Thorac Res Pract. 2023; 24(4): 186-193 DOI: 10.5152/ThoracResPract.2023.22114

Original Article

An Analysis of Coronavirus Disease 2019 Infection-Related Characteristics of Chronic Obstructive Pulmonary Disease Patients with and without Inhaler Training: A Case–Control Study

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Cite this article as: Ceyhan Y, Tekinsoy Kartın P, Güler S. An analysis of coronavirus disease 2019 infection-related characteristics of chronic obstructive pulmonary disease patients with and without inhaler training: A case–control study. *Thorac Res Pract.* 2023;24(4):186-193.

Abstract

OBJECTIVE: Patients with chronic obstructive pulmonary disease are among the most risky groups for Coronavirus Disease 2019. The study was conducted with a case–control group design in order to determine the coronavirus disease 2019 infection-related characteristics of chronic obstructive pulmonary disease patients with and without inhaler training.

MATERIAL AND METHODS: A total of 106 patients, being case group (n = 53) and control group (n = 53), were included in the study sample through purposive and simple random sampling methods. While the control group did not receive training, the case group received inhaler training in 2017-2018. Inhaler training was conducted face-to-face using the demonstration method. Patients were evaluated according to their coronavirus disease 2019 (approved by a physician positive polymerase chain reaction) status from the beginning of the pandemic to the time they were included in the study (June 2021).

RESULTS: The rate of incorrect inhaler use was determined to be 39.6% of the patients in the control group, which is statistically different from the case group ($P < .001$). It was also determined that 17.9% of the patients in the study sample had contracted coronavirus disease 2019. It was found that the presence of symptoms for at least 1 month following the negative polymerase chain reaction result was significantly higher in the control group ($P = .018$). It was determined that the case group patients were more careful compared to the control group in terms of coronavirus disease 2019 measures ($P < .031$). The patients in the case group reported that inhaler medicines were also effective in protecting against other respiratory system diseases ($P = .006$).

CONCLUSION: Few patients with chronic obstructive pulmonary disease have been infected. It was concluded that the coronavirus disease 2019 symptoms lasted longer in the control group than in the case group.

KEYWORDS: COPD, COVID-19, inhaler, inhaler training
Received: *June 28, 2022* ***Accepted:*** *March 6, 2023* ***Publication Date:*** *July 21, 2023*

INTRODUCTION

The new virus, which emerged in 2019, was quite similar to the severe acute respiratory syndrome-coronavirus. It was named SARS-CoV2 because of this similarity.[1] Severe acute respiratory syndrome-coronavirus, which led to a severe epidemic in 2003 and caused thousands of people to lose their lives, appeared again in China in December 2019 and spread all over the world in January 2020. The first case in Turkey was reported on March 11, 2020, and on the same day, the World Health Organization (WHO) declared COVID-19 as a lethal pandemic.[2] Due to COVID-19, more than 490 million people were infected and over 6 million people lost their lives. The number of confirmed cases in Turkey reached 15 million, and the number of those who died was close to 100 000.[3] The high prevalence of the disease is related to its being highly contagious.

The COVID-19 infection is contracted through droplets or direct contact. Not taking protective measures such as the use of a face mask and shield in crowded environments or touching the mouth, nose, eyes, and ear cavities without sufficient hand hygiene causes the virus to enter the body easily. The virus is usually involved in the respiratory system, and symptoms such as dyspnea and cough are intensively observed. In addition, fever, fatigue, arthralgias, and loss of taste and smell have also been reported a lot.[4,5] Individuals above the age of 65 and those with a chronic disease are among the risk groups that COVID-19 affects the most. Due to the involvement of the virus in the respiratory system, patients with chronic obstructive pulmonary disease (COPD) are at great risk in terms of COVID-19. World Health Organization reports that COVID-19 constitutes a high risk for respiratory system diseases which increase the need for oxygen.[6] In a meta-analysis study conducted, it was found that the most risky group was the COPD patients among 1558 COVID-19 patients with comorbid diseases.[7]

