

Is COVID-19 responsible for asthma and COPD exacerbations?

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Abstract

COVID-19 is an infectious disease that is transmitted by the respiratory tract and was first identified in the Wuhan province of China. The causative agent of the disease is SARS-CoV-2. There is little known about this disease and its agent, which affected the whole world in a short time and became a pandemic. Molecular interactions between COVID-19 and chronic respiratory diseases are unknown. In this study, we examined the patients admitted to our outpatient clinic with the diagnosis of Asthma and Chronic Obstructive Pulmonary Disease (COPD) exacerbation. We investigated how much of the exacerbations during the pandemic period are caused by the COVID-19 virus and whether there have been any changes in the treatment of and approaches to exacerbations stemming from COVID-19. COVID-19 was detected in 135 of the patients. Clinically, fever, myalgia, and headache findings were significantly more common in patients with a positive COVID-19 PCR CoV 2 test in patients who were diagnosed with an attack of Asthma or exacerbation of COPD ($p < 0.001$). The number of hospitalizations, the need for intensive care, the need for ventilation support, and the number of mortality were high in asthma and COPD patients with positive SARS-CoV-2 tests ($p < 0.05$). Based on the results of our study, patients with COPD and asthma exacerbations due to COVID-19 should be evaluated from a wider perspective. As is known, chronic diseases are poor prognostic factors for COVID-19, but asthma and COPD chronic disease are prominent among them. If there is a need for different approaches for the treatment of these patients, these approaches should be determined urgently.

Keywords: COPD exacerbation, Asthma exacerbation, COVID-19

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Introduction

At the end of 2019, a viral, contagious, atypical pneumonia outbreak was announced in Wuhan province, China. In January 2020, COVID 19 disease was reported for the first time. There are many unknown aspects of the virus, SARS-CoV-2, which causes the disease. It is known that the disease transmitted by droplets causes infections in the lungs. There are many studies in which various comorbidities are determined for coronavirus disease [1]. How many of the patients diagnosed with COVID have asthma and how many of them have the chronic obstructive pulmonary disease (COPD) is unknown. After all, asthma and COPD are comorbidities of COVID-19. We should determine how many of those who present with asthma and COPD attacks are infected with COVID-19. Asthma and COPD exacerbations are characterized by the sudden increase of existing findings. Patients experience an increase in shortness of breath, cough, and phlegm. There might be changes in the color of phlegm. Increased tiredness might be experienced. Effort capacity reduces. Although this is mostly caused by infections, it might also be due to unknown reasons [2-4]. During the pandemic period, if these patients come to the hospital with an attack, we should be alert and scan about COVID-19 Polymerase Chain Reaction (PCR). Since this infection is a disease that primarily affects the lungs, we think that patients with chronic diseases in their lungs will be more susceptible. Therefore, patients with asthma and COPD, in particular, should be investigated more thoroughly for COVID-19. Patients infected with COVID-19 should be investigated specifically for asthma and COPD disease irrespective of age and comorbid diseases, and their treatment, follow-up, and long-term results should be evaluated.

According to previous studies, cardiovascular diseases and diabetes seem to be the most important comorbidities for COVID-19. Chronic respiratory diseases, on the other hand, involve decreased lung capacity and chronic lung inflammation. In addition, respiratory rhinovirus, syncytial virus, or other coronaviruses (OC43, E229) cause significant physiological changes

through the immune response and may adversely affect the respiratory tract of patients and lead to exacerbation [2,7]. In severe cases, ARDS (Acute respiratory distress syndrome) may progress [8-10]. In studies conducted so far, the rate of patients reporting chronic respiratory diseases among those infected with COVID-19 has been low. In a study of 140 cases in Wuhan, China, there was no asthma patient, and 1.4% of the patients had COPD [11]. In another multicenter study including 476 COVID-19 infected cases, 4.6% of the patients had COPD and 0% had asthma [12]. Asthma and COPD rates reported in many studies or reviews with comorbidities in patients infected with COVID-19 were very low. Later on, the rates reported in newer studies have been higher with the increasing awareness [13].

