



## COVID-19 vaccination coverage in patients with chronic obstructive pulmonary disease – A cross-sectional study in Hungary



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### ARTICLE INFO

#### Article history:

Received 29 September 2022

Received in revised form 2 November 2022

Accepted 13 November 2022

Available online 18 November 2022

#### Keywords:

Chronic obstructive pulmonary disease (COPD)

Vaccination

COVID-19

SARS coronavirus

CAT

mMRC

### ABSTRACT

**Introduction:** Coronavirus infection is a particular risk for patients with chronic obstructive pulmonary disease (COPD), because they are much more likely to become severely ill due to oxygen supply problems. Primary prevention, including COVID-19 vaccination is of paramount importance in this disease group. The aim of our study was to assess COVID-19 vaccination coverage in COPD patients during the first vaccination campaign of the COVID-19 pandemic.

**Methods:** A cross-sectional observational study (CHANCE) has been conducted in COPD patients in the eastern, western and central regions of Hungary from 15th November 2021. The anthropometric, respiratory function test results and vaccination status of 1,511 randomly selected patients were recorded who were aged 35 years and older.

**Results:** The median age was 67 (61–72) years, for men: 67 (62–73) and for women: 66 (60–72) years, with 47.98 % men and 52.02 % women in our sample. The prevalence of vaccination coverage for the first COVID-19 vaccine dose was 88.62 %, whereas 86.57 % of the patients received the second vaccine dose. When unvaccinated (n = 172) and double vaccinated (n = 1308) patients were compared, the difference was significant both in quality of life (CAT: 17 (12–23) vs 14 (10–19); p < 0.001) and severity of dyspnea (mMRC: 2 (2–2) vs 2 (1–2); p = 0.048). The COVID-19 infection rate between double vaccinated and unvaccinated patients was 1.61 % vs 22.67 %; p < 0.001 six months after vaccination. The difference between unvaccinated and vaccinated patients was significant (8.14 % vs 0.08 %; p < 0.001) among those with acute COVID-19 infection hospitalized. In terms of post-COVID symptoms, single or double vaccinated patients had significantly fewer outpatient hospital admissions than unvaccinated patients (7.56 vs 0 %; p < 0.001).

**Conclusion:** The COVID-19 vaccination coverage was satisfactory in our sample. The uptake of COVID-19 vaccines by patients with COPD is of utmost importance because they are much more likely to develop severe complications.

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**Abbreviations:** 6MWD, six-minute walking distance; ACE2, angiotensin-converting enzyme 2; CAT, COPD Assessment Test; COPD, chronic obstructive pulmonary disease; COVID-19, Coronavirus disease 2019; CRP, C-reactive protein; FEV<sub>1</sub>, forced expiratory volume in 1 s; FVC, forced vital capacity; GLI, Global Lung Function Initiative; GOLD, Global Initiative for Chronic Obstructive Lung Disease; IFN- $\gamma$ , interferon gamma; IL, interleukin; IRB, Institutional Review Board; MERS, Middle East Respiratory Syndrome; mMRC, modified MRC questionnaire; RSV, Respiratory Syncytial Virus; SARS, Severe acute respiratory syndrome; SARS-CoV-2, Severe Acute Respiratory Syndrome Coronavirus 2; TNF- $\alpha$ , tumor necrosis factor alpha; TUKEB, National Scientific and Ethical Committee.

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<https://doi.org/10.1016/j.vaccine.2022.11.020>

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## 1. Introduction

The Coronavirus disease 2019 (COVID-19) is an acute respiratory viral infection caused by a novel and highly pathogenic human coronavirus namely Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) [1]. In most cases, it causes mild to moderate respiratory symptoms, and those who got infected recover without specific treatment. However, the elderly and people with diseases such as chronic obstructive pulmonary disease (COPD) are at much higher risk of developing serious complications [2]. COPD as an underlying disease, is associated with a reduced respiratory reserve, and therefore a further deterioration in respiratory capacity due to possible pneumonia can be particularly dangerous in this patient group [3]. Corticosteroids taken for the disease may predispose to increased susceptibility to infections, and smoking, the main causative factor, increases the risk of developing complications of coronavirus [1–3]. On the basis of this, there are several aspects to consider protecting COPD patients against the coronavirus epidemic, but the first and most important is the uptake of COVID-19 vaccine as part of primary prevention.

It is known that the most common comorbidities in people hospitalized are chronic heart, lung and kidney diseases, diabetes, asthma, COPD and dementia [4]. Not only does the vaccine protect against acute infection, but several studies have shown that against SARS-CoV-2 it reduces the chance of developing long-COVID symptoms with just one or two doses of the vaccine, with symptoms including fatigue, headache, weakness, persistent muscle pain, hair loss, dizziness, shortness of breath, loss of smell, lung scarring, and sexual dysfunction [5,6]. The vaccine also protects against the development of respiratory failure, which can be fatal in COPD [7]. Protection can be achieved by infection or vaccination, mediated and controlled by two main branches of the immune system: humoral immunity mediated by antibodies, and cellular immunity. Antibodies inhibit the development of infection by binding the virus, and in the case of SARS-CoV-2 with severe acute respiratory syndrome, antibodies can prevent the development of infection if present in high enough concentrations in the blood [8].

