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Synergistic effects of COVID-19 and *Pseudomonas aeruginosa* in chronic obstructive pulmonary disease: a polymicrobial perspective

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Abstract

This article discusses the connection between the novel coronavirus disease 2019 (COVID-19) caused by the coronavirus-2 (SARS-CoV-2) and chronic obstructive pulmonary disease (COPD). COPD is a multifaceted respiratory illness that is typically observed in individuals with chronic exposure to chemical irritants or severe lung damage caused by various pathogens, including SARS-CoV-2 and *Pseudomonas aeruginosa*. The pathogenesis of COPD is complex, involving a variety of genotypes and phenotypic characteristics that result in severe co-infections and a poor prognosis if not properly managed. We focus on the role of SARS-CoV-2 infection in severe COPD exacerbations in connection to *P. aeruginosa* infection, covering pathogenesis, diagnosis, and therapy. This review also includes a thorough structural overview of COPD and recent developments in understanding its complicated and chronic nature. While COVID-19 is clearly linked to emphysema and chronic bronchitis at different stages of the disease, our understanding of the precise interaction between microbial infections during COPD, particularly with SARS-CoV-2 in the lungs, remains inadequate. Therefore, it is crucial to understand the host–pathogen relationship from the clinician's perspective in order to effectively manage COPD. This article aims to provide a comprehensive overview of the subject matter to assist clinicians in their efforts to improve the treatment and management of COPD, especially in light of the COVID-19 pandemic.

Keywords Emphysema · Chronic bronchitis · COVID-19 · COPD · Inflammation · Antibiotic resistance

Introduction

COVID-19 is caused by the SARS-CoV-2 virus and can result in mild to severe illness, including lung infections like pneumonia and acute respiratory failure. COPD is a chronic inflammation of the lungs that results in symptoms like breathlessness, cough with mucus, and wheezing. The prevalence of COPD cases globally is 3.7% and is often caused by tobacco use [1]. COPD patients exhibit a wide variety of clinical presentations and are classified into two main events, emphysema and chronic bronchitis, which can worsen if left untreated and lead to mortality. The loss of elasticity in the bronchial tubes causes chronic bronchitis, while a loss in surface area and increased lung volume causes emphysema [2]. The decreased exchange of gases, chronic cough, and sputum production can lead to respiratory failure, inflammation of the cardiovascular systems, and the development of systemic tumors, leading to a decreased quality of life. COVID-19 and COPD have similarities in symptoms, such as cough and dyspnea, and individuals with COPD are at higher risk for severe illness and mortality if they contract COVID-19 [3]. Reports suggest that shielding mechanisms should be put in place for these individuals. There is currently no evidence for the use of inhaled corticosteroids in treating COVID-19 or COPD exacerbations, and antibiotic resistance is a factor that needs to be considered. It is important for physicians and patients to work together to fight against COPD exacerbations by making lifestyle changes and exploring novel therapeutic options [4].

Differential diagnosis of the COVID-19 and COPD by symptoms

Physicians are having difficulty discriminating between SARS-CoV-2 symptoms, bacterial infection, and COPD exacerbations. COVID-19 and COPD both cause cough and shortness

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of breath. Additionally, most COVID-19 patients experience weariness, disorientation, muscle pains, and bacterial diarrhoea symptoms including nausea, vomiting, and headaches, among other things [3]. COVID-19 symptoms are mild at initially, but lung function quickly and severely deteriorate due to lung alveolar rupture. The prodrome of early mild symptoms appears to be more problematic in COPD suspects [5]. As a result, a lack of awareness of the differences between illnesses may cause a delay in early diagnosis and treatment. In cases of symptoms such as fever, impaired smell, gastrointestinal issues with COPD patients should be treated with extreme caution [6].

