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Impact of the COVID-19 pandemic on the clinical features of patients with chronic obstructive pulmonary disease: an observational cross-sectional study

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Abstract

The presence of chronic obstructive pulmonary disease (COPD) and COVID-19 infection is a detrimental combination for patients and can cause negative clinical consequences. The investigation aimed to compare sociodemographic and clinical parameters of COPD individuals hospitalized for exacerbations before and at the end of the COVID-19 pandemic. An observational cross-sectional study including 222 patients with COPD was conducted in two stages: a survey and assessment of clinical and laboratory data of patients hospitalized from September 2022 to March 2023 (n=98) and processing of the medical histories of patients with COPD who received hospital treatment in 2017 and 2018 (n=124). A comparative analysis of patients who received inpatient treatment for COPD showed that the frequency of patients with Global Initiative for Chronic Obstructive Lung Disease (GOLD) I was half as high after the COVID-19 pandemic, whereas the individuals with GOLD IV were more frequent during the same period ($p<0.05$). Multiple regression analysis proved the effects of smoking status and previous COVID-19 infection on the health status of patients with COPD according to COPD Assessment Test data ($p<0.05$). There was an increase in the frequency of comorbid pathologies in the post-COVID period: hypertension, coronary heart disease, gastrointestinal diseases, anemia ($p<0.05$), and other diseases. This study highlights the significant influence of the COVID-19 infection on people with COPD, which manifested as impaired lung function and an increased incidence of comorbidities.

Key words: chronic obstructive pulmonary disease, coronavirus infection, hospitalization, respiratory tract, comorbidities.

Introduction

Chronic obstructive pulmonary disease (COPD) is a common lung disease causing restricted airflow and breathing problems [1,2]. COPD is a leading cause of death, along with coronary heart disease and stroke in Kazakhstan [3,4]. COPD is characterized by damage to the respiratory tract and/or alveoli, which results in the development of irreversible bronchial obstruction with symptoms of chronic respiratory failure [5,6]. Individuals with this medical condition frequently have lung damage or mucus accumulation. Symptoms include chronic coughing (which may be accompanied by mucus production), breathing difficulty, wheezing, and general fatigue. The major causes of COPD are usually tobacco smoking and environmental pollution. Those identified with this disease are more likely to have further health issues [2]. It has been established that the frequency of exacerbations of COPD affects the progression of the disease, impaired pulmonary function, and mortality of patients [7,8]. Exacerbations of COPD are often caused by viral agents, partially viruses of influenza, coronavirus, rhinovirus, or respiratory syncytial virus [9,10].

Infection COVID-19 can affect the upper and lower respiratory tracts, causing diseases of varying severity, from asymptomatic to acute respiratory failure and death. After a disease, various complications can occur, including damage to the cardiovascular, urinary, digestive, nervous, endocrine, hematopoietic, and other systems [11,12]. Studies indicate that COPD patients have a higher susceptibility to COVID-19 [13-15]. It is due to mechanisms of the virus entry and active reproduction in COPD patients that include overexpression of the ACE2 gene encoding a specific receptor to angiotensin-converting enzyme 2 in epithelial cells [13], dysfunction of the immune system, involving a decrease in interferon (IFN-β and λ) production by bronchial epithelium cells and lymphopenia, as well as dysfunction of T cells [16].

At the same time, some scientists state a low frequency of occurrence of patients with COPD among the sample of patients with COVID-19: in the range of 1-3% [17-19]. There is a hypothesis that the disease itself, or measures aimed at its treatment, can reduce the risk of infection with the coronavirus, but this hypothesis needs to be refuted or proven. Potentially, more vulnerable groups of the population (such as the elderly) are usually prone to COPD, and they are preventively better protected against COVID infection.

On the other hand, COVID-19 patients with COPD have an increased risk of negative aftereffects [14]. Severe coronavirus infection in persons with COPD is associated with older age, male sex, lower levels of education, being underweight or obese, a forced expiratory volume in 1 second (FEV1) estimate of less than 50%, and a higher score of at least 18 on the COPD Assessment Test (CAT) [20]. A lack of education is frequently associated with a worsening of COPD due to a number of interconnected causes [21]. It is caused by factors such as a lack of access to health information, bad lifestyle choices, restricted healthcare

access, delayed diagnosis, and ineffective management. Socioeconomic disadvantages contribute to the course and severity of COPD by intensifying environmental exposures such as air pollution and risk factors at work. Cohort studies have shown that COPD increases the mortality risk associated with COVID-19 [22,23]. The negative consequences of COVID-19 in patients with COPD are linked to restricted perfusion and ventilation of the lungs, as well as coagulation disorder and endothelial cell dysfunction, which increase the frequency of microthrombosis and the risk of secondary bacterial infections that might cause bacterial pneumonia [14,24,25].