The frequency of acute COPD exacerbations is associated with disease progression, impaired lung function, and mortality among COPD patients [9]. Exacerbations are mainly caused by viral infections, such as rhinovirus, influenza virus, and RSV (Respiratory Syncytial Virus) [10]. The SARS-CoV-2 virus enters the cell by binding to the angiotensin-converting enzyme 2 (ACE2) receptor expressed on type II epithelial cells, mainly the air sacs of the lung, which is highly expressed in the lung epithelium of COPD patients [11]. In addition, the COVID-19 coronavirus epidemic poses a greater risk to people with chronic lung disease who have reduced immune defenses due to the disease or immunosuppressive medication they have received [12]. Therefore, the aim of our study was to assess the COVID-19 vaccination coverage among COPD patients during the COVID-19 pandemic in Hungary and to identify patients who received COVID-19 vaccines and to compare the quality of life, respiratory symptoms, number of exacerbations, respiratory function and the presence of post-COVID residual symptoms (post-COVID syndrome) during the six months following vaccination in unvaccinated and vaccinated people.

## 2. Methods

### 2.1. Study design and population

A cross-sectional observational study has been conducted in COPD patients in eastern, western and central regions of Hungary from 15th November 2021. Patients are enrolled from outpatients pulmonology clinics, and their data is being collected according to

routine clinical practice. The study is conducted in three main stages with the inclusion of approximately 60 study sites in November 2021, and May and November of 2022. An interim analysis was pre-planned after the end of the first stage, the results of which are presented below. Altogether, 1,511 patients were included who received oral and written information about the survey before signing the consent form. The study was approved by the Hungarian National Institute of Pharmacy and Nutrition (docket No: IV/7743–1/2021/EKU) based on the positive assessment by the National Scientific and Research Ethics Committee of Hungary (registration number CHMED\_2021/01), and the research complies with the Declaration of Helsinki. Inclusion criteria for the study were age over 35 years, known COPD patient (post-bronchodilator FEV<sub>1</sub>/FVC < 70 %) [13], diagnosed by a specialist at least one year before enrolment, and receiving inhaled therapy. Exclusion criteria were the following: the patient did not meet any of the expectations listed above, or if the patient was not able to complete the part of the questionnaire(s) that applied to him/her.

### 2.2. Measurements

Patients attending the clinic were recorded for anthropometric, respiratory function test results and COVID-19 vaccination status, previous history of COVID infection and post-Covid symptoms. Patients were asked whether they had received their first or second dose of COVID-19 vaccine, and they were asked to answer yes or no. They were asked exactly when they received the vaccine(s) if the answer was yes. Gender was bivariate: male or female. Our questionnaire asked about smoking habits: currently a smoker, never smoked, or had quit smoking with response options. We asked about chronic diseases, comorbidities, medications used for COPD, number of severe and moderate exacerbations in the six months following vaccination(s). We also asked about the number of visits to health care facilities during the survey period, i.e. general practitioner, emergency department, pulmonary department and pulmonary outpatient services. We asked if the patient had had a SARS-CoV-2 infection in the six months following vaccination(s) yes/no, if yes, exactly when the infection occurred, and if the patient had required hospitalisation during acute COVID-19 infection the answer choice was yes/no. We asked whether he/she required outpatient pulmonary care for post-COVID symptoms, for which the answer choice was also yes/no.

### 2.3. Examination of respiratory function

All patients underwent a baseline respiratory function test by automated computerized spirometer to assess respiratory function. Dynamic lung volumes were defined as the amount of air expelled in the first second [(FEV<sub>1</sub> (ref%)), vital capacity [(FVC (ref%)), the degree of airway obstruction (FEV<sub>1</sub>/FVC), inspiratory capacity in liters and percentage [(IVC (L), IVC (ref%)), with GLI-defined (Global Lung Function Initiative) normal spirometry (z-score) [14]. Patients were classified in GOLD A-D stages according to current GOLD guidelines [13]. The symptom severity, measured with COPD Assessment test (CAT) score and number of exacerbations in the past 12 months [13,15].

### 2.4. Quality of life examination

The COPD Assessment test was used as a quality-of-life measurement. The patients responded to eight questions, scoring the symptoms from 0 to 5, where 0 indicates healthy condition, and 5 indicates severe symptoms. Cough, the amount of sputum, hyperinflation, exercise capacity when climbing stairs, and the level of energy were evaluated subjectively, as well as whether

the patients dared to leave home, or whether their illness affected their sleep [16].

### 3. Modified MRC dyspnea questionnaire (mMRC - modified medical research 2.1. Council questionnaire)

The mMRC dyspnea scale stratifies the severity of dyspnea and consists of five statements; it almost completely covers the whole spectrum of respiratory distress, from having no problems (grade 0) to completing respiratory failure (grade 5). Patients were scored between 0 and 5 points, all questions were related to everyday activities and were easy to understand for patients. The score could be calculated in a few seconds, with the score being the number that best fitted the patient condition [17].