Initiation of the COPD in association with contagion

The smoke from cigarettes contains harmful substances such as nicotine, heavy metals, carcinogens, and oxidants, which can lead to the development of chronic obstructive pulmonary disease (COPD). In addition to this, exposure to cigarette smoke also increases the risk of infections such as *P. aeruginosa* and COVID-19 [7]. The SARS-CoV-2 virus, which causes COVID-19, attaches to a specific receptor molecule called ACE-2 (Angiotensin Converting Enzymes-2) found in the lungs [8]. The virus has a spike-like structure that helps it attach to and enter host cells, where it replicates and causes tissue damage [4]. The virus has a spike-like structure that helps it attach to and enter host cells, where it replicates and causes tissue damage [8]. Chemical particles formed from the toxic compounds in cigarette smoke can worsen the severity of COVID-19 infections by disrupting the respiratory system and triggering NF-kB-dependent inflammatory responses [9]. These NF-kB-dependent inflammatory particles are involved in the protection against the toxic produced by the smoke, but the loss of the NF-kB p50 subunits results in the amplification of the inflammatory responses to the smokes oxidants from tobacco, inducible nitric oxide synthase and toxic substances produced COVID-19 infection which directly causes damage to the alveoli and alveolar tree [10, 11]. The RTP801 protein, which inhibits growth and aids in apoptosis, is induced by virulence-inducing agents such as tobacco or SARS-CoV-2, leading to the formation of NF-kB inflammatory responses [12]. The Nrf2 transcription factor has been shown to play a role in the initiation and progression of inflammatory responses towards SARS-CoV-2 infections in the lungs [13, 14].

Progression of the disease to alveolar branches and its injury by SARS-CoV-2 as PPMs

Progression of the disease is more of like damage to alveolar branches and its destruction. According to the studies progression of the disease indecently causative of some intermittent molecules that are more clinically relevant in phenotypic variation such as emphysema and chronic bronchitis [15]. Emphysema is an event where the failure of the lung elasticity property which makes the loss of the alveolar cells leads to apoptosis and cell death. This event not only causes cell death but also leads to loss of growth factors, damage from oxidative stress, virulence keys from COVID-19, intracellular secondary responses to the chemical exposure or the smoke [16]. Interestingly, alveolar macrophages, which are found in the alveolar epithelial airways, are thought to be more resistant to the apoptotic effects of SARS-CoV-2, or cigarette smoke [17]. As a result, the lung may develop an apoptotic mechanism in order to survive the condition. Ceramides are a by-product of the smoke's apoptotic impact, which stimulates inflammatory responses directly [18].

COPD is also infected by a broad range of viruses and bacteria, which are the most prevalent causes of exasperation [19]. Infections by potentially pathogenic microorganisms such as SARS-CoV-2 and *P. aeruginosa*, which mimic or block-specific receptors, leading to the development of host–pathogen interactions and damage to the alveolar tree, are the major reasons of the event worsening [7, 20]. Damaged Nrf2 function results in a loss of protection against SARS-CoV-2 and *P. aeruginosa* activity, as well as the development of microbial exasperations [16]. When the lungs get infected with COPD and different contagions, the airways are the first system to be damaged, resulting in inflammation and the production of a large volume of mucus with a distinct appearance. The smaller alveolar pipes are surrounded by a large number of inflammatory cells, which promote intraluminal mucus deposition and the transmission of enormous live viruses from one person to the next [18].

End stage -consolidation with infections

The recent report suggest that the progression of the disease caused by other than cigarette smoke, says nothing to do with the current event, the progression of the disease is already responded to the inflammatory responses and continued worsening of the condition by SARS-CoV-2-depended mucus production [7]. This special feature was

activated by the temporary effect of the NF-kB in the lungs system stimulated by the synergistic actions of the SARS-CoV-2 infection with the oxidants. Later, the event and system involve the participation of the cytokines which makes the COPD as an autoinflammatory disorder (Fig. 1). There are many evidences reported for the activation of autoreactive T cells functioning or the production of the specific antibodies against the SARS-CoV-2 infections in COPD Exasperations [12, 21]. Inexorable damage to the lung tissues by the enormous oxidants and virions in addition supplemented by the loss of the immunity provided by the respiratory system leads to the aging of the lungs, lose in the elastic activity of the lung [22].