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In addition to its involvement in many vital organs, COVID-19 exacerbates the existing respiratory system diseases in patients due to the damage it causes.[8] It has been reported that COVID-19 occurring in COPD patients has more bilateral lung involvement, that the duration from the start of the symptoms to presenting to the hospital is short, that dyspnea is severe, that the number of respirations per minute is high, and that their need for intensive care is 1.88 times higher.[9] It has been found that the risk of severe disease in COPD patients infected by COVID-19 is 4 times as much and that their rates of hospitalization in ICU and mortality are higher.[10] Based on the information mentioned above, it is obvious that COPD patients are a high-risk group in the COVID-19 pandemic process. In this process, it is highly important to continue the treatments of patients more carefully and to provide patients with training more frequently.

The most effective treatment for COPD is inhaler medicines. On the condition that patients use their medicines correctly and timely, they experience the symptoms caused by COPD more mildly.[11] However, it is known that most patients use their medicines incorrectly.[12] This situation continues to keep the negative effects of the ongoing COVID-19 epidemic on COPD patients on the agenda. In a systematic compilation study published in 2020, it was emphasized that COPD patients should continue taking their medicines in the same regimen and that if they are infected by COVID-19 in this process, they should not stop using their inhaler medicines.[13] Similarly, Global Initiative for Chronic Obstructive Lung Disease (GOLD) has announced in its report that there is no evidence suggesting that COPD patients should stop using their medicines, and therefore, they should continue their treatment.[14] Moreover, Chinese Thoracic Society has stated in its report that COPD patients should continue using inhaler medicines and that they should do it with a correct technique.[15] However, the studies conducted are new and limited, and information about COPD patients who are infected by COVID-19 is inadequate. Especially, no study was encountered which examined the correct or incorrect use of inhalers by COPD patients in the COVID-19 process and the effects of this situation on COVID-19. Therefore, it is believed that an original contribution will be made to the literature by determining how COPD patients who were provided with training on inhaler use by the researchers were affected by COVID-19. It was aimed in the study to determine COVID-19-related characteristics of COPD patients with and without training on inhaler use.

MAIN POINTS

- One of the chronic diseases most affected by the pandemic is chronic obstructive pulmonary disease patients.
- The importance of regular and correct use of inhaler medications by patients has come to the fore again.
- However, due to the intensity of the pandemic, both hospital admissions and inhaler training of patients with chronic obstructive pulmonary disease were disrupted.
- It was considered important to investigate the effects of correct inhaler use in patients with coronavirus disease 2019 infection.

The aim of this study was to explain the answers to the following questions: (1) does using inhaler medicines positively contribute to COPD patients in terms of thinking protection against COVID-19? And (ii) can COPD patients who received inhaler medicine use training be protected better against COVID-19 in comparison to those who did not receive training?

MATERIAL AND METHODS

Research Type

The study was conducted as a case–control group research.

Participants

The population of the study consisted of COPD patients who presented to Kırşehir Ahi Evran University Training and Research Hospital Thoracic Diseases Outpatient Clinic. The research was conducted between March and June 2021. One hundred six patients were included in the sample, with 53 patients in each of the case group and control group (Figure 1). In determining the case group, the purposive sampling method was used, and the COPD patients who had been given training on inhaler use by Ceyhan and Tekinsoy Kartin[16] in their study conducted between 2017 and 2018 were considered. In the previous study, a total of 67 COPD patients were provided with inhaler use training. The patients whose contact information was available were contacted again. Thus, the case group was formed with 53 patients. The inhaler usage skills were questioned again before starting this study. It was checked how the patients applied according to each type of inhaler they used. The fact that the patients continued the correct application was associated with the application method of the previous study. In the previous study,[16] each patient was shown the use of one-to-one inhaler by demonstration method and then patients were called twice a week for 4 weeks and it was followed whether the applications were performed correctly. Therefore, at the end of the study, all patients reached the ability to use the correct inhaler. Patients continued to apply correctly because they also benefited from the skill they gained in their symptoms. In addition, it was very pleasing to obtain the result that highly accurate inhaler applications were maintained approximately 2 years after the study.