#### 3.1. Definition of exacerbation

COPD exacerbation was defined in accordance with the current GOLD definition. An acute worsening of respiratory symptoms, requiring change in treatment. In the case of moderate exacerbation, the prescription of an antibiotic or systemic corticosteroid was required, whereas in severe exacerbation the patient had to have required an emergency department visit, or hospitalization [13,15].

#### 3.2. Definition of COVID-19 infection

Any person who had at least one of the following symptoms during the study period: cough, rise in temperature, fever, dyspnoea, sudden onset of anosmia, ageusia or dysgeusia and SARS-CoV-2 nucleic acid or antigen was detectable in the clinical specimen.

#### 3.3. Body mass index (BMI)

Body mass index (BMI) was calculated by dividing the body weight in kilograms by the square of body height in meters (kg/m<sup>2</sup>).

#### 3.4. Statistical analysis

All statistical analyses were conducted in SPSS 28.0.0. Since most of the continuous data did not follow the normal distribution (verified by Saphiro-Wilk test), non-parametric statistical methods were used. Continuous variables were interpreted and represented by medians and interquartile ranges. Categorical data were presented with case numbers and proportions. Mann-Whitney tests were used to detect the differences of continuous variables between the two groups; in case of more than two groups Kruskal-Wallis tests were conducted. Frequency differences of cat-

**Table 1**  
The prevalence of COVID-19 vaccination by principal clinical and sociodemographic features.

	Unvaccinated		Once vaccinated		Double vaccinated		Total		p-value
	n = 172	(%)	n = 31	(%)	n = 1308	(%)	n = 1511	(%)	
<b>Sex (n, %)</b>									
Men	77	44.77	14	45.16	634	48.47	725	47.98	0.626
Women	95	55.23	17	54.84	674	51.53	786	52.02	
<b>Age (years)</b>									
Median [IQR]	61	[55–68]	55	[52–64]	67	[62–73]	67	[61–72]	<0.001
<b>BMI</b>									
Median [IQR]	26.3	[11,23–29]	29.0	[11,24–32]	27.6	[11,24–30]	27.5	[11,24–30]	0.052
<b>Smoking habit (n,%)</b>									
Active	100	58.14	18	58.06	584	44.64	702	46.46	<0.001
Non-smoker	24	13.95	4	12.90	194	14.83	222	14.69	0.694
Former smoker	48	27.91	9	29.03	530	40.52	587	38.85	<0.001
<b>FEV<sub>1</sub>ref%</b>									
Median [IQR]	58	[40–73]	60	[49–73]	60	[46–74]	59	[45–74]	0.192
<b>GOLD stage (n, %)</b>									
A	14	8.14	3	9.68	168	12.84	185	12.24	0.090
B	121	70.35	19	61.29	942	72.02	1082	71.61	0.184
C	1	0.58	0	0.00	9	0.69	10	0.66	0.636
D	36	20.93	9	29.03	189	14.45	234	15.49	0.004
<b>Comorbidity (n, %)</b>									
Hypertonia	107	62.21	21	67.74	927	70.87	1054	69.76	0.028
Diabetes mellitus	28	16.28	7	22.58	235	17.97	270	17.87	0.381
Heart failure	19	11.05	4	12.9	118	9.02	141	9.33	0.302
Ischaemic heart disease	16	9.3	7	22.58	303	23.17	343	22.7	<0.001
Allergies	35	20.35	3	9.68	237	18.12	274	18.13	0.152
Osteoporosis	25	14.53	3	9.68	189	14.45	216	14.29	0.455
Lung cancer	4	2.33	1	3.23	47	3.59	52	3.44	0.420
Other cancer	10	5.81	2	6.45	113	8.64	125	8.27	0.219
Depression	16	9.3	4	12.9	126	9.63	146	9.66	0.527
Anxiety	26	15.12	5	16.13	183	13.99	214	14.16	0.633
Sleep disorder	29	16.86	6	19.35	222	16.97	257	17.02	0.725
Glaucoma	3	1.74	0	0.00	39	2.98	42	2.78	0.210
<b>CAT Median [IQR]</b>	17	[12–23]	16	[12–21]	14	[10–19]	15	[11–20]	<0.001
<b>mMRC Median [IQR]</b>	2	[2]	2	[2]	2	[1,2]	2	[1,2]	0.048
<b>Covid-19 infection (n, %)</b>	39	22.67	5	16.13	21	1.61	65	4.30	<0.001
<b>Hospital treatment (n, %)</b>	14	8.14	1	3.23	1	0.08	16	1.06	<0.001
<b>Post-Covid hospitalisation (n, %)</b>	13	7.56	1	3.23	0	0.00	14	0.93	<0.001

Data are presented as median (IQR) or as frequency and percentage; GOLD: Global Initiative for Chronic Obstructive Lung Disease; CAT: COPD Assessment Test; mMRC: Modified Medical Research Council Dyspnoea Scale; FEV<sub>1</sub>: forced expiratory volume in 1 s post-bronchodilator; BMI: body mass index; GMWD: six-minute walking distance; SD: Standard deviation; p < 0.05 means the two indicators were significantly correlated;

egorical variables were examined by Fisher’s exact test. Cross-tabulation analysis was used to describe the data to explain the association between unvaccinated and double vaccinated patients along different variables. 95 % confidence interval was considered for all statistical tests, and the significance limit used was  $p < 0.05$ .