The aim of this work was to estimate the risk factors, clinical characteristics, laboratory and instrumental data, and course of COPD exacerbations by comparing patients requiring hospitalization before and at the coronavirus pandemic end.

Materials and Methods

Cross-sectional research was conducted in the inpatients of the Pulmonology Department and Respiratory Centre of City Clinical Hospital Nr. 1, in Almaty, Kazakhstan. 98 patients who received treatment between September 2022 and March 2023 were surveyed. At the same time, authors analyzed the medical histories of 124 COPD patients hospitalized in the same months from 2017 to 2018. Persons with previously diagnosed chronic obstructive pulmonary disease and those who underwent spirometry after admission to the hospital, where COPD was confirmed by the detection of partial respiratory obstruction (FEV1/FVC<0.7 post-bronchodilation), were subjected to a survey. The exclusion criteria were age <38 years, active pulmonary tuberculosis, acute cerebrovascular disorders, and severe cognitive impairment. The selection process for the study and control groups, along with the criteria used to exclude certain cases, is illustrated in Figure 1.

The questionnaire was developed from standardized questionnaires and consisted of questions regarding demographics, educational level, living conditions, tobacco use, use of biomass for heating and cooking, comorbidities, and current therapies. In addition, data on residence in a certain area of the city, profession, paid and unpaid employment, education, the habit to smoke, family income level, index of body mass (BMI), intensity of physical trainings, aggravated heredity for respiratory diseases, comorbidity, status of vaccinations, drugs received and the effect of treatment, adherence to therapy, frequency of exacerbations in the last year, CAT, modified Medical Research Council (mMRC) assessment tests, as well as the Charlson Comorbidity Index were included.

Airway constriction was assessed using the Global Initiative for Chronic Obstructive Lung Disease (GOLD) scale, which was determined on the basis of forced expiratory volume in 1 s (FEV1). Upon admission, the following clinical and laboratory parameters were determined:

respiratory symptoms; hemoglobin level; and the number of erythrocytes, leukocytes, platelets, neutrophils, lymphocytes, and eosinophils. All patients underwent instrumental examinations during hospitalization, including spirometry, chest radiography, and electrocardiography. Comorbidity was assessed by identifying all diseases present in the patient and evaluating the diseases included in the list to calculate the Charlson index. To evaluate the Charlson index, authors used the following gradation: 0-1 – none complication, 2 – slight complications, and 3 – heavy complications. All the people who took part in the study had signed an agreement for their data analysis. This research has been accorded with all ethic committee demands of the Al-Farabi Kazakh National University (protocol No. IRB-A403. IRB00010790 Al-Farabi Kazakh National University (IRB#1).

Digital data have been processed by the statistical software of GraphPad Prism 9.1. Quantitative data are represented as means, and qualitative data are represented as absolute frequencies and percentages. The Kolmogorov-Smirnov test was used to evaluate data normality. The differences between categorical and continuous variables have been estimated by the Fisher exact test or chi-square and unpaired t-test, respectively. An analysis of variance (ANOVA) has been performed to compare independent data between two groups or more. Multiple linear regression has been applied to estimate the relationship between one dependent variable and two or more independent variables. The difference has been regarded as sufficient in cases with an obtained p-value less than 0.05.

Results

The socio-demographic data and risk factors are presented in *Supplementary Table 1*. The average patient's age was 62±12.6 years; 56% were male. Most patients (72.4%) lived in the city of Almaty, while 27.6% lived in the Almaty region. Furthermore, the number of patients living in city districts varied from 7.1% to 12.2%. Approximately 24.5% of the patients had tertiary education, and 75.6% had secondary and specialized education. Most patients (56.1%) had a low family income, 40.8% had an average level, and 3.1% had a high level. There were 31.6% smokers, 35.7% ex-smokers, and 32.7% never-smokers. A total of 34.7% of the patients were exposed to smoke from burning biomass for home heating and cooking for at least two years of life.