Relative sensitivity of the COPD individual to COVID-19

The SARS-CoV-2 virus enters the lungs in a sequential process involving the attachment of cellular components to the host individuals and forwarded by endocytosis, which is bridged by membrane bound spike-like viral protein particles with S1 receptor binding subunit and another protein called S2 membrane fusion subunit [5, 17]. Interestingly, SARS-CoV-2 exploits the ACE-2 leading to communication as a receptor molecule for cellular compartment attachment. There have been reports of increased ACE-2 activity owing to the presence of SARS-CoV-2 protein receptor spike mutations, as this creates a more convenient pathway for the virion particles to enter [23]. Furthermore, in the severe COPD individuals, loss of the Normal functioning of the ACE-2 results in increased inflammatory responses further leads to vasoconstriction and vascular damage. Once after the entry, the fusion between SARS-CoV-2 and host cells takes place with the help of spike-like proteins present on the surface of the virus, which uses the various proteolytic enzymes such as furin, transmembrane serine protease 2 (TMPRSS2) and cathepsin [24]. The pathophysiological conditions of the suspects from the COPD shows more sensitive to SARS-CoV-2 infections due to variations in production of ACE-2, regulation of this enzyme which is used as a key factor in reducing the SARS-CoV-2 infections in COPD individuals [10].

Pathophysiology with SARS-CoV-2, ACE-2 an open chapter?

Several studies have reported that smoking and exposure to toxic chemicals from cigars may enhance viral entry and attachment to ACE-2 receptors present in the lung cells, thereby increasing the risk of COVID-19 infection [17]. ACE-2 enzymes were found to be abundant in the nasal epithelium and decreased as they moved towards the lower respiratory tract, making them more sensitive to COVID-19 epitopes. In vitro studies have also shown that exposure to smoke can lead to cell metaplasia, mucus production, and cell death, which could make COPD individuals more vulnerable to COVID-19 [11]. IL-6, a proinflammatory cytokine, is known to emerge during severe exacerbations of COPD. However, a meta-analysis showed no correlation between IL-6 concentration and pulmonary function test in COPD individuals [25]. During viral infections, IL-6's action is negligible, and the cytokine release syndrome may be responsible for the "calumniatory" effect. Altered bursts of IL-6 in COPD have been reported, which may make the system more susceptible to SARS-CoV-2 in-burst. Upregulated concentrations of Th2/M2 cytokines, including IL-6, CCL22, IL-4, IL-13, and IL-10, were observed in the bronchoalveolar lavage of COPD individuals, with IL-13 being particularly elevated [26, 27].

Virion particles use the endocytic machinery to enter the host endocytic pathway and fuse with lysosomes. Reports suggest that an increase in endolytic proteins, such as EEA1, RAB-7, and LAMP-1, could facilitate viral entry and characterise the deregulatory mechanism of the endolytic machinery in the lungs of COPD individuals [28]. ACE-2 was found to stimulate autophagy and inflammation in the context of SARS-CoV-2 infection, but reports suggest that endocytic machinery failure and dysregulation could cause injury to endothelial cells, endothelial cell apoptosis, secondary inflammatory responses on vascular tissues, oxidative stress, and remodelling activities [21].

Synergistic corelations of COVID-19 and *P. aeruginosa* infections during the exasperations of COPD

P. aeruginosa is a Gram-negative bacillus commonly found in lung infections that cause morbidity and mortality, particularly in severe cases of chronic lung diseases like COVID-19 [22]. This bacterium is highly virulent compared to other microorganisms found in various medical materials. *P. aeruginosa* is commonly found in the respiratory tract due to its preference for a wet environment. Epidemiological features of *P. aeruginosa* in association with COPD have been studied, revealing a low prevalence in mild cases but an increased risk during acute exacerbations [24]. Studies have reported that *P. aeruginosa* clinical isolates are found more frequently in patients with severe airway obstructions and chronic bronchitis [10]. However, the link between bacterial colonization and severe airway obstruction is limited due to sample size, selection criteria, and antimicrobial therapy. Epidemiological studies from mechanically ventilated patients with AECOPD are challenging due to respiratory deterioration. FEV-1 is a good predictor for isolating the