#### 4. Results

In total, the data of 1,511 patients with chronic obstructive pulmonary disease were examined, the sample consisted of 725 male (47.98 %) and 786 (52.02) female patients. The median age of the observed population was 67 years (61–72), 67 (62–73) years for men, 66 (60–72) years for women. Of the patients, 14.69 % (n = 222) were non-smokers. The observed patients had been smoking an average of 17.5 cigarettes a day for 35.43 years. Almost half of the patients (46.46 %) (n = 702) were still active smokers. Of the 1,511 patients, 12.24 % (n = 185) were classified as GOLD A stage, 71.61 % (n = 1082) as GOLD B stage, 0.66 % (n = 10) as GOLD C stage and 15.49 % (n = 234) as GOLD D stage. The prevalence of COVID-19 vaccination coverage with principal clinical and sociodemographic characteristics is presented in Table 1.

The prevalence of vaccination coverage for the first COVID-19 vaccine dose was 88.27 %, and 86.57 % of patients received the second vaccine dose. More male patients received two vaccine doses against coronavirus than females (87.44 % vs 72.77 %). COVID-19 vaccination coverage was 90.81 % in GOLD A, 87.06 % in GOLD B, 90.0 % in GOLD C and 80.77 % in GOLD D. Patients of older age, patients with more co-morbidities and non-smokers had significantly higher rates of being vaccinated twice (see Table 1).

When unvaccinated (n = 172) and double vaccinated (n = 1,308) patients were compared, the difference was significant both in quality of life (CAT: 17 (12–23) vs 14 (10–19);  $p < 0.001$ ) and severity of dyspnea (mMRC: 2 (2–2) vs 2 (1–2);  $p = 0.048$ ). The number of hospital admissions for acute severe and moderate exacerbation of COPD in the six months after vaccination between unvaccinated and two vaccinated patients was significant, see Table 2. The COVID-19 infection rate of double vaccinated and unvaccinated patients was 1.61 % (n = 21) vs 22.67 % (n = 39) six months after vaccination, respectively. The difference between unvaccinated and vaccinated patients was significant (8.14 % vs 0.08 %;  $p < 0.001$ ) among those with acute COVID-19 infection hospitalized. In terms of post-COVID symptoms, single or double vaccinated patients had significantly fewer outpatient hospital admissions due to post-COVID syndrome than unvaccinated patients (7.56 % vs 0 %;  $p < 0.001$ ).

In the study sample, 31 people received a single vaccine dose, 14 men and 17 women: median age 55 (52–64), median BMI 29 (24–33), median FEV<sub>1</sub> (ref%): 60 (49–73). More than half (58 %) of them were current smokers, about one-third (29 %) had quit smoking. After one vaccine dose, five people (16.13 %) became infected with SARS-COVID-19 within six months, of whom one person required hospital care due to the infection and post-COVID care (see Table 1).

The third table shows inhaled medications of COPD patients in the single and the double vaccinated as well as the unvaccinated groups. Patients receiving two vaccines used significantly less short-acting beta agonists (SABAs;  $p = 0.030$ ) than unvaccinated patients during the six months following vaccination (see Table 3).

Table 2

Number of severe and moderate exacerbations in unvaccinated and double vaccinated, and number of visits to healthcare facilities by COPD patients.

Severe exacerbation	Unvaccinated		Double vaccinated		Total		p-value
	n	%	n	%	n	%	
0	152	88.37	1215	92.89	1367	92.36	0.035
1	19	11.05	89	6.80	108	7.30	0.044
2	1	0.58	4	0.31	5	0.34	0.558
Moderate exacerbation							
0	103	59.88	921	70.41	1024	69.19	0.004
1	65	37.79	359	27.45	424	28.65	0.004
2	4	2.33	28	2.14	32	2.16	0.875
Number of visits to health care facilities							
	Unvaccinated		Double vaccinated		Total		p-value
GP care	1	(1–2)	1	(0–2)	1	(0–2)	0.656
Emergency care	1	(0–1)	0	(0–0)	0	(0–0)	<0.001
Outpatient pulmonary care	1	(0–1)	0	(0–1)	0	(0–1)	0.012
Care in the pulmonary ward	0	(0–0)	0	(0–0)	0	(0–0)	0.562

Data are presented as median (IQR) or as frequency and percentage; COPD: chronic obstructive pulmonary disease; COVID-19: Coronavirus disease 2019;  $p < 0.05$  means the two indicators were significantly correlated;

Table 3

Inhaled medications taken by chronic obstructive pulmonary disease patients in unvaccinated, once vaccinated and double vaccinated groups.