Most study participants were of working age; specifically, 45.9% were paid workers, and 12.2% were unpaid workers. In total, 41.8% of the patients were pensioners. The most common professionals among the study participants were teachers (6.1%), drivers (5.1%), builders (4.1%), engineers (3.1%), civil servants (3.1%), and nurses (3.1%). Moreover, the percentage of people working in other professions was approximately 2%. 36.7% of the patients worked in environments with harmful production factors and in cold, gassed, and

dusty conditions. The average BMI (body mass index) was 26.8. Most patients had moderate physical activity (62.2%), and 37.8% performed intensive physical activity. Dietary health was assessed according to the recommendations of the World Health Organization (WHO). Among them, 56.1% followed healthy diets.

When studying hereditary factors, authors examined the incidence of chronic pulmonary and hypersensitivity disorders, such as COPD, bronchiectasis, and bronchial asthma, in close family members (first-degree relatives). Burdened heredity was detected in 13.3% of the cases. The clinical data of the patients in the aftermath of the COVID-19 pandemic are presented in *Supplementary Tables 2 and 3*. According to these results, coughing with sputum production (93.9%) and permanent dyspnea (99%) have been diagnosed as major deviations in patients with breath pathology. In terms of symptoms, the patients' mean CAT values were 23.0±6.9 points, the modified mMRC values were 2.5±1.3, and over 74.5% of the patients had more than 20 points on the CAT. The CAT (COPD assessment test) scale is a validated indicator that generally characterizes the impact of COPD on the patient's health. If the CAT value is less than 10 on the validation scale, the impact is considered insignificant; from 10 to 20 – average; from 21 to 30 – significant, and more than 30 is excessive. In the post-COVID period, only 5% of patients had a slight impact of COPD on their general status, while in most cases (almost 75%) the pathology led to a significant and excessive health impairment. In 20% of cases, the level of exposure has been classified as medium. Among these patients, 41.8%, 12.2%, and 4.1% had received a COVID-19 vaccine, an influenza vaccine, and a pneumococcal vaccination, respectively.

Furthermore, concomitant diseases were detected in 87.8% of the patients (Charlson Comorbidity Index >1). *Supplementary Table 2* shows the primary treatments received by patients with COPD. According to the data, 35.7%, 45.9%, and 54.1% of the patients were prescribed a combination of ICS and LABA, received M-anticholinergics, and short-acting beta2-agonists, respectively. In combination with beta-agonists, corticosteroids contribute to the smoothing of COPD exacerbations, as they inhibit the synthesis of pro-inflammatory cytokines by repressing gene transcription. As a result, the number of foci of inflammation in the lungs decreases. However, the disadvantage of corticosteroids usage is the suppression of the synthesis of antiviral interferon and a number of immune cytokines that resist bacterial infections.

Additionally, 15.3% of patients received courses of steroid therapy (oral and parenteral). Notably, arterial hypertension and ischemic coronary pathology were predominant complications among patients with COPD, with incidence rates of 66.3% and 33.7%, respectively. Other diseases were less common, including type 2 diabetes mellitus (7.1%), peptic ulcer disease and anemia (6.1%), chronic pancreatitis, chronic cholecystitis (5.1%),

bronchiectasis (4.1%), and chronic hepatitis C (CHC) at 3%. A total of 30.6% of patients had a history of COVID-19. Multiple regression analysis revealed the effects of smoking status and past coronavirus infection on the health status of individuals with COPD (CAT test data). The influence of patient age on the Charlson comorbidity index was also found ($p < 0.05$) (*Supplementary Table 4*).

A comparative analysis of patients who received inpatient treatment for COPD in 2017-2018 (before the COVID-19 pandemic) and 2022-2023 showed that the frequency of patients with GOLD I was half as high at the end of the coronavirus pandemic, whereas persons with GOLD IV were more frequent during the same period ($p<0.05$) (*Supplementary Table 5*). Patients classified as GOLD I were defined as mild and had a forced expiratory volume of 80% or more. Individuals with GOLD II were characterized as having moderate severity status with an expiratory volume of 50% to 80%. The GOLD III category was considered severe with a forced expiratory volume between 30% and 50%. The highest degree of airway obstruction was observed in patients with very severe stage GOLD IV with a forced expiratory volume of less than 30%. In the post-COVID period, only 4% of patients with COPD had a mild stage of the disease; the status of 28% was considered moderate; 32% – heavy, and 37% – very severe. The authors did not find any influence of demographic indicators on the level of airflow limitation (*Supplementary Table 6*).