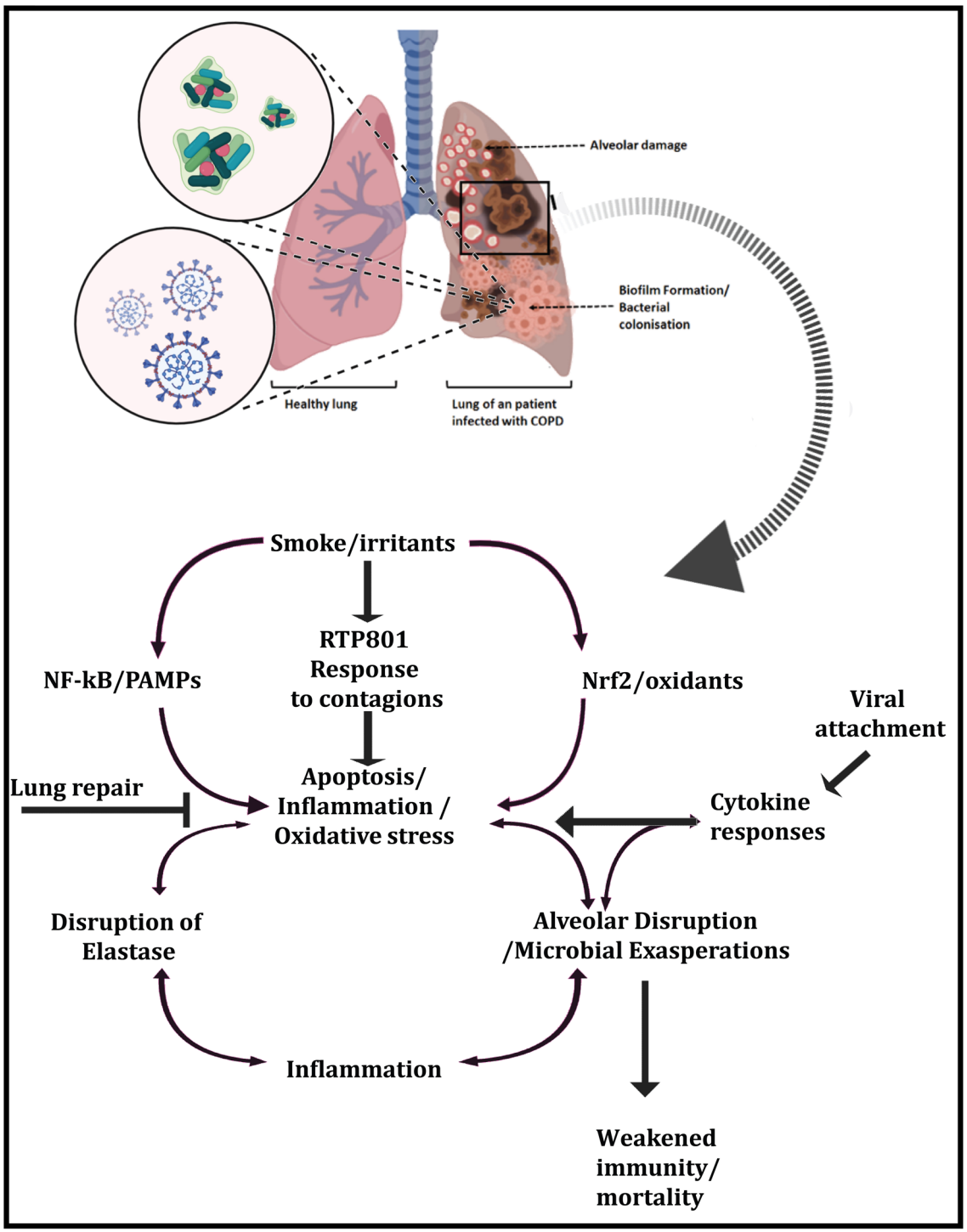

Fig. 1 The figure describes the pathogenesis and damage to alveolar branches in COPD, which can be demonstrated through the start, progression, and consolidation phases. Exacerbations are triggered by host cell responses that are greatly supplemented by inflammation and oxidative stress, and can be caused by exposure to irritants or smoke. Nrf2 can play a role in lung protection and repair. Consolidation occurs due to decades of exposure to tobacco irritants, which results in the lungs gradually decaying. Autoimmunity may cause an increase in TH17-positive cells in COPD patients, and telomere damage can result in a damaged lung