Medication (n, %)	Unvaccinated		Once vaccinated		Double vaccinated		Total		p-value
	172	%	31	%	1308	%	1511	%	
SABA	147	85.47	26	83.87	1022	78.13	1173	77.63	0.030
LAMA	14	8.14	1	3.23	146	11.16	161	10.66	0.086
LABA	3	1.74	1	3.23	56	4.28	60	3.97	0.130
LABA and LAMA	46	26.74	9	29.03	411	31.42	466	30.84	0.236
ICS and LABA	27	15.70	7	22.58	131	10.02	165	10.92	0.003
LABA and LAMA and ICS	79	45.93	13	41.94	525	40.14	617	40.83	0.172
Rare combination	3	1.74	0	0.00	27	2.06	30	1.99	0.409
No data available	0	0.00	0	0.00	12	0.92	12	0.79	0.202

Data are presented as frequency and percentage; SABA: short-acting bronchodilators; LABA: long-acting bronchodilators; LAMA: long-acting muscarinic antagonist; ICS: inhaled corticosteroids;  $p < 0.05$  means the two indicators were significantly correlated;

We calculated the odds ratio (OR) with cross-tabulation analysis (Table 4). Patients with older age ( $\geq 65$  /  $< 65$ ), non-smokers (OR: 1.72; 95 %CI: 1.24–2.37;  $p < 0.001$ ), and lower GOLD stage (A,B) COPD had a significantly higher proportion of two vaccinations. Patients who received two vaccinations also had significantly better quality of life (OR: 2.37; 95 %CI: 1.71–3.27;  $p < 0.001$ ) and degree of dyspnoea (OR: 1.19; 95 %CI: 0.86–1.65;  $p < 0.001$ ) than unvaccinated patients. Vaccinated patients had a significantly milder course of disease compared to unvaccinated patients, i.e. fewer patients were hospitalized for COVID-19 infection (OR: 11.2; 95 %CI: 1.35–92.59;  $p = 0.012$ ) and had a significantly lower rate of post-COVID hospitalization (OR: 10.0; 95 %CI: 1.20–82.96;  $p = 0.016$ ) (see Table 4).

### 5. Discussion

In the present study, an investigation was conducted whether the COVID-19 vaccination rate in Hungarian COPD patients was adequate. Quality of life, respiratory symptoms, number of exacerbations, respiratory function, COVID-19 infection rates and outpatient treatment utilization due to the presence of post-COVID residual symptoms were compared in vaccinated and unvaccinated patients during the six months following vaccination. Our results show that in the first vaccination campaign of the COVID-19 pandemic in Hungary, the vaccination coverage of COPD patients reached the target because 86.57 % of patients had two vaccine doses. There was a significant difference in the number of hospital admissions for acute exacerbations of COPD in vaccinated and unvaccinated patients for both severe and moderate exacerbations six months after vaccination. In addition, there was also a significant difference between their quality of life (COPD Assessment Test), severity of dyspnea (mMRC), COVID-19 infection, and the number of outpatient hospital admissions for post-COVID symptoms.

The importance of vaccination and primary prevention cannot be overemphasized, as in COPD the defense mechanism of the body does not function properly, and the respiratory surface area is

reduced, decreasing the respiratory reserve, which can quickly lead to respiratory failure in the event of pneumonia [18]. Some patients already require oxygen therapy on a daily basis and can be at risk particularly from coronavirus infection [19]. The most important means of prevention is vaccination against COVID-19 because it is the only solution to reduce the chances of developing serious complications that often follow the infection. In Hungary people are informed about the benefits of getting vaccinated by doctors, health personnel, professional organizations and the civil society, and there is a strong social action to increase vaccination coverage. Our target is a national coverage of at least 80 %, especially in people over the age of 60, who are overweight, suffer from any chronic illnesses and have high-risk jobs e.g., healthcare workers, and teachers. Government measures are also intended to protect the public, e.g., the mandatory use of facial masks in all enclosed public spaces (shops, offices, and public transport) and in all open spaces where proper distance cannot be maintained. In addition, the official certificate of immunity (valid immunity certificate or recent negative antigen test/PCR result) is required in public enclosed spaces that are very common places to visit daily (e.g., healthcare facilities, restaurants, nightclubs, gyms, etc.) [20]. During the COVID-19 pandemic – especially in the first vaccination campaign – there was a fairly effective official quarantine system in place, with 10 days of isolation for those who got infected as well as for their contacts. The combination of all these measures explains the extremely high vaccination rate in COPD patients (86.57 %), which is much higher than the average Hungarian population (63.50 %) [21]. The distribution of different COVID-19 vaccines in the 60–69 age group in Hungary during the study period was as follows: Pfizer/BioNTech: 40.93 %, Sinopharm: 25.33 %, Sputnik-V: 17.89 %, Oxford/AstraZeneca: 9.98 %, Moderna: 5.87 % [21].

The current COVID-19 coronavirus epidemic is still an ongoing issue, with the majority of infected people experiencing mild or no symptoms at all, but there is still a chance of about 15–20 % to develop a severe or critical condition [22]. It was already clear at the outbreak of the epidemic that the majority of deaths would be due to chronic illnesses, including COPD or cardiovascular disease. Although the specific reasons for this association are not clear yet, but one explanation could be the different levels of angiotensin-converting enzyme-2 (ACE-2) expression in lower airway epithelial cells, as the virus largely uses the ACE-2 receptor to enter the host mucosa and to establish an active infection [23]. This observation may explain why COVID-19 causes more severe diseases in this patient group, but it also highlights the importance of smoking cessation, being the most common cause of COPD [11].

