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COVID-19 Pandemic: What Considerations Should Be Taken during the Assessment and Management of COPD Exacerbation?

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Abstract

The on-going coronavirus disease 2019 (COVID-19) pandemic could contribute to higher mortality in population with underlying respiratory diseases, including chronic obstructive pulmonary disease (COPD). The aim of this review was to inform readers pertaining to the correlation of COPD exacerbation and severe acute respiratory syndrome-2 (SARS-CoV-2) infection along with considerations that could be taken in the clinical diagnosis and management. The literature search was conducted on Google Scholar, Scopus, and PubMed databases using related terms (such as, but not limited to, "COVID-19," "SARS-CoV-2," "COPD management," "N-acetylcysteine," and "corticosteroids") on November 1–9, 2021. Recent studies suggest that COVID-19 and COPD are correlated through three pathways, namely, angiotensin-converting enzyme 2 expression, dysregulation of biological parameters, and occurrence of pneumonia. Early detection of COVID-19 in patients with underlying COPD is difficult because they share similar symptoms, attributed to advanced progression of the infection and subsequently deteriorates lung function. During COPD management, clinicians are expected to take consideration on the effect of systemic corticosteroids if patients develop COVID-19. In conclusion, COVID-19 and COPD and its management are potentially correlated, contributing to the worsening of the disease. There is a need of immediate research to reveal the true correlation between COVID-19 and COPD to improve the management.

Introduction

Coronavirus disease 2019 (COVID-19) pandemic has impacted multiple sectors not only in caused health problems [1], [2], [3], [4], [5] but also disrupted health-care services [6], environmental management, and economy [7], [8], [9]. Several drugs have been evaluated for COVID-19 [10], [11], [12], [13], [14] and vaccines are also available although the acceptance is difference among countries [15], [16]. In addition, policies also have been adopted in each country [17]. However, the pandemic continues around the globe. The wide spectrum of impact from the COVID-19 was also found in certain group of patients who experience worse impact from the severe acute respiratory syndrome-2 (SARS-CoV-2) infection [18]. In fact, people with underlying comorbidities are more likely to suffer severe course and progression of COVID-19 than those without [19]. A meta-analysis study revealed that respiratory system disease, as one of underlying diseases (others are hypertension and cardiovascular diseases), contribute to the risk factors of severe COVID-19 [20]. Worse COVID-19 symptoms were also reported in patients with chronic respiratory diseases compared to those without [21], [22].

A long-term lung disease, chronic obstructive pulmonary disease (COPD) is one of the non-communicable diseases, which has become a public health problem worldwide [23], [24], [25]. At least in every 4 min, there is one American experiences COPD-related death [26]. Exacerbations in COPD patients could be triggered by viral or bacterial infection (among others) [27]. With the on-going COVID-19 pandemic, hence, patients with underlying COPD could be more susceptible. The following discussions will include the possible and evidenced relationship between COVID-19 and COPD exacerbations. When the relationship exists, modifications on managing patients with COPD are expected. The latest recent work explaining the management for patients with COPD exacerbations and COVID-19 was reported more than a year ago [28]. With more knowledge obtained regarding the nature of SARS-CoV-2 and its correlation with COPD exacerbation, there are many updates that have not been covered in previous literatures. Hence, our work has a novelty in discussing the correlation

between COPD exacerbations and SARS-CoV-2 infection along with its management using updated research findings.

COPD Exacerbation

COPD is a common, yet preventable and treatable disease indicated by consistent respiratory symptoms and airflow restriction with abnormalities of airway and/or alveolar [25]. The worsening of this disease within a short duration is called COPD exacerbation, in which the sufferer may require medical care and specific treatment [24], [28], [29]. Based on the pathophysiological features, exacerbations associated with airway inflammation are local and systemic, leading to severe airflow obstruction, imbalance between ventilation perfusion and increased oxygen demand, pulmonary arterial pressure, and cardiac output [30]. Exacerbations could significantly impact COPD patients who are undergoing long-term management, related to patients' health status, quality of life, hospitalization length, and economic burdens [23], [31]. Recurrent exacerbations in COPD patients might result in dramatically increasing morbidity [32, [33]. Exacerbation-related repeated inflammation could reduce the 1st s forced expiratory volume (FEV1) and tissue damage concomitant to expiratory airflow obstruction which is followed by CO_2 entrapment in lungs [34].