The control group, on the other hand, was chosen by using simple random sampling method. The patients in the control group were determined among COPD patients who were in the registration system of the physician cooperating in the study and visited the hospital for examination in the last 1 year according to random numbers table. The patients whose contact information was available were contacted, and those who agreed to participate in the study formed the control group of the study.

Inclusion Criteria for the Study

Chronic obstructive pulmonary disease patients who had previously received inhaler use training, who were accessed through their contact information, who still used inhaler medicines in correct steps, and who volunteered to participate in the study were included in the case group. Chronic obstructive pulmonary disease patients who were followed up by the same chest diseases physician, who showed similar

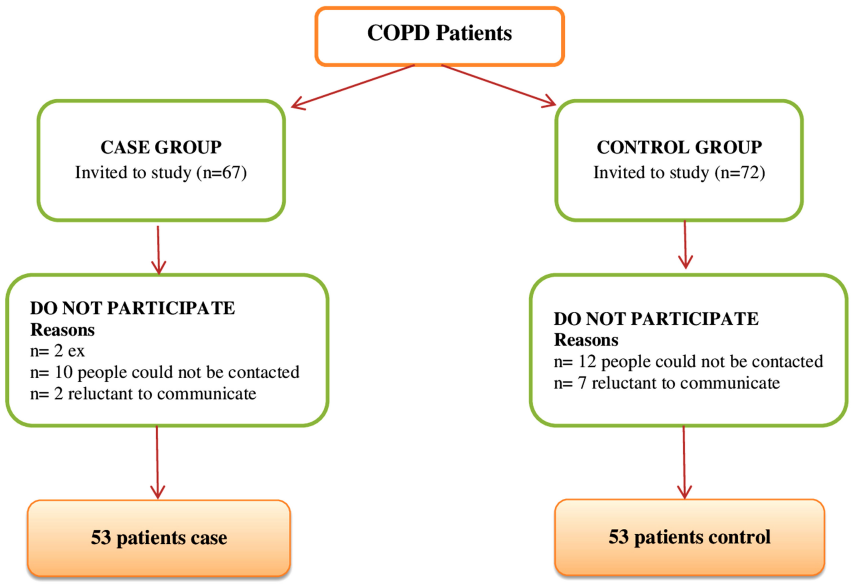

Figure 1. Sample diagram.

characteristics to the case group, who received similar treatment, who had previously not received inhaler use training, who could be accessed, and who agreed to participate in the study were included in the control group.

Data Collection Tools and Their Properties

The study data were collected through a survey form prepared by the researchers by reviewing the literature.[4,5,14,17,18] The form included questions inquiring about the patients' sociodemographic information and their knowledge of COVID-19, their status of contracting COVID-19, the severity of the disease, and the effects of inhaler medicines on COVID-19.

The data were collected through phone interviews. Each interview with the patients lasted approximately 15 minutes. Those who wanted to have the interview when they were available were called later. This method was preferred in order to isolate the patients from the risks of the clinical environment during the pandemic period. The Canadian Thoracic Society has recommended in its report that the training and rehabilitation programs for COPD patients should be continued during the pandemic period and that this should be carried out by using telehealth technologies.[19] Thus, the patients in the study were not exposed to any risk of infection.

Statistical Analysis

The data were analyzed through Statistical Package for the Social Sciences Statistics version 23.0 software (IBM Corp.; Armonk, NY, USA). Compatibility with normal distribution was examined through Kolmogorov–Smirnov test. In the comparison of the data with normal distribution for pairwise groups, independent 2-sample *t*-test was used, and in the comparison of the data without distribution, the Mann–Whitney *U*-test was employed. In the comparison of categorical variables according to groups, chi-square and Fisher's exact test were used, and multiple comparisons of the rates were analyzed with Bonferroni adjusted *Z*-test. Analysis results were presented as mean ± SD and median (minimum–maximum) for quantitative data and as frequency (percentage) for categorical variables.