The medical opinion is pretty straightforward: the benefits of vaccination far outweigh the potential risks and side effects of vaccines. All types of vaccines against COVID-19 infection are effective not only against COVID-19 infection but against serious complications such as respiratory failure and/or death in COPD [24]. In addition, all current vaccines elicit the desired immune response in COPD despite the weakness of their humoral and cellular immune response [24,25]. The mechanism of memory T-cell defence is different from antibody-mediated immunity. T cells cannot prevent infection of host cells, but they respond very rapidly after infection and limit the spread of the virus throughout the body, thus protecting against severe disease in the event of coronavirus infection [8].

According to a study conducted before these vaccines were widely available, patients with COPD who were infected with coronavirus were significantly more likely to die from the infection than the non-patient control population infected with COVID-19 [26]. COPD significantly increases the risk of hospitalization, intensive care unit admission, and death. Those who suffer from COPD, are of older age, have co-morbidities such as cardiovascular disease, high blood pressure and diabetes, or even take oral corticosteroids

**Table 4**  
Comparison of unvaccinated and double vaccinated COPD patients using cross-tabulation analysis.

Variable	Odds Ratio	95 % CI	p-value
Gender			
Male vs Female	0.86	0.62–1.18	0.180
Age (years)			
$\geq 65$ / $< 65$	0.33	0.23–0.46	<0.001
Smoking			
yes vs no	1.72	1.24–2.37	<0.001
Number of comorbidities			
$\geq 2$ / $< 2$	0.79	0.55–1.12	0.103
Number of severe exacerbation			
$\geq 1$ / $< 1$	1.71	1.03–2.87	0.019
Number of moderate exacerbation			
$\geq 1$ / $< 1$	1.59	1.14–2.21	0.002
GOLD			
AB / CD	0.65	0.44–0.96	0.016
CAT			
$\geq 16$ / $< 16$	2.37	1.71–3.27	<0.001
mMRC			
$\geq 2$ / $< 2$	1.19	0.86–1.65	<0.001
COVID-19 infection			
yes vs no	17.97	10.27–31.45	<0.001
Hospital treatment			
yes vs no	11.2	1.35–92.59	0.012
Post-COVID hospitalisation			
yes vs no	10.0	1.20–82.96	0.016

COPD: Chronic obstructive pulmonary disease; GOLD: Global Initiative for Chronic Obstructive Lung Disease; CAT: COPD Assessment Test; mMRC: Modified Medical Research Council dyspnea Scale; CI: Confidence interval;

teroids may be predisposed to increased susceptibility to infections [18]. Smoking alone increases the risk [27] of developing complications caused by the virus, acute respiratory distress syndrome (ARDS) or pulmonary vascular thromboembolic events [28]. In fact, COPD patients are at high risk of death from other respiratory infections too, such as influenza and community-acquired pneumonia [18,29].

A cross-sectional study in Beijing examined the uptake rate of COVID-19 vaccines in their COPD patients during the first vaccination campaign [30], which turned out to be relatively low (39.0%), although the research study described that the majority of their patients were willing to accept the COVID-19 vaccine. The main reason for the low COVID-19 vaccination rate was possibly that nearly half of the patients who did not receive the vaccine were not recommended to do so by their doctors [30]. Some previous studies highlighted the important role of advice from medical and health care staff in promoting vaccination and correcting patient misconceptions and improving confidence [31,32]. Another study described that the uptake of COVID-19 vaccine by patients with tumors was only 17.8%, and a significant proportion of them believed that the vaccine could have a negative impact on chemotherapy, i.e., that it would set back their recovery [32]. The role of health personnel in promoting any vaccine, including COVID-19, is indisputable [30–32].

Post-acute COVID-19 disease (“long COVID”) is a multisystemic disease that can sometimes occur after a relatively mild acute phase too. Persistent or progressive respiratory, cardiac and/or neurological symptoms may require specialist involvement. Post-acute COVID-19 disease is defined as having symptoms after three weeks from the onset of the acute COVID infection, and it is called chronic (long) when symptoms still persist after 12 weeks [33]. A US study found that only 65% of people returned to their previous level of health within 14–21 days of a COVID-positive test [34]. For the time being, we can only speculate about the reasons why this disease sometimes occurs to be delayed, including persistent viraemia due to a deficient antibody response, relapse or reinfection, an inflammatory immune response, and possibly mental factors such as post-traumatic stress. Long-term respiratory, musculoskeletal and neuropsychiatric complications have also been described in connection with other coronaviruses [Severe acute respiratory syndrome (SARS); Middle East respiratory syndrome (MERS)] [35].