There was an increase in the frequency of comorbid pathologies at the end of the COVID-19 pandemic: arterial hypertension, coronary heart disease, gastrointestinal diseases, anemia ($p<0.05$), and other diseases. In addition, the Charlson comorbidity index was significantly higher during this period. Comparison of COPD patients who did and did not have a history of confirmed COVID-19 revealed no significant differences between the clinical characteristics of the patients.

However, when authors compare a number of parameters of patients with COPD before the COVID pandemic and those who contracted the coronavirus after the start of the pandemic, a significant difference in percentage can be noted (Figure 2). In particular, as a result of the obtained coronavirus infection, the respiratory function of patients with COPD decreased by 15%. It was a smaller amount of people with a mild form of pathology (9% less), but, on the other hand, there were more people with a severe form of the disease (6% more). COVID-19 led to an increase in the frequency of some complications: hypertension – by 32%, ischemic heart disease – by 21%, gastrointestinal disorders – by 23%, pneumosclerosis – by 13%, and lymphadenopathy – by 25%. Complications are summarized by the Charlson index. And if its value is more than 3, then complications are considered severe. The coronavirus disease contributed to the increase in the number of complication cases, with a high index of 61%.

Thus, it can be stated that the coronavirus infection can be the cause of the development of accompanying health disorders in patients with a diagnosis of COPD. The study's findings show that socio-demographic characteristics, notably education levels and income, as well as smoking habits and biomass smoke exposure, all have a substantial impact on the severity of COPD. The majority of the patients in the research had a moderate to severe form of the illness, with a large percentage having concomitant disorders such as hypertension and ischemic heart disease, particularly after COVID-19. Furthermore, post-COVID consequences impair respiratory function, increase the prevalence of severe COPD (GOLD IV stage), and raise the Charlson Comorbidity Index. The study emphasizes that the influence of COVID-19 on COPD patients has resulted in a significant rise in complications and a decrease of lung function.

Discussion

In the prompt research, the authors estimated the clinical characteristics of individuals with COPD admitted with exacerbations to pulmonology departments at the end of the COVID-19 pandemic and compared their data with those of patients treated before the pandemic. Kazakhstan's first case of novel coronavirus infection was reported in March 2020. As of February 27, 2023, more than 1.4 million cases had been identified, and 90845 patients with pneumonia, symptoms of COVID-19, and negative PCR test results were treated. In this study, documented cases of COVID-19 were found in 30.6% of the patients with COPD. It is assumed that substantially more individuals are infected with SARS-CoV2 than the documented cases. This is because people diagnosed during mass testing or seeking medical help were documented and registered as cases [26]. Moreover, studies in the United States and Europe have demonstrated that coronavirus seropositivity is approximately 10 times higher than it has been noted in previous publications [27,28]. Thus, authors can speculate about the broader coronavirus influence on the studied individuals.

This study proved that the health status of persons with COPD, as assessed according to CAT, was significantly affected by COVID-19. CAT makes it possible to characterize the disease based on the presence of the following symptoms: cough, sputum production, chest tightness, and dyspnea appearance during stairs climbing or home activity. Numerous studies have shown that COPD symptoms negatively impact the patient's quality of life, overall health, and prognosis [29,30]. In addition to limiting daily activities and reducing physical activity, COPD symptoms can disrupt sleep and increase the likelihood of anxiety and depression. Patients with COPD and prevalent symptoms are more likely to experience exacerbations and have worse disease outcomes. This research proved that persons with COPD as well as with a history of confirmed COVID-19 may experience adverse clinical consequences in the future.

Moreover, patients hospitalized at the end of the COVID-19 pandemic had lower lung function scores. Previous studies found an association of the airflow limitation level with the risk of hospitalization and the prognosis of patients with COPD [31-33]. However, another study found no effect of different degrees of airflow limitation on future COPD exacerbations and mortality [34]. In addition, authors' data confirmed results of studies that showed the influence of smoking status on the risk of developing COPD and the health status of patients [35-37].