Exacerbations in COPD are caused by various factors, and recent studies are still unable to reveal their exact cause. However, respiratory tract infections by bacteria, viruses, or atypical organisms have been found to play a major role in inducing the exacerbation [27], [35]. The presence of environmental pollution is also among the frequent causes of COPD exacerbations [36], [37]. Amidst the COVID-19 pandemic, concerns on COPD exacerbations are high since around a half of the total cases are caused by viral infections, which are predominated by rhinovirus and respiratory syncytial virus [27], [38]. Viruses could attack airway epithelium increasing its susceptibility against bacterial infections [27], [35]. It is unknown for sure, whether exacerbations are due to mutations of existing bacteria or the acquisition of new bacterial strains because bacteria are also often found in the sputum of clinically stable patients [35].

COVID-19

SARS-CoV-2 is a novel coronavirus that infects human with a human-to-human transmission through droplets/aerosol, close contact, or fomite routes [39], [40]. The virus has a close relationship with coronaviruses in bats as well as the SARS-CoV-1 virus that is responsible for acute respiratory syndrome (SARS). Penetration to host cells is facilitated by angiotensin-converting enzyme 2 (ACE2) receptor which is expressed in the human airway epithelium and lung parenchyma [41]. The novel virus is more dangerous than SARS-CoV-1 because it has stronger affinity with ACE2 receptor and higher infection rate [42]. Tiny droplets or aerosols, with a diameter ranged from 1 to 2000 μm, produced from an infected person could act as a transmission medium of the coronavirus [43].

Lungs become the primary targets of SARS-CoV-2 because relatively higher expression of ACE2 is found on the type II alveolar cells (AT2) [44]. However, lung is not the only organ with ACE2, where the protein itself is found in the epithelial cells of myocardial cells, renal tubules, and gastrointestinal cells [45]. Moreover, myocardial infarction is also the cause of ACE2 overexpression which contributes to the development of cardiac injury [46]. Consequently, SARS-CoV-2 infection could cause multiple organ failures [47]. Typical signs patients infected with SARS-CoV-2 fever, myalgia, fatigue, nausea, confusion, pains, headaches, dysgeusia, anosmia, diarrhea, and vomiting [48]. Cough, acute respiratory syndrome, and shortness of breath are respiratory symptoms experiences by COVID-19 patients [49]. Impacts of COVID-19 ranged from mild to severe, depending on the underlying condition of the patients. Patients with comorbidities, including COPD exacerbation, could receive worse impact of COVID-19 [50], [51]. Hence, it is important to elucidate the correlation between COPD and COVID-19.

Correlation of COPD Exacerbation and COVID-19

Although, it has been reported as the most commonly occurring comorbidities in SARS-CoV-2-infected patients, there are only a very few studies drawing correlation between chronic respiratory disease and COVID-19 [52]. Results from several studies suggest that the COVID-19 might worsen the condition of COPD patients along with the increasing risk for exacerbation [53], [54]. Indeed, a study conducted in China revealed significantly lower prevalence of chronic respiratory disease in patients with SARS-CoV-2 infection than that of general population [55]. Yet, studies from the United States and Europe, the prevalence of COPD in COVID-19 patients is at least as high as (if not greater) in the general population [56], [57]. Different results obtained by above studies might be attributed to the underdiagnosis

and misreporting of COPD among patients with SARS-CoV-2 infection [57], [58]. Some other studies agree that worse symptoms could be found if the infected patients have chronic respiratory diseases than patients who do not [21], [22]. Moreover, the stated group of patients experienced increased chance of being admitted to intensive care as well as increased mortality rate [50], [51]. Therefore, it is safe to conclude that there is an association between COVID-19 and COPD exacerbation, where some researches have tried to elucidate the underlying mechanisms as to how the virulence of SARS-CoV-2 plays a role in the exacerbation (Figure 1).