Symptoms of post-acute COVID-19 range widely from persistent cough, shortness of breath, chest pain, headache, neurocognitive disturbances, muscle pain and weakness, digestive disturbances, skin rashes, metabolic disturbances (e.g., poor diabetes control), thromboembolic complications, anxiety, to sleep disturbances [36]. There is also a high risk of sarcopenia, malnutrition, depression and delirium in elderly survivors of severe acute COVID-19 disease. A priority for medical staff and doctors is to listen to patients and take their symptoms seriously when they are recovering in an unusual way. The promotion of vaccination is also of particular importance in this regard, as studies have shown that vaccinated individuals have a lower risk of developing post-COVID syndrome even after a single vaccine dose [37,38]. It has been described that those who received two doses of COVID-19 vaccine were less likely (about 50%) to develop long COVID symptoms or to experience symptoms for a shorter period of time than those who received only one vaccine dose or were unvaccinated [39]. Our present study supports this, with significantly lower rates of post-COVID symptoms both in the single and double vaccinated. All these studies result in and raise awareness among patients that vaccination not only protects against acute infection but can also help to reduce longer-term complications, especially if the full vaccination series is taken up. Unfortunately, many unknown factors remain regarding the prediction of long COVID, including the efficacy of booster vaccination, and further research is needed on the

relationship between the decline in antibody levels over time and symptoms before we can predict the exact impact of vaccination on individuals.

There is evidence that regular physical activity can positively modify and improve many anatomical, physiological metabolic processes, neuroendocrine and psychological functions. Increased fitness levels can thrive the immune system’s efficiency, positively influence both cellular and humoral immune responses, which may impact the severity of infectious disease symptoms [40,41]. The aging process has a debilitating effect on the functioning of organs and their systems, one of these consequences is a reduction or depletion of immune function (immunosenescence) [42]. This is one of the factors that contribute to a weaker immune response to vaccinations, and to a higher incidence of infections, autoimmune diseases and tumors. Older people may be at particular risk from COVID-19 and its complications, so vaccination is very important for them [43,44]. Immunosenescence can be delayed by exercise, which was tested by Janet L. and his colleagues. They analysed in total 125 older adults (55–75 years) and their immune profiles who were actively exercising [45]. Their research found out that exercise slows down the shrinking of the thymus. Regular exercise also influences a number of other immune-related parameters, suggesting that frequent exercise has the potential to control the immune response and delay age-induced immune depletion [45]. In addition, it has been shown that in old age it reduces the slight increase in C-reactive protein levels seen in sedentary people. Likewise, lipopolysaccharide-stimulated tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), interleukin (IL)-6 and IL-1 $\beta$  production is lower in the elderly who are active than in those who do not exercise regularly [45–48] (see Table 5). Regular physical activity and exercise not only improves lung function, vital capacity and respiratory adaptation, but also reduces the severity of various respiratory diseases, enhances the immune response to vaccination, increases willpower, improves mood and mood, strengthens the immune system and provides a better quality of life [48].

In conclusion, coronavirus vaccines are effective in reducing the risk of developing COVID-19 and also protect against the development of long COVID. The uptake of COVID-19 vaccines in COPD patients is extremely important because they are much more likely to develop serious complications, are more likely to be hospitalized, and have higher mortality rates compared to patients without COPD. In our sample, the vaccination coverage was satisfactory, with significantly better quality of life, fewer exacerbations, and fewer post-COVID residual symptoms detected in double vaccinated patients compared to unvaccinated patients six months after vaccination.

**Table 5**  
Immunological changes as a result of regular exercise.

↓ Blood concentration of inflammatory molecules (IL-1 $\beta$ , IL-18, TNF- $\alpha$ , IFN- $\gamma$ , CRP)
↓ Exhausted T-cell count
↑ Immune response to vaccination
↑ Natural killer cell migration and activity
↑ T-cells’ ability to divide
↑ Naïve T cells
↑ Phagocytic ability of neutrophil granulocytes
↑ Microbial killing
↓ Toll-like receptor signaling
↑ CD4/CD8 ratio
↑ Sensitivity of $\beta$ 2-adrenergic receptor

IL: interleukin; TNF- $\alpha$ : tumor necrosis factor alpha; IFN- $\gamma$ : interferon gamma; CRP: C-reactive protein;

### 5.1. \*Limitations

The disadvantage of our study is that it was not known exactly which COVID vaccine had been administered to the patients. Five types of vaccines were available in Hungary during the first vaccination campaign: Pfizer/BioNTech, Moderna, Oxford/AstraZeneca, Sinopharm, Sputnik V. COPD patients received the same as the general Hungarian population. The first two vaccines were the same type of vaccine and vaccination was not mandatory, only recommended. Another disadvantage is that the exact post-COVID symptoms that the patient consulted a doctor for were not asked about, and the level of antibodies produced by the vaccine was not checked by laboratory tests. Another one of the downsides is that patients were not followed for their third or fourth vaccination, and that our questionnaire did not ask specifically about physical activity levels. Our quality of life questionnaires, the CAT and mMRC, although validated, were also subjective. The numbers of severe and moderate exacerbations were recorded based on patient narratives after vaccination, which were also subjective. Nevertheless, our data are still extremely valuable and unique regarding the COVID-19 vaccination coverage in Hungarian COPD patients, the vaccine efficacy on acute infection, and the presence of post-COVID syndrome.