According to the results of this current research, the prevalence of comorbid diseases such as hypertension, coronary heart disease, gastrointestinal diseases, and anemia increased at the end of the COVID-19 pandemic. Among concomitant diseases, hypertension was the most prevalent comorbid condition in patients with COPD, and its frequency increased in the post-COVID-19 period. The heightened potential for developing high blood pressure among COVID-19 patients may be related to a disturbance in the systems that control the renin-angiotensin-aldosterone system (RAAS). The RAAS is an indispensable mechanism for managing hemodynamics by controlling blood pressure, fluid volume, and sodium and potassium balance. Notably, ACE 2 negatively affects RAAS activation by converting ANG 1 to ANG 1-9 and ANG 2 to ANG 1-7 [38]. SARS-CoV-2 binding to ACE2 can lead to angiotensin II level increase and decrease angiotensin-1-7 concentration. This shift causes free radical generation, retention of Na^+ cations, the constriction of vessels, inflammation, and fibrosis [39]. Patients with COVID-19 show elevated levels of ANG 2, which are directly proportional to the viral load [40,41]. The RAAS is involved in the development of various pathologies, including hypertension, myocardial infarction, heart failure, and complications of diabetes mellitus [42,43].

The second most common pathology accompanying COPD at the end of the COVID-19 pandemic was coronary heart disease (CHD), resulting in coronary artery remodeling and constriction. Several pathogenic mechanisms have been implicated in the CHD appearance in cases of coronavirus infection. These include an inflammatory response mediated by cytokines, endothelial dysfunction, hypercoagulability, and hypoxic damage because of oxygen delivery lack [44]. COVID-19 is known to initiate an intense inflammatory response in the body that can damage the inner lining of arteries (endothelium), leading to increased plaque formation and reduced blood flow to the heart [45,46]. This increases the risk of arterial narrowing and cardiac damage. The levels of inflammatory molecules, such as interleukin-1 (IL1), interleukin-6 (IL6), tumor necrosis factor-alpha (TNFα), and C-reactive protein (CRP), were found to be significantly elevated in patients who had contracted COVID-19 [47]. In response to the pro-inflammatory response induced by COVID-19, endothelial cells present adhesion molecules such as intercellular adhesion molecule-1, P-selectin, and E-selectin on their surface. This allows for increased adherence of white blood cells [48]. Due to this

inflammatory process and the resulting oxidative stress, various molecules increase blood coagulation and the risk of thrombosis [49].

In this study, gastrointestinal (GI) illnesses were observed in 21.4% of COPD patients. In the pre-COVID period, the rate was only 7.3%, almost three times lower. COVID-19 patients typically present with respiratory symptoms and fever; however, some patients who test positive for COVID-19 report gastrointestinal symptoms, such as reduced appetite, diarrhea, and nausea [50]. An increased risk of severe gastrointestinal disease due to COVID-19, especially when risk factors like diabetes mellitus and glucocorticoid use are present, has been noted. The gastrointestinal tract's vulnerability to coronavirus might be caused by an elevated expression of ACE2 receptors in the intestine. The cause of digestive symptoms could be direct viral invasion and tissue and organ damage due to an immune response. Moreover, the development of gastrointestinal disorders a month after contracting COVID-19, including conditions such as acute pancreatitis, dysmotility, gastroesophageal reflux disease, dyspepsia, peptic ulcer disease, and liver and biliary tract diseases, has been confirmed [51]. The data imply that people with COPD are more likely to experience gastrointestinal issues in the post-COVID-19 phase.

The study of the relationship between COPD and COVID-19 has been ongoing for more than three years. Although many aspects of their complex interactions have been understood, how the COVID-19 pandemic has affected the disease remains unclear. The research attempted to clarify how the clinical characteristics of COPD patients changed at the end of the COVID-19 pandemic, but this study has several limitations. One of the main limitations was that it did not cover all possible medical, socioeconomic, and genetic aspects of the coronavirus pandemic that could affect the status of individuals. In addition, the present study may not reflect the true picture of the prevalence of comorbidity among patients with COPD, since comorbid patients are more often admitted to cardiology, oncology, neurology, and other specialized departments, and the comorbidity index in such patients may be higher.

