these critical distinctions.

An important limitation of the current study is that we did not inquire about the extent of passive smoking, various occupational inhalation exposures, or other provoking factors such as the level of air pollution. However, we have to highlight, that it is extremely difficult to reliable collect data on these topics, especially when we consider a long-term exposure, such as the one needed for developing COPD. In case of exacerbations, data on a short time-frame can be available (eg: meteorological report of the area), it not really feasible on the long-term. Additionally, we did not stratify patients according to the exact type of tobacco used (eg, conventional cigarettes, vaping or heated tobacco products - HTP), however both vapes and HTP-s had only been available in Hungary for less than 10 years, meaning that they might have only a minor effect on COPD demography. We also did not ask about the uptake of other important vaccinations, such as influenza and pneumococcal vaccines, as the research was conducted during the COVID-19 pandemic. Therefore, we only inquired about the uptake of COVID-19 vaccinations from the patients.

Other limitations of our study include its observational nature, reliance on self-reported symptoms, and lack of longitudinal follow-up, which prevents causal inference. This large-scale national study did not aim to analyze the effectiveness of various treatments, as such analysis would require following elderly, sometimes severely ill COPD patients. The sole objective of the research was to present COPD patients who have never smoked and to showcase their demographic and clinical characteristics.

Furthermore, the study did not aim to exclude asthmatics, provided they also had a COPD diagnosis (COPD-A group, according to GOLD 2023/2024 etiology classification). Our aim was to assess all COPD patients, including those with concomitant asthma. Since the COPD-A group accounts for about 15% of the Hungarian COPD population and these patients are generally harder to treat, it is crucial to collect data for optimizing care for this high-risk population. Patients with a pure asthma diagnosis were excluded in accordance with the study's exclusion criteria.

The cross-sectional design and potential biases, such as healthcare access and patient cooperation, may influence the results, emphasizing the need for comprehensive, longitudinal research to validate our findings and explore their implications for COPD management and prevention.

Conclusions

In conclusion, our study sheds light on the intricate distinctions between smoking and non-smoking COPD patients, emphasizing the broader spectrum of COPD beyond its conventional association with smoking. Our findings reveal that non-smokers experience a better quality of life and superior respiratory function, albeit with a greater prevalence of certain comorbidities. This underscores the complex interplay of genetic, environmental, and possibly age-related factors[87,100–106] influencing COPD manifestations. Additionally, our research highlights significant differences in inhaler medication usage patterns, reflecting the underlying pathophysiological differences attributed to smoking status. The nuanced understanding of these patterns underscores the importance of personalized COPD management strategies that consider the patient's smoking history and clinical profile. Furthermore, the study underlines the critical role of vaccination in preventing exacerbations and managing COPD, revealing suboptimal vaccination rates among the patient population. This points to a need for improved public health strategies to enhance vaccination coverage among COPD patients. Our findings advocate for a more nuanced understanding of COPD, challenging conventional perspectives and emphasizing the need for targeted interventions. Future studies are essential to deepen our understanding of COPD's complexities, paving the way for more effective, personalized treatment and management approaches.

Abbreviations

% pred, % of predicted value; AECOPD, acute exacerbations of chronic obstructive pulmonary disease; BMI, body mass index; CAT, COPD Assessment Test; CI, Confidence Interval; COPD, chronic obstructive pulmonary disease; COVID-19, Coronavirus disease 2019; EESZT, National eHealth Infrastructure; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; GLI, Global Lung Function Initiative; GOLD, Global Initiative for Chronic Obstructive Lung Disease; ICS, inhaled corticosteroids; LABA, long-acting bronchodilators; LAMA, long-acting muscarinic antagonist; MI, acute myocardial infarction mMRC, modified MRC questionnaire; OR, odds ratio; SABA, short-acting beta agonist; SARS, Severe acute respiratory syndrome; SARS-CoV-2, Severe Acute Respiratory Syndrome Coronavirus 2; WHO, World Health Organization.

Data Sharing Statement

The data that support the findings of this study are available on reasonable request from the corresponding author.

Ethical Statement

The authors are accountable for all aspects of the work, ensuring that any questions related to the accuracy or integrity of the study are appropriately investigated and resolved. The study protocol was approved by the Hungarian National Institute of Pharmacy and Nutrition (document number OGYÉI/57035-4/2021) and received a positive evaluation from the Hungarian National Research Ethics Committee (document number TUKEB IV/7743-1/2021/EKU). The research permit was obtained on October 4, 2021, and the study adhered to the principles of the Declaration of Helsinki (2013 revision). Patients received both oral and written information prior to the assessment and provided informed consent.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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