## 6. Conclusion

Coronavirus disease (COVID-19) is an infectious disease caused by a new type of coronavirus (SARS-CoV-2). The disease is usually mild in healthy young people, with the highest risk of morbidity and mortality in older people and those with chronic diseases. Vaccine uptake is of paramount importance in controlling the spread of SARS-CoV-2. In chronic diseases, such as COPD, it is also very important for patients to take the COVID-19 vaccine because they are much more likely to develop serious complications. Our sample had a good vaccination rate. Those who got vaccinated had a significantly better quality of life, fewer severe and moderate exacerbations as well as fewer post-COVID residual symptoms (post-COVID syndrome) six months post-vaccination.

### CRedit authorship contribution statement

Conceptualization: Alpar Horvath, Balazs Santa, Gabor Tomisa and Janos Tamas Varga Data curation: Gabor Tomisa, Monika Fekete, Balazs Santa, Vince Fazekas-Pongor Formal analysis: Monika Fekete, Gergo Szollosi, Balazs Santa, Vince Fazekas-Pongor, David Major Investigation: Balazs Santa, Alpar Horvath, Gabor Tomisa, Janos Tamas Varga Methodology: Alpar Horvath, Balazs Santa, Gabor Tomisa, Janos Tamas Varga Supervision: Zoltan Ungvari, Stefano Tarantini, Alpar Horvath, Balazs Santa, Gabor Tomisa and Janos Tamas Varga Visualization: All authors. Writing - original draft: All authors. Writing - review & editing: All authors. Final approval of manuscript: All authors.

### Data availability

Data will be made available on request.

### Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

## Acknowledgements

**Funding:** The research was funded by Chiesi Hungary Ltd.

The authors would like to thank all clinicians partaking in the collection of clinical data:

Alb Krisztina Éva, Alföldi Ibolya, Bánvölgyi Aranka, Bárány Magdolna, Bártfai Zoltán, Bartha Anna, Beke Márta, Bencze Ágota, Bende Zoltán Gyula, Bérdi Eszter, Berzai Eszter Júlia, Bitay Zsuzsanna, Bolya Zsuzsanna, Borota Mirela, Böszörményi Katalin, Breining Ildikó, Búrzuk Valéria, Czompó Márta, Csajbók Valéria, Csicsári Katalin, Csollák Mária, Csontos Éva, Diós Edit, Donka Tünde, Draskóczy Andrea, Ferencz Barbara Aranka, Filkorn Rózsa, Frank Emil, Füleki Margit, Füzesi Edit, Füzesi Katalin, Gönczi Mariann, Hajdu Krisztina, Hanganonyi Csilla Mária, Horváth Gabriella, Huszár Hermína Eveline, Igyártó Rozália, Jakab Zoltán, Jancsik Ljubomir, Juhász Erzsébet, Juhász Tibor, Kalmár Éva, Kaposi Katalin, Kató Ernő, Kecskés Teréz, Kerényi Ildikó Zsuzsanna, Kis Sándor, Kiss Gabriella, Kollár Erzsébet, Kondora Zsanett, Kontz Katalin, Kónya Melinda, Körmendy Szabolcs Dénes, Kuberka Zoltán, Kuczkó Éva Mária, Kukuly Alla, Kukuly Miklós, Kurucz Anikó, Kurucz Edina, Lukács Zsuzsanna Éva, Madai Ildikó Zsuzsanna, Maha Jakóob, Major Katalin, Makk László, Medek Livia, Mészáros Imre, Mózes Imre István, Nádudvary Ildikó, Nagy Andrea, Nagy Emília, Osvai László, Papp Márta, Pappné Dr. Ferenczy Nóra, Poncsák Mária, Puskás Emese, Radeczky Éva, Radu Simona, Schlezák Judit, Selypes Ágnes Erzsébet, Simorjay Zsuzsanna, Sipos Anikó, Sipos Valéria, Somogyi István, Steierlein Mária, Süveges Tibor, Szabó Csilla, Szabó Éva Teréz, Szabó Gyöngyi, Szabó Marianna, Szabó Márta, Szakács Éva, Száraz Éva, Szarka Ildikó, Szeleczki Róza, Szenes Éva Julianna, Szereday Ildikó, Szigeti Ilona, Szilas Gábor, Szkunzjak Viktória, Szolnoki Erzsébet, Tamás Gabriella, Tankó Magda, Tehenes Sándor, Tóth Sándor, Tóth Tivadar, Tóth Zsuzsanna, Unger Erika, Varga Ágnes, Várnai Beáta, Vecsey Erika, Vidák Zsolt, Vincze Árpád, Vinkler Ilona, Vitus Ernő, Walcz Erzsébet, Zagyva Tamás.

## Footnote

**Reporting checklist:** The authors have completed the STROBE reporting checklist.

**Ethical statement:** The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study protocol was approved by the Hungarian National Institute of Pharmacy and Nutrition (docket No.: IV/7743-1/2021/EKU) based on the positive assessment by the National Scientific and Research Ethics Committee of Hungary (registration number CHMED\_2021/01), and it complies with the Helsinki Declaration (as revised in 2013). Patients were given oral and written information prior to the assessment, and then they signed a statement of consent.

## Declarations

**Consent for publication:** Not applicable.

**Availability of data and materials:** The data that support the findings of this study are available on request from the corresponding author.

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