maximum number of *P. aeruginosa* during acute exacerbations of COPD, and antibiotic therapy for the bacterial isolates must be based on antibiogram predicted at the lower respiratory tract [29].Infections with SARS-CoV-2 and *P. aeruginosa* can lead to major chronic illnesses such as COPD and pneumonia. The pathophysiology of these infections reveals a hormonal liaison, from the organism's entry into the host to immune evasion and the development of purulent mucoidal sputum secretions, hypoxia, and the need for constant ventilator support during severe stages of the infection. Both types of infections induce large inflammatory cell responses, leading to an increase in pro-inflammatory cytokines detected in the pulmonary systems [30]. COVID-19 infections in the lungs are caused by the activation of the coagulation system, leading to poor diagnostic methods in distinguishing COVID-19 from *P. aeruginosa* infections. Endothelial dysfunction is also seen in cases of COVID-19 persistent infections and bacterial sepsis [28]. A systemic review analyzed recent trends in *P. aeruginosa* and SARS-CoV-2 infections and observed an imbalance in the antibiotic stewardship profile of *P. aeruginosa* after infection with SARS-CoV-2. The hospital environment allows bacteria to thrive in a wet environment, leading to the development of nosocomial infections. *P. aeruginosa* is rarely seen in healthy people's natural microflora but is more likely to be found in the gastrointestinal tract, throat and nasal mucosa, and notably in the lungs [20]. Production of mucoid colonies by *P. aeruginosa* is peculiar but distorted in patients suffering from SARS-CoV-2 infections due to the large amount of elastase produced, which causes host tissue damage and impairs normal lung function [31]. Rapid destruction of the lung parenchyma cells occurs in COVID-19 scenarios, resulting in the death of the individual. Antibiotics such as penicillin, ticarcillin, piperacillin, and aminoglycosides, including gentamicin, tobramycin, amikacin, meropenem, imipenem, ciprofloxacin, cefoperazone, and ceftazidime, are all effective against *P. aeruginosa* strains obtained in the community. Some clinical isolates of *P. aeruginosa* are intermediate to cephalosporins like ceftriaxone and cefotaxime, as well as monobactams like aztreonam [32]. Patients diagnosed with SARS-CoV-2 infections may exhibit varying antibiotic susceptibility patterns, with some drugs being sensitive and others intermediate. Nosocomial infections are a significant risk factor in most hospitals, leading to infections that are highly resistant to therapeutic drugs. Studies have compared antibacterial therapies for infections caused by acute exacerbations and chronic bronchitis to determine the prevalence of infection and its treatment. In order to combat SARS-CoV-2 infection with bacterial coinfections, endogenous anticoagulants such as anti-thrombin and activated protein C are being tested [33].

Protease-activated receptors (PARs) are G-coupled receptor molecules involved in various cell-mediated processes, including coagulation and inflammatory reactions. During incidents involving *P. aeruginosa* and SARS-CoV-2 in the lungs, four PARs are produced, resulting in severe tissue injury and degradation [34, 35]. *P. aeruginosa* is commonly found in severe chronic lung infections, including COPD and CF, especially in patients on mechanical ventilators in the ICU due to severe exacerbations. However, *P. aeruginosa* infections are not necessarily an indicator of more serious chronic lung disorders, and patients with severe COPD infected with *P. aeruginosa* are more likely to receive antibiotic therapy [23].