Materials and Methods

Sample population

This study was performed in the chest diseases clinic of the university hospital of the Health Sciences School. Patients diagnosed with asthma and COPD who came for examination for chest diseases during the pandemic (from 11.03.2020 to 31.03.2021) were included in the study. Patients who allowed nasopharyngeal swabs to be taken and whose SARS-CoV-2 PCR test was positive were included in the study. The tests were performed initially by the University School of Medicine until the hospital system developed in-house PCR testing protocols (Roche Cobas SARS-CoV-2 platform). The files of the patients were retrospectively scanned from the hospital database. Files of 5345 patients were scanned retrospectively. Nine hundred and forty-seven of these patients were diagnosed with asthma and 1635 with COPD (Figure 1). Most of the patients applied for exacerbations. We evaluated the smoking histories, symptoms, and examination findings of these patients. We evaluated whether their asthma was under control as well as their comorbidities and inhaled steroid use. Their COVID-19 PCR test and tomography results were also evaluated. We determined how many patients with exacerbation had positive SARS-CoV-2 test. We tried to observe patients with the corona disease who presented with exacerbation

in terms of various specific conditions.

Ethics committee approval was obtained from the ethics committee.

Statistical analysis

The SPSS software version 18.0 (Statistical Package for the Social Sciences Inc, Chicago, IL, USA) was used for statistical analysis. The Kolmogorov-Smirnov test was used to evaluate whether the variables were distributed normally. Continuous variables were expressed as mean (\pm) standard deviation (SD) or median (min-max) according to distribution state. Nominal variables were expressed as numbers and percentages. Categorical variables were compared using the Chi-square test. Student's t-test or Mann-Whitney U (Bonferroni) test was used to compare parametric or nonparametric variables for two independent group analyses. Statistical significance was set at $p < 0.05$.

The datasets generated and analyzed during

the current study are available from the corresponding author on reasonable request. Patients provided written informed consent to take part in the study.

Results

A total of 5345 patient files were examined. These patients were those who were diagnosed with asthma and COPD and presented with exacerbation. Apart from these patients, there were 746 newly diagnosed patients (Figure 1). These patients were not included in the study. Patients with pneumonia, bronchitis, bronchiectasis, newly diagnosed asthma and COPD who presented to the chest diseases outpatient clinic were excluded from the study. The results of patients diagnosed with asthma are shown in Table 1. In patients diagnosed with asthma, a COVID-PCR swab test was taken from all those who presented with an asthma attack. PCR test was positive in 33 of 947 patients. The ratio of women to men in asthma patients with positive PCR test was 15 (45.5%) to 18 (54.5%).

Table 1. Characteristics of patients with asthma stratified by PCR Cov 2 tests

	Asthma Pcr CoV 2 Positive	Asthma Pcr CoV 2 Negative	<i>p</i> value
N=947	33	914	
Age*	57 (35-80)	61(35-80)	0.875
Female\Male n(%)	15(45.5) \ 18(54.5)	444(48.6) \ 470(51.4)	0.724
Co Morbidite DM	23 (69.7)	566 (96.1)	0.336
Co Morbidite HT	18 (54.5)	540 (59.1)	0.336
Co Morbidite HLP	20 (60.6)	613 (67.1)	0.336
Smoking History Never	25 (75.8)	547 (59.8)	0.168
Smoking History Current	5 (15.2)	192 (21)	0.168
Smoking History Former	3 (9.1)	175 (19.1)	0.168
Treatment KS	23(69.7)	574(62.8)	0.174
Treatment LABA	16 (48.5)	551(60.3)	0.174
02 SAT (%)*	96 (89-99)	96 (89-99)	0.953
Cough n(%)	23 (69.7)	565 (61.8)	0.234
Sputum n(%)	24 (72.7)	558 (61.1)	0.385
Dyspnea n(%)	16 (48.5)	431 (47.2)	0.510
Fever n(%)	27(81.8)	124(13.6)	0.000
Miyalji n(%)	27(81.8)	123(13)	0.000
Headache n(%)	24(72)	119(13)	0.000
Pneumonic Consolidation n(%)	30(90)	70(7.6)	0.000
Need for Hospital Insurance n(%)	14(42)	123(13)	0.03
Need For Intensive Care Unit n(%)	5(15)	1(0.1)	0.078
Need ventilation n(%)	5(15)	1(0.1)	0.134
Mortality	9(27)	0	0.004