Ethical Approval

Ethical rules and principles of the Declaration of Helsinki were followed at every stage of the study. Before starting the research, an ethical approval was obtained from the Clinical Research and Publication Ethics Committee of Kırşehir Ahi Evran University (protocol no.: 2021-05/46, date: March 9, 2021). In addition, COPD patients were asked to confirm their participation in the study via telephone.

RESULTS

It was determined that there was no statistically significant difference between the patients in the case and control groups in terms of mean age ($P = .114$) and median duration of COPD diagnosis ($P = .058$). It was found that there was a statistically significant difference between the groups in terms of their distribution according to their employment status ($P = .027$), and that the difference resulted from the retired individuals in the case group. It was determined that 79.2% of the patients in the case group and 50.9% of the patients in the control group were retired. A statistically significant difference was found between the distributions of COPD symptoms according to the groups ($P = .019$), and the difference was found to have originated from the cough and fatigue symptoms in the control group. While cough and fatigue were detected in 30.2% and 17% of the case group, respectively, cough and fatigue were determined in 52.8% and 35.8% of the control group, respectively. It was found that there was a statistically significant difference between the groups in terms of correct use of inhaler ($P < .001$) and that the difference originated from the case group. While 100% of the case group reported correct use of inhaler, this rate was found to be 60.4% in the control group (Table 1).

The condition of the patients caught in COVID 19 was questioned. It was noted that this was diagnosed by the doctor

Table 1. Comparison of the Groups According to Their Sociodemographic and Clinical Characteristics (n = 106)

Characteristics	Case	Control	Total	Stats.	*P*
Age	66.0 ± 7.7	63.0 ± 11.2	64.5 ± 9.7	1.596	.114*
	65.0 (45.0-84.0)	64.0 (33.0- 88.0)	65.0 (33.0-88.0)		
Gender					
Female	4 (7.5)	11 (20.8)	15 (14.2)	3.805	.051*
Male	49 (92.5)	42 (79.2)	91 (85.8)		
Education					
Illiterate	0 (0)	3 (5.7)	3 (2.8)	4.423	.490*
Literate	0 (0)	1 (1.9)	1 (0.9)		
Primary school	36 (67.9)	32 (60.4)	68 (64.2)		
Secondary school	7 (13.2)	6 (11.3)	13 (12.3)		
High school	6 (11.3)	6 (11.3)	12 (11.3)		
Bachelor's degree	4 (7.5)	5 (9.4)	9 (8.5)		
Marital					
Married	52 (98.1)	47 (88.7)	99 (93.4)	—	.113**
Single	1 (1.9)	6 (11.3)	7 (6.6)		
Working					
Housewife	4 (7.5)	9 (17)	13 (12.3)	10.984	**.027***
Worker	0 (0)	3 (5.7)	3 (2.8)		
Officer	1 (1.9)	4 (7.5)	5 (4.7)		
Retired	42 (79.2)[a]	27 (50.9)[b]	69 (65.1)		
Self-employment	6 (11.3)	10 (18.9)	16 (15.1)		
Time of diagnosis	9.2 ± 9.2	7.8 ± 9.9	8.5 ± 9.5	11.060	.058**
	6.0 (2.0 - 50.0)	5.0 (1.0 - 52.0)	5.0 (1.0 - 52.0)		
Symptoms of COPD***					
Dyspnea	50 (94.3)	53 (100)	103 (97.2)	18.384	**.019***
Cough	16 (30.2)[a]	28 (52.8)[b]	44 (41.5)		
Sputum	24 (45.3)	27 (50.9)	51 (48.1)		
Fatigue	9 (17)[a]	19 (35.8)[b]	28 (26.4)		
Wheezing	17 (32.1)	17 (32.1)	34 (32.1)		
Perspiration	2 (3.8)	5 (9.4)	7 (6.6)		
Insomnia	3 (5.7)	6 (11.3)	9 (8.5)		
Hoarseness	2 (3.8)	0 (0)	2 (1.9)		
Regular use of inhaler					
No	3 (5.7)	5 (9.4)	8 (7.5)	—	.716**
Yes	50 (94.3)	48 (90.6)	98 (92.5)		
Terms of use of inhaler					
Incorrect	0 (0)	21 (39.6)	23 (21.7)	20.045	**<.001***
Correct	53 (100)	32 (60.4)	83 (78.3)		
Chronic disease					
None	18 (34)	19 (35.8)	37 (34.9)	0.042	.839*
Have	35 (66)	34 (64.2)	69 (65.1)		
Which chronic disease***					
Hypertension	32 (91.4)	26 (76.5)	58 (84.1)	0.042	.839*
Diabetes mellitus	9 (25.7)	6 (17.6)	15 (21.7)		
Heart disease	16 (45.7)	17 (50)	33 (47.8)		
Goiter	1 (2.9)	0 (0)	1 (1.4)		
Cancer	0 (0)	2 (5.9)	2 (2.9)		
Rheumatoid arthritis	1 (2.9)	1 (2.9)	2 (2.9)		