Post COVID-19 scenario during COPD

COPD prevalence varies across regions and countries. Understanding COVID-19's impact on COPD exacerbation is important. In a study, 1.5% of COPD patients with comorbidities experienced severe damage due to COVID-19, with a 50% mortality rate. COPD patients with COVID-19 have a higher probability of ICU admissions and mechanical ventilations, resulting in a worse recovery rate [36, 37]. Clinical management is not indicated in the early stages of COPD, and it is one of the variables linked with COPD's impact during COVID-19. Older COPD patients with respiratory failure are at a higher risk of severe COVID-19 and death Table 1.

A dominant infection, whether caused by bacteria or virus, may infiltrate the pulmonary area through a dominant key factor alteration in the host response to the current event, resulting in epithelial cell death and apoptosis. Similar publications on post-H1N1 viral infections have described 16 individuals with underlying pneumonia who were infected with a secondary infection from viruses with a high level of transforming growth factor-beta 1 (TGF-B1), known to promote fibrosis, and chemotactic migration, leading to a thick deposition of extracellular matrixes [44, 45]. The renin-angiotensin complex in the host was also discovered to have a greater affinity for binding with the SARS-CoV-2 spike proteins with the ACE-2, reducing the free ACE-2 receptor accessible by blocking the active epitope on the lung [46].

However, apart from the immune-cellular modification due to SARS-CoV-2 in the lungs, specific quorum secreted by *P. aeruginosa* during co-infection with COVID-19 can be considered as a "tributary." In continuation with the previous judgement, methylation resulting from N6-methyl adenine alginate, flagellar, and quorum sensing-associated genes, which are responsible for the production of robust exopolysaccharide-mediated biofilm, motility, and various virulence factors, respectively, could modulate the cellular functions as well as the luxuriant colonization of self, thus justifying the term "synergism" [47, 48]. The hypothesis was proven by the author through rt-PCR analysis of various

Table 1 The GOLD classification of COPD based on the symptoms and diagnostic criteria

Stages	Gold classification	Scoring criteria	Symptoms	Therapeutic measures	Bacterial colonization	Microorganism in colonization	Diagnostic methods	Reference
Stage 1: Mild	(A) Low risk Less symptoms	FEV1 > 80%	No symptoms	Short acting Bronchodilators	No colonization (–)	No reports on bacterial colonization	Bronchodilator reversibility test, spirometry, genetic counselling	Fabbri and Hurd, (2003); Murphy and Panos, 2013; Vestbo et al., 2013; Glogovskaet al., 2015; Eikhofet al., 2017; Eklöfet al., 2019; Tuder and Petrache, 2012; Huang et al., 2019 [18, 38–43]
Stage 2: Moderate	(B) Low risk more symptoms	FEV1 50–80%	Mild symptoms (Mucus less cough)	Long-acting bronchodilators (LABA)	Very low (+)	*P. aeruginosa* *Haemophilus influenza* *Acinetobacter boumannii* *Streptococcus pneumonia* *Klebsiella pneumonia* *Moraxella catarrhalis* *Enterobacteriacea* *Staphylococcus aureus*	Bronchodilator reversibility test, Spirometry,Genetic counselling	
Stage 3: Severe	(C) High risk less symptoms	FEV1 30–50%	Mid systemic exasperation (Sputum production, pleuritic chest pain)	Long-acting muscarinic antagonists (LAMA) and long-acting bronchodilators (LABA)	Low (++)		Bronchodilator reversibility test, Spirometry, Blood test, Genetic counseling, Sputum examination	
Stage 4: Very severe	(D) High risk more symptoms	FEV1 < 30%	Shortened and difficulty in breathing, Emphysema and Chronic Bronchitis Severe exasperations	Long-acting muscarinic antagonists (LAMA), Long-acting bronchodilators (LABA) and Inhaled corticosteroids (ICS)	High (++++)		Chest X-ray or CT scan, Spirometry, Blood test, Sputum examination, Genetic counselling	