DM; Diabetes Mellitus, HT; Hypertension, HLP; Hyperlipidemia, KS; Corticosteroids, LABA ; Long Action Beta Agonist
*median(min-max)

Table 2. Characteristics of patients with COPD stratified by PCR CoV 2 tests

	COPD, Pcr CoV 2 Pozitif	COPD, Pcr CoV 2 Negatif	<i>p</i> value
N=1635	164	1471	
Age*	57 (35-80)	61 (35-80)	0.875
Female\Male n(%)	65(39.6) \99(60.4)	609(41.6)\862(58.4)	0.667
Co Morbidite DM	107 (65.2)	830 (56.4)	0.03
Co Morbidite HT	105 (64)	954 (64.9)	0.863
Co Morbidite HLP	125 (67)	934 (61.9)	0.836
Smoking History Never	33 (20.1)	263 (17.9)	0.774
Smoking History Current	77 (47)	716 (48.7)	0.774
Smoking History Former	54 (32.9)	492 (33.4)	0.774
Treatment KS	104(63.4)	881(59.9)	0.382
Treatment LABA	102 (62.2)	946(64.3)	0.592
02 SAT (%) *	97 (89-99)	97 (89-99)	0.215
Cough n(%)	106 (64.6)	964 (65.5)	0.818
Sputum n(%)	105 (64)	958 (65.1)	0.779
Dyspnea n(%)	73 (44.5)	647 (44)	0.897
Fever n(%)	123(75)	220(31)	0.000
Miyalji n(%)	153 (93)	376 (25)	0.000
Headache n(%)	147 (89)	403 (27)	0.000
Pneumonic Consolidation n(%)	160 (97)	189 (12)	0.000
Need for Hospital Insurance n(%)	74(46)	385(26)	0.001
Need For Intensive Care Unit n(%)	54(32)	114(7)	0.015
Need Ventilation n(%)	54(32)	17(14)	0.035
Mortality n(%)	14(8)	13(0.8)	0.002

DM; Diabetes Mellitus, HT; Hypertension, HLP; Hyperlipidemia, KS; Corticosteroids, LABA ; Long Action Beta Agonist

*median(min-max)

There was no significant difference between the female to male ratio in patients with negative PCR test ($p = 0.724$). There was no significant difference between the comorbidities, smoking history, cough, sputum, and dyspnea symptoms of asthma patients with positive and negative PCR tests ($p = 0.336-0.168-0.174-0.234-0.510$). When the symptoms and complaints of the patients were evaluated, fever, myalgia, and headache findings were significantly higher in patients with COVID-19. ($p < 0.001$).

In patients diagnosed with COPD, COVID-PCR swab tests were taken from all those who presented with exacerbation (Table 2). The PCR test was positive in 164 of the 1635 patients. The ratio of women to men in PCR-positive patients with COPD was 65 (39.6) to 99 (60.4). There was no significant difference between the ratio of females to males in patients with negative PCR test

($p = 0.724$). There was no significant difference between comorbidities, smoking history, cough, sputum, and dyspnea symptoms of patients with positive and negative PCR tests ($p = 0.863-0.774-0.818-0.779-0.897$). Only patients with diabetes mellitus (DM) had a significantly higher history of DM. ($P = 0.03$) When the presenting symptoms of the patients were evaluated, fever, myalgia, headache findings were significantly higher in patients with the COVID-19 disease. ($p < 0.001$)

The number of hospitalizations, the need for intensive care, the need for ventilation support, and the number of mortality were high in asthma and COPD patients with positive SARS-CoV-2 tests ($p < 0.05$).