*Chi-square test.
**Fisher's exact test,
***Multiple response.
[a-b]There is no difference between groups with the same letter in each line.Values with $P < .05$ are significant.
COPD, chronic obstructive pulmonary disease.

according to the positive PCR test. Six individuals in the case group and 13 individuals in the control group contracted COVID-19. About 94.7% of the patients recovered from the COVID-19 infection with various symptoms.

The disease-related characteristics of the patients infected with COVID-19 are presented in Table 2. A statistically significant difference was found between the groups in terms of the distribution of long-term presence of symptoms (*P* =

Table 2. Comparison of COVID-19-Related Variables According to the Groups (n = 19)

COVID-19-Related Variables	Case	Control	Total	*P*
Hospitalization				
No	4 (66.7)	9 (69.2)	13 (68.4)	1.000**
Yes	2 (33.3)	4 (30.8)	6 (31.6)	
Intensive care (n = 6)				
No	2 (100)	1 (25)	3 (50)	—
Yes	0 (0)	3 (75)	3 (50)	
Oxygen use at home				
No	4 (66.7)	7 (53.8)	11 (57.9)	1.000**
Yes	2 (33.3)	6 (46.2)	8 (42.1)	
Pneumonia due to COVID-19				
No	4 (66.7)	9 (69.2)	13 (68.4)	1.000**
Yes	2 (33.3)	4 (30.8)	6 (31.6)	
Long-term presence of symptoms (symptom persisting for the last month despite negative PCR)				
No	6 (100)	5 (38.5)	11 (57.9)	—
Yes	0 (0)	8 (61.5)	8 (42.1)	
Use of inhaler medication in the COVID-19 process				
No	0 (0)	3 (23.1)	3 (15.8)	.517**
Yes	6 (100)	10 (76.9)	16 (84.2)	
Feeling improvement in symptoms with inhalers				
No	0 (0)	3 (23.1)	3 (15.8)	.517**
Yes	6 (100)	10 (76.9)	16 (84.2)	
Thinking that using the right inhaler is beneficial in the COVID-19 process				
No	1 (16.7)	7 (53.8)	8 (42.1)	.177**
Yes	5 (83.3)	6 (46.2)	11 (57.9)	
COVID-19 precautions***				
Mask	47 (100)	40 (100)	87 (100)	**.031***
Distance	47 (100)	40 (100)	87 (100)	
Cleaning	45 (95.7)	39 (97.5)	84 (96.6)	
Reducing exit from home	45 (95.7)	39 (97.5)	84 (96.6)	
Avoiding the crowd	46 (97.9)	38 (95)	84 (96.6)	
Avoiding the family visitation	43 (91.5)	37 (92.5)	80 (92)	
Regular use of inhaler medicines	11 (23.4)[a]	2 (5)[b]	13 (14.9)	
Use of disinfectants	12 (25.5)[a]	1 (2.5)[b]	13 (14.9)	
Routine doctor checkup	3 (6.4)	0 (0)	3 (3.4)	
Thinking that inhaler medicines provided protection against other respiratory system diseases (n = 106)				
No	35 (66)	43 (81.1)	78 (73.6)	**.006***
Yes	18 (34)[a]	10 (18.9)[b]	28 (26.4)	

*Chi-square test.
**Fisher's exact test.
***Multiple response.
[a-b]There is no difference between groups with the same letter in each line.Values with $P < .05$ are significant.
COVID-19, coronavirus disease 2019; PCR: polymerase chain reaction.