genes (such as alg, CdrA, and Pel) in COVID-19 suppressed personnel [49]. A similar analytical approach was used to understand the modulatory effect of *P. aeruginosa* on alginate biosynthesis and the type IV secretion system in two COVID-19 infected patients, resulting in a robust study [47]. The author significantly contributed by describing the dependency of alginate-based genes for co-colonization during SARS-CoV-2 infection, as observed through rt-PCR analysis of the relative expression of hcp, clpV, vgrG, and tss/hsi genes. To support previous literature, analysis of the microbial contamination in the nasal areas of SARS-CoV-2 infected patients reported an increase in the abundance of *P. aeruginosa* as the SARS-CoV-2 net load increased, resulting in a re-modulation of the nasal transcriptome epithelial biome. The paper cited concerns regarding the severity of the "synergism" maintained [50].

Treatment strategy for COPD interference with COVID-19 as a contagion

The primary goal of pharmacological strategies is to prevent and control COPD symptoms, reduce severe exacerbations caused by infections like COVID-19, and develop immunity to such breakdowns. Antibiotic medication has not been effective in slowing the course of the disease, as it is considered the hallmark of the disease [49]. The only way to prevent the disease from progressing is to intervene to quit smoking and protect the patient from chemical irritants. Behavioural treatment is offered, coupled with pharmaceutical medications such as bupropion and nicotine replacement, to support the prior assertion. Patients are treated step-by-step, depending on the severity of their ailment, including COVID-19. The therapy should be long-term, with a consistent medication concentration maintained for several days, free of any side effects caused by COPD exacerbation [51]. The pharmacological treatment administered to each patient is different and should be constantly monitored. Treatment can be adjusted based on the severity and infectivity of coinfections such as COVID-19. A new class of treatment therapy, inhibitors of Phosphodiesterase type 4 (PDE4), is in the late stage of clinical trials for COPD [52].

Bronchodilators are one of the concept strategies based on short acting beta-agonists such as salbutamol, pirbuterol, isoetherine, bitolterol, and feneterol, as well as long-acting beta-agonists such as salmeterol and formoterol, which have been shown to have a higher mortality rate when used in COVID-19 patients with COPD [53]. Bronchodilators, such as anticholinergic and antimuscarinic drugs such as ipratropic bromide and methylxanthines, are usually administered through inhalation via aerosols, dry powder, or nebulizer [54]. These bronchodilators aid in the improvement and full emptying of the lungs during the expiration process, resulting in a decrease of sluggish hyperinflation during the resting stage tolerance provided during exercise. However, the effects of these bronchodilators are not fully apparent throughout the short treatment time. The change in forced expiratory volume in one second is a criteria for evaluating the effectiveness of bronchodilators [55]. Special caution should be exercised while administering systemic corticosteroids to COPD patients infected with COVID-19, as this increases survival rates. However, there have been reports of secondary negative effects of system corticosteroids on the host. Beclomethasone dipropionate, budesonide, flunisolide, fluticasone propionate, and triamcinolone acetonide are examples of glucocorticoids or inhaled corticosteroids. Mometasone and ciclesonide are two new glucocorticoids in clinical trials that are said to have a very long period of action within a day of administration against SARS-CoV-2 replication in vitro by stimulating non-structural protein called endoribonucleases, which aids the host in identifying viral double standard RNA particles and type 1 IFN responses [56]. Prodrug ciclesonide is triggered by esterase's which are said to have possible side effects. These medicines do not relax the smooth muscle of the respiratory airways, hence they have no impact on acute bronchoconstriction, and thus do not aid in the clearance of exasperations caused by SARS-CoV-2 [57]. These glucocorticoids function by adhering to cytoplasmic rectors, which then facilitate binding to regulatory proteins like as heat shock proteins and immunophilin. Thus, the conformational shift caused by the glucocorticoids–receptor complex results in regulatory protein dissociation, dimerization, and nucleus translocation, resulting in a change in parallel gene expression. The most prevalent and ultimate cause of COPD severe exasperations is viral and bacterial infections. As a result, these Corticosteroids are used in conjunction with long-acting Beta agonists (LABA) and LABA plus long-acting muscarinic antagonists as part of a combination treatment. In individuals with a greater eosinophil blood level, the impact of these steroids is more favourable [58].