Discussion

We expect the effect of COVID-19 to be more pronounced in patients with chronic respiratory diseases, especially asthma and COPD.

Although the rate of asthma and COPD as comorbid diseases was reported to be low in studies, these rates have become higher with the increasing awareness [13]. Asthma and COPD are likely to become more severe comorbidities with increased age. In our study, we could not see a clear difference between those who were and were not diagnosed with COVID among the patients seen on an outpatient basis. In this study, we wanted to examine the impact of COVID-19 on patients, especially in those with asthma and COPD, by examining those who had positive COVID-19 PCR test. All of our patients were diagnosed with asthma or COPD and we did not make a comparison with normal healthy individuals. Significantly more patients with a diagnosis of COVID-19 had fevers, myalgia, and headache.

Evidence suggests that respiratory virus infection will severely affect patients with chronic respiratory diseases such as asthma and COPD. Therefore, lower respiratory tract infections are considered to be important risk factors for exacerbation and hospitalization [14]. The World Health Organization (WHO) classifies asthma and COPD as major public health problems. COPD was the third leading cause of death worldwide in 2016 [15]. We have known for 18 years that asthma patients are more vulnerable to respiratory viruses than those without asthma. As with other viruses, COVID-19 is a risk factor for asthma exacerbation. If the patient's asthma is not well controlled, exacerbation due to viruses may be very severe [16]. Interferon (IFN)- α , IFN- β , and many IFN- λ responses are missing in the lung cells of asthmatic patients [17]. According to disease control and prevention centers and the American Academy of Allergy, Asthma and Immunology, asthma is a risk factor for severe COVID-19 [18]. According to a meta-analysis of COPD and smoking patients, SARS-CoV-2 is more severe in these patients [19]. Corona disease is more severe and more fatal in COPD [20]. It has a more severe course, especially in active smokers. Remarkable measures are needed to reduce this result. Although COVID-19 remains largely unknown, beneficial conclusions can be made through observational findings by

examining patients with COPD and asthma [21]. Factors contributing to the acute worsening of COPD and asthma have been identified, but infection, including seasonal coronaviruses, remains the main trigger [22]. There are very few dedicated studies investigating the risk specific to patients with chronic respiratory diseases with a history of COPD and asthma. This study addresses this knowledge gap to help clinicians assess the situation.

Undoubtedly, we anticipate that COVID-19 will be more progressive in patients who require hospitalization. [6-10] COVID-19 disease causes advanced pneumonia in the lungs. There may be no lesions in computed tomography (CT) in the first days when the symptoms first occur [22]. Pneumonia delays the hospitalization process and recovery of symptoms in COPD patients [23]. It increases the likelihood of mechanical ventilation in COPD patients [24]. In asthmatic patients, having pneumonia increases the likelihood of rehospitalization and having an asthma attack. The effectiveness of betamimetics decreases in asthma patients with pneumonia [25]. Since the disease is thought to be more severe in patients with asthma and COPD, there have been studies suggesting hypotheses such as early antibiotic initiation and prophylactic antibiotic administration in these patients [26]. In our study, almost all patients with positive COVID-19 PCR test had pneumonic infiltration. ($p < 0.001$) In our patients included in our study, we added macrolide-derived antibiotics to reduce the progression for those with a diagnosis of COVID-19.

At the same time, based on the results of the studies, we recommended hygiene control, washing hands, and using an inhaler device with the right technique for asthma patients diagnosed with COVID-19. We recommended the use of asthma treatment more carefully and regularly, especially during the pandemic period [27-29].