.018), and it was determined that the difference originated from the case group. It was determined that long-term symptoms were not present in 100% of the case group and 38.5% of the control group. When the groups' distribution in terms of COVID-19 precautions was examined, it was found that there was a statistically significant difference between the groups (P = .031) and that this difference resulted from the regular use of inhaler medicines and use of disinfectants for cleaning purposes in the case group.

It was determined that 23.4% of the case group and 5% of the control group used their medicines regularly. Disinfectant use rate was 25.5% in the case group and 2.5% in the control group. In terms of thinking that inhaler medicines provided protection against other respiratory system diseases, a statistically significant difference was found between the groups (P = .006), and the difference resulted from the case group patients'

DISCUSSION

In the study, in which the COVID-19-related characteristics of COPD patients were examined according to their receiving inhaler use training, the study sample consisted of mostly male patients above the age of 65. It is known that COPD frequently develops in males at advanced ages. In the GOLD 2022 report, it has been stated that airflow restriction increases more after bronchodilator in males above the age of 40 compared to females and that the highest prevalence is observed in patients over the age of 60.[14] This information is consistent with the study in that 85.8% of the patients were male and at advanced ages.

It has been reported that the COPD-related symptoms that patients complain about the most are dyspnea, cough, phlegm, and wheezing. These complaints observed in the patients are also the most reported symptoms in COPD patients.[14] In the study conducted by Wang et al[20] on COPD patients over the age of 60 who were infected with COVID-19, it was reported that the infection led to serious problems in the respiratory system, progressed very fast, and displayed a poor prognosis. When the symptom distribution of the case group and control group is examined, it is noteworthy that the control group experienced more symptoms and that there was a statistically significant difference between the groups in this regard (Table 1). The reason for this is thought to be related to the correct and regular use of inhaler. Inhaler medicine use is the most effective way in alleviating/eliminating symptoms in COPD patients.[11] Inhaler medicines should be prepared appropriately, be inhaled down to the terminal bronchioles, and be kept here for an adequate period. In order to follow these steps successfully, it is necessary to have inhaler use skills. Regarding the correct inhaler use rates in the patients, while it was 96.2% in the case group, this rate was as low as 60.4% in the control group, which was statistically significant. The fact that the patients in the case group had received inhaler training between 2017 and 2018 and that the great majority of them still had inhaler use skills with correct steps also shows the effectiveness of the training they had received. As a result of the training given on the correct use of inhaler, fewer symptoms were observed in the case group in comparison to the control group. In the literature, there are similar studies conducted which showed that COPD symptoms were mitigated as a result of the patients gaining inhaler medicine use skills. Göriş et al[17] reported in their study that the correct use of inhaler was effective in reducing the frequency of attacks and dyspnea. In the study conducted by Gregoriano et al[18] it was reported that following the inhaler use training, cough, dyspnea, and feeling of obstruction while walking or climbing the stairs were significantly reduced in the patients who used to use inhaler with an incorrect technique. These findings support the findings obtained in the present study.

It is positive that although all COPD patients participating in the study were in the high-risk group, the number of those who were infected with COVID-19 was low. Similar to the present study, it has been reported that in the pandemic period, presentation to hospitals with COPD and inflammation has generally decreased.[14] This situation may have resulted from the patients' being careful about face mask/shield use and measures such as social distancing and hygiene. It has also been reported that the patients' concern about being exposed to the infection during hospital presentation may have caused them to decrease the number of follow-ups.[14] These reports demonstrate the patients' making the correct decisions about their own health and managing the disease appropriately. It is expected that patients who show an effort to manage their disease can be open to training and willing to improve themselves through innovations. Therefore, it is thought that the patients, who wanted to receive training on their disease and grasped the importance of being followed up by healthcare professionals, may have adapted more to the measures against the epidemic. Accordingly, it is an expected situation that the patients in the case group were infected less and had higher levels of adaptation to the measures taken in order to control the epidemic. The fact that the number of patients in the case group who were infected with COVID-19 in the present study was lower compared to the control group patients may have been the result of the previous training that the case group patients had received. In addition, the statistically significant difference being in favor of the case group in terms of regular use of medicines and disinfectants against the COVID-19 epidemic supports our stance (Table 2).