Antibiotics and quorum quenchers to treat infections in COPD during COVID-19

When the bacterial infections that the physician suspects are variable, clinical approaches for treating the exasperations of COPD must be explored. The outcomes of clinical trial procedures are given a thorough examination in order to determine which treatments are most effective for patients. However, antibiotic treatment does not appear to provide relief from COPD's severe exasperations. These medicines are useful for treating exasperation when the suspect starts coughing or when the patient requires mechanical ventilation after the bacterial infection has been established. Bacterial infections were also recorded often during the COVID-19 in

many instances of severe COPD, where the risk factors for coinfection to death are quite high, and which are detected by multiplex PCR [59]. However, due to acute exasperations manifestations and other factors, isolating bacterial coinfections with COVID-19 is challenging. Ampicillin plus azithromycin, doxycycline, amoxicillin-clavulanate, trimethoprim-sulfamethoxazole, clarithromycin, and levofloxacin are among the broad-spectrum antibiotics suggested by the WHO to treat infections caused by COPD during COVID-19 [32].

Evident from the reports suggest that, a total of 50% of exasperated infections are non-bacterial, with a very low prevalence of antibiotic resistant infectious contagion producing infection. This statement is also supported by the drugs poor penetration power into the bronchial system and its fluids [20]. Combination therapy, such as inhalation of steroids and long-acting Beta2 agonists, mucolytics, and antibiotics, are reported to have a significant impact in preventing COPD exacerbations. However, the majority of antibiotic therapy clinical trials do not address or provide a clear structure of antibiotic treatment selection and its link to internal efficacy [60]. However, irrational and indiscriminate use of antibiotics to treat bacterial diseases resulted in the formation of multidrug resistant organisms. As previously mentioned, infectious bacteria multiply within cells through quorum sensing processes, causing acute exasperation of the respiratory system. These quorum sensing mechanisms result in the formation of biofilm, a highly resistant mass of polysaccharides that may grow on any surface [61]. The introduction of new quorum sensing inhibitor compounds aims to disrupt the quorum sensing process in bacterial cells [62, 63]. The inhibition of Quorum sensing mechanism is known as Quorum quenching which initiated by the blocking the quorum sensing by the enzymatic degradation of AHL molecules or Auto inducers. Many compounds produced from plants, algae, and fungus are effective in inhibiting the quorum sensing mechanism in most bacteria. Some naturally occurring compounds that are possible inhibitors of the QS system include horse radish-iberin [64], garliv-ajoene [65], turmeric-curcumin [66] and others. In most clinical trials, evidence of quorum sensing suppression has been found to be effective in controlling *P. aeruginosa* infection [61–69]. Many of the compounds, including those mentioned above, have a vital function in lowering microbe pathogenicity, and will be a unique treatment technique in the medical era.

Conclusion and future perspectives

The complex relationship between the infectious pathogen and host immunological response is crucial in determining the aspect ratio in respiratory disorders. The regulation of ACE-2 in pulmonary expression plays a critical role in inhibiting SARS-CoV-2 infections, which can impact the development of the disease. Exacerbations of COPD are significant criteria for mortality and can reduce the quality of life, working capacity, and require expensive treatments. The use of inhaled corticosteroids against SARS-CoV-2 infections or clinical outcomes related to COPD exacerbations lacks strong evidence. Antibiotic resistance is another feature to be considered, particularly in cases of coinfections associated with SARS-CoV-2 and *Pseudomonas aeruginosa*. COPD patients are more likely to acquire SARS-CoV-2 infections and experience higher mortality rates. Therefore, it is essential to address COPD exacerbation by changing lifestyles and introducing novel therapeutic approaches to combat these conditions.

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Author contributions S.K.B. collected the data, wrote the manuscript and prepared figures and R.P.S. designed the study, reviewed the data and corrected the draft.

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Declarations

Conflict of interest The authors declare that they have no conflict of interest.

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