In order to understand to what extent asthma and COPD will be considered as comorbid diseases in COVID-19, we need to learn the number of cases of asthma and COPD in multiple regions. Unfortunately, the numbers given are very low

and this may be due to underdiagnosis. After it was understood that asthma and COPD are some of the most important factors that can change the course of the disease, more numbers have been reported in the later studies [30]. Further, we do not know how many asthma and COPD patients were admitted to the hospital. Some patients may have chosen to never apply to the hospital [31]. The fact that COPD is not known and ignored by the public also causes underdiagnosis [32]. During the pandemic period, asthma and COPD diagnoses or reports may have been overlooked due to intense workload, near-collapse of healthcare systems, and panic in countries around the world. Not being able to use spirometry during the pandemic period was also another important factor. However, there is increasing evidence from studies that COPD and asthma are comorbid diseases [33-35]. Analysis of comorbidities was performed in 1590 COVID-19 patients across China, and a probability ratio of 2.681 (95% CI 1.424-5.048; $p=0.002$) was found in terms of admission to ICU, mechanical ventilation, and death probability for COPD [36-37]. In our study, we evaluated the immediate clinical, radiological, and laboratory conditions of outpatients. All of these patients with a diagnosis of corona received inpatient treatment. Almost all patients without a diagnosis of COVID (non-COVID asthma, non-COVID COPD) received outpatient treatment. Although there were patients with a good overall condition, they received inpatient treatment because they had comorbid diseases (COPD, asthma). Moreover, some of these patients were transferred from the service to the intensive care unit (ICU) and needed mechanical ventilation. Monitoring even one of these patients in the intensive care unit is considered statistically significantly higher since all other non-COVID patients were treated as outpatients. In a multi-center study conducted in China, patients with moderate COPD infected with COVID-19 were compared with patients with severe COPD and the study found that the mortality rate was higher in patients with severe COPD [12]. In many other studies, similar differences were found between hospitalizations in the ICU, although the rates of COPD were statistically lower [34].

An important discovery regarding COVID-19 is that the virus uses ACE2 (Angiotensin-converting enzyme 2) scavenger receptor to enter cells. ACE2 is a pathway that makes it easier for the virus to enter cells. The renin-angiotensin-aldosterone system (ACE2) is a transmembrane metalloprotease expressed in a variety of tissues, including the intestines, heart, upper and lower respiratory tract. The ACE2 receptor is overexpressed in the epithelium of the bronchioles in COPD patients and asthma patients compared to the normal population. This may explain the more severe course of COVID-19 [35-37].

When we look at biological parameters in patients infected with SARS-CoV-2, we see that some proinflammatory cytokine levels and other biological parameters are increased. Many studies show a significant link between C-reactive protein (CRP), interleukin (IL)-6, lactate dehydrogenase, amyloid A protein, neutrophils/lymphocytes, D-dimer, and cardiac troponin levels, and the severity of COVID-19. These values were significantly higher in severe COVID-19 patients compared to non-severe patients [38]. This deregulation is a condition independent of having a chronic respiratory disease, however, the results will not be the same for patients with chronic respiratory diseases compared to those without chronic respiratory disease. In fact, a higher concentration of tumor necrosis factor-alpha (TNF- α) in asthma patients prior to infection compared to controls is positively correlated with bronchial hyperreactivity [39,40]. In addition, a high TNF- α level lowers the functional expiratory volume in 1 second (FEV1) in patients with asthma and COPD [41]. Therefore, it may increase the risk of exacerbation in asthma patients during SARS-CoV-2 infection.

Limitations

The most important limitation in our study was we could not include ferritin, CRP, procalcitonin, and lymphocyte values of all patients in the study. We did not include different comorbidities to rule out their effects and to associate the symptoms of the COVID-19 disease directly with asthma and COPD. We

included DM and hypertension (HT) because many patients have concomitant DM or HT.

Conclusions

COVID-19 has a severe course in patients with asthma and COPD. Hospitalization rates, ventilator support needs, and mortality rates of these patients are high. Since COVID-19 infection is a disease that primarily affects the lungs, we think that patients who already have chronic diseases in their lungs will be more affected. Therefore, especially those with asthma and COPD should be examined more thoroughly for COVID-19. Patients infected with COVID-19 should be examined specifically for asthma and COPD disease irrespective of age and comorbid diseases, and their treatment, follow-up, and long-term results should be evaluated.

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No financial contribution has been received.

Conflict of interest

No potential conflict of interest was reported by the authors.

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