Conclusions

The study determined that the pandemic had a substantial impact on the clinical course of COPD, aggravating underlying problems and resulting in a more severe disease trajectory. The post-COVID period showed a large increase in individuals with GOLD IV stage COPD, suggesting a decline in lung function and a higher frequency of serious health issues. COVID-19 increased existing respiratory restrictions, pushing many into more severe categories of airflow restriction, indicating the pandemic's impact on vulnerable populations with pre-existing respiratory conditions.

The study reveals a link between socio-demographic factors and COPD severity, with patients with lower education, family income, and higher smoking exposure more likely to experience severe exacerbations. This highlights the importance of socioeconomic status in COPD patients' health due to limited healthcare access and preventative measures. Smoking status and COVID-19 infection also significantly impact health outcomes, with smoking causing quicker lung function degradation. The COVID-19 pandemic has highlighted the need for public health initiatives to improve healthcare access and support smoking cessation among these communities in order to reduce COPD burden. The study also discovered a substantial rise in comorbidities, such as hypertension and ischemic heart disease, in COPD patients throughout the pandemic. Their higher prevalence in post-COVID patients indicates the virus's deeper systemic effects, which aggravated pre-existing cardiovascular and respiratory disorders. These findings imply that managing COPD after a pandemic must account for the increased risk of comorbid conditions, demanding more extensive treatment programs that target both respiratory and systemic health. Demographic characteristics like as age and BMI had no significant influence on COPD severity, indicating that lifestyle and environmental exposures were more important in predicting disease development during the pandemic.

The COVID-19 pandemic had a substantial influence on COPD in hospitalized patients, resulting in more severe disease stages and comorbidity rates. The study underlines the need of targeted therapies such as improved healthcare access, smoking cessation programs, and complete management of respiratory and non-respiratory comorbidities. Future study should look at the long-term consequences of COVID-19 on COPD patients, such as the evolution of respiratory and systemic comorbidities and the efficacy of targeted therapies such rehabilitation programs and vaccinations in post-pandemic healthcare settings.

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Online supplementary material:
Supplementary Table 1. Sociodemographic characteristics and risk factors relevant to chronic obstructive pulmonary disease (n=98).
Supplementary Table 2. Clinical characteristics of chronic obstructive pulmonary disease patients (n=98) at the end of COVID-19 pandemic.
Supplementary Table 3. Comorbidities in chronic obstructive pulmonary disease patients.
Supplementary Table 4. Multiple linear regression analysis.
Supplementary Table 5. Comparison of characteristics between chronic obstructive pulmonary disease patients: 1) before (n=124) and at the end of COVID-19 pandemic (n=98); 2) with (“+”) and without (“-”) a history of confirmed COVID-19.
Supplementary Table 6. Demographic characteristics of chronic obstructive pulmonary disease patients according to degrees of airflow limitation at the end of the COVID-19 pandemic.