In the case group, there were no symptoms in the patients within the last month following the negative PCR test result after COVID-19 infection, while it was reported that 61.5% of the control group suffered from symptoms (P < .05) (Table 2). This result can be explained by the fact that the patients in the case group continued the correct use of inhaler when they were infected with COVID-19, while the majority of the control group patients did not have this skill. In reports published, it has been emphasized that COPD patients should continue to use inhalers effectively, especially during the pandemic period and when they contracted the COVID-19 infection[13,14], and thus potential inflammations could be prevented.[19] Although the patients in the control group stated that they continued to use inhaler in their COVID-19 infection process (Table 2), it is thought that the medicines that were not used in the correct steps would have little effect

on the symptoms. In a report published on this issue, it was stated that using the inhaler medicines correctly was effective in controlling the symptoms of the respiratory system caused by the COVID-19 infection in COPD patients.[21] All information stated above supports the findings obtained in the present study. In addition, the patients in the case group believed that the inhaler used provided protection against other respiratory system diseases other than COPD (Table 2). This result created a difference compared to the control group (P = .006). Thus, it is seen that there is a correlation between this line of thinking in the case group and correct inhaler use skills. These patients meticulously continued to use inhaler medicines even under the pandemic conditions that affected the whole world while fighting against COPD which they had been suffering from for years, and they benefited from this. Hence, the importance of using inhaler medicines correctly and regularly has been understood once more.

CONCLUSION

As a result of the study, it was determined that the patients who had previously participated in a training program on inhaler use behaved more carefully about their disease and followed treatment options more meticulously. Chronic obstructive pulmonary disease patients with inhaler training contracted COVID-19 less compared to those without training and experienced the infection less severely. Moreover, it was observed that the patients with training protected themselves against the infection better and obeyed the restrictions more. It was also determined that thanks to the correct use of inhaler medicines, the patients in the case group were affected less by other disorders of the respiratory system. According to these results, it can be recommended that COPD patients should be informed about their diseases through appropriate training programs, that they should be provided with information on the importance and correct use of medicines, that the number of rehabilitation programs should be increased, and that the patients should be followed up in the long term.

The main limitation of the study is that it was conducted on a small group. Especially, the insufficient number of patients to be included in the case group in the center where the study was conducted and thus including fewer patients in the study than the maximum number is the main limitation of the study. Therefore, it is necessary to provide COPD patients with inhaler use training and to conduct studies in different centers on wider populations. Another limitation of the study is that the patients were contacted over the phone. Although this was to the benefit of the patients under pandemic conditions, it prevented the researcher from observing inhaler use skills. Also, it should be noted that the results of the study are limited to the group on which it was conducted and therefore cannot be generalized.

Ethics Committee Approval: This study was approved by Clinical Research and Publication Ethics Committee of Kırşehir Ahi Evran University (Approval No.: 2021-05/46, Date: March 9, 2021).

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

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – Y.C.; Design – Y.C., P.T.K.; Supervision – Y.C., P.T.K., S.G.; Data Collection and/or Processing – Y.C.; Analysis and/or Interpretation – Y.C., P.T.K., S.G.; Literature Search – Y.C., P.T.K., S.G.; Writing Manuscript – S Y.C., P.T.K., S.G.; Critical Review – P.T.K., S.G.

Declaration of Interests: The authors have no conflict of interest to declare.

Funding: This study received funding from Kırşehir Ahi Evran University Research Projects with the project number SYO.A4.21.010.

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