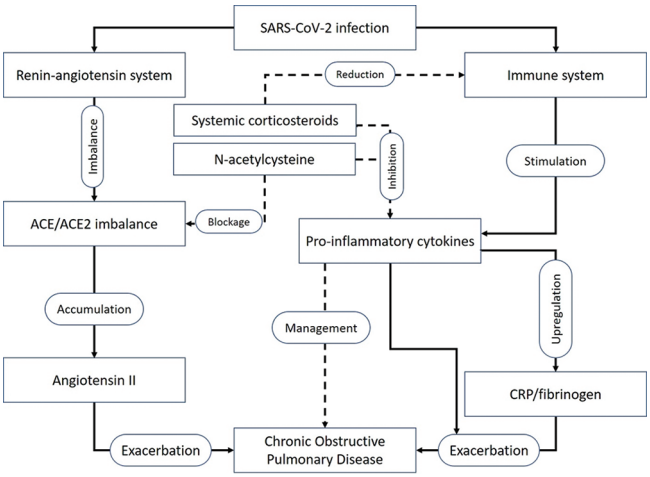

Figure 1: Relationship of SARS-CoV-2 infection with COPD exacerbation. Solid lines describe the role of SARS-CoV-2 infection in exacerbations of COPD. Dashed lines indicate the relationship of drugs given in the management of COPD patients with COVID-19

One of the proposed mechanisms is the involvement of ACE2; a protein expressed on the cell surface in various tissues, facilitating the penetration of SARS-CoV-2 into the host cells [59], [60]. In patients with COPD, this protein is found excessively expressed in the epithelium of the bronchioles [61]. Hence, there are possibilities of COVID-19 worsening through ACE2 overexpression in COPD patients. However, the problem with this proposed mechanism lies on the overexpression of ACE2, where a study in the US disproves the significance of different ACE2 release between COPD and healthy samples [62]. Moreover, ACE2 is downregulated on SARS-CoV-2 infection leading to the elevation of angiotensin (Ang) II plasma that is responsible for the increase of respiratory symptoms [63]. Taken altogether, the dysregulation of ACE2 seems to contribute to the susceptibility to the virus and severity of COVID-19 among patients with COPD which requires further scientific exploration.

Another proposed mechanism of the COPD exacerbation during SARS-CoV-2 infection could be based on the dysregulation of biological parameters including tumor necrosis factor-alpha (TNF-α), interleukin (IL)-6, C-reactive protein (CRP), lactate dehydrogenase, amyloid A protein, D-dimers, the ratio of neutrophils/lymphocytes, and cardiac troponin [64], [65]. The alteration of the stated parameters may not be dependent on the chronic respiratory disease [66], but the consequences received by the patients with COPD could be different in comparison to those without. For example, increase on TNF-α level during COVID-19 might contribute to the development of COPD exacerbation due to its role in bronchial hyperreactivity [67]. It is also known to be associated with a low maximal expiratory volume per second in patients suffering from COPD [68], which could possibly lead to the exacerbation when the COVID-19 occur.

Notably, the increased level of IL-6 correspond to SARS-CoV-2 infection could be linked to the degradation of lung function [69]. Its increased level has also been linked with higher mortality rate among patients with COPD [70]. IL-6 is also responsible for the upregulation of CRP and fibrinogen [71], in which these molecules were significantly increased in COPD patients [72]. In this case, COPD patients might experience more exacerbations and higher mortality rate [73].