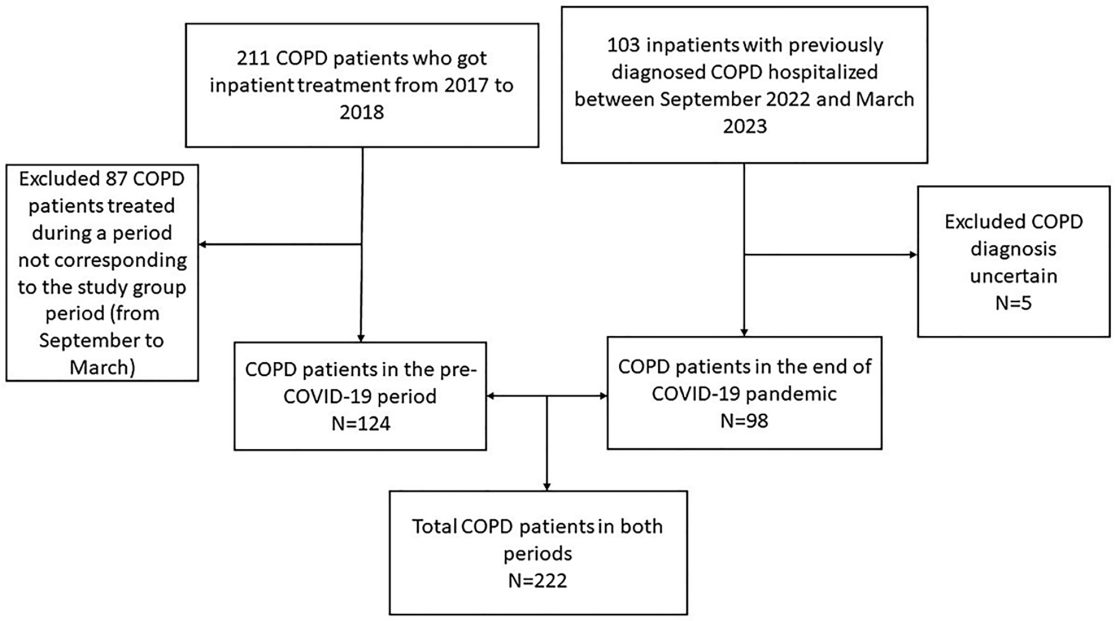

Figure 1. Flow chart of the study.

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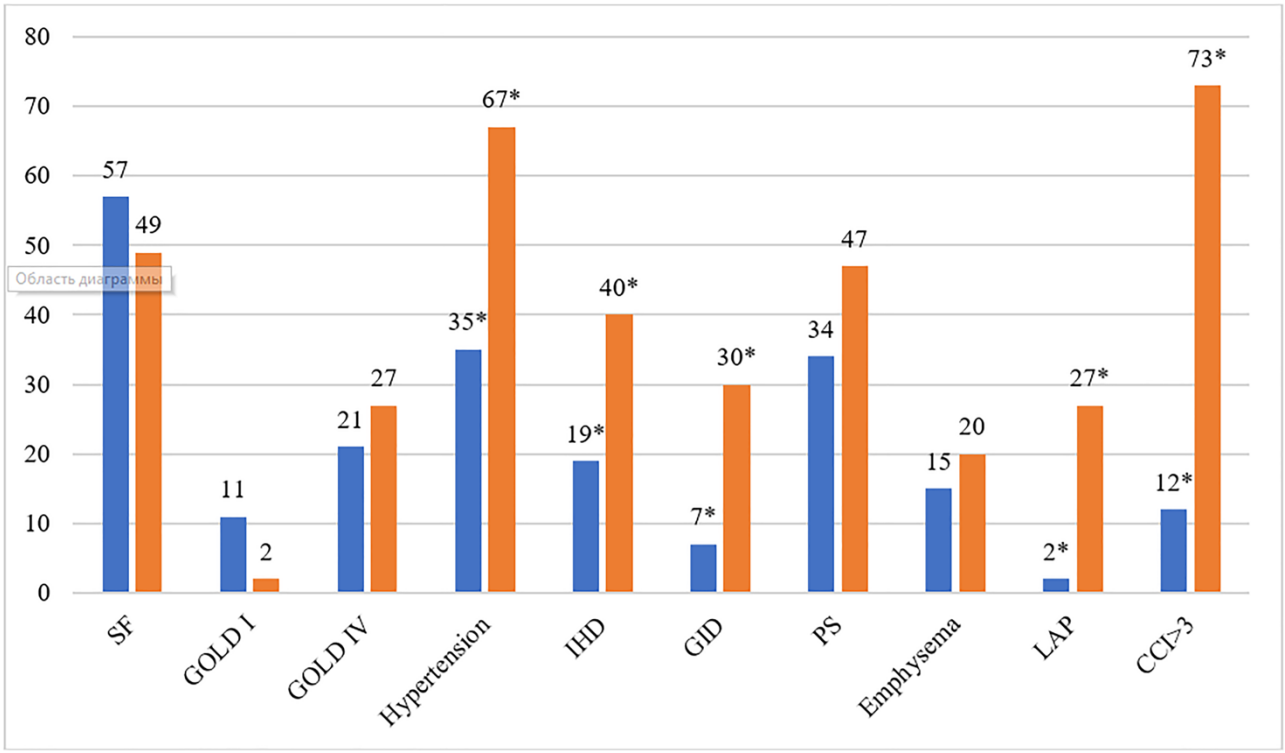

Figure 2. Patient's parameters with CODP depending on COVID disease, %. SF, spirometry function; IHD, ischemic heart disease; GID, gastrointestinal disorders; PS, pneumosclerosis; LAP, lymphadenopathy; CCI, Charlson comorbidity index. Blue columns, COPD patients in pre-COVID-19 period; orange columns, COPD patients in post-COVID-19 period, who had coronavirus infection; *p<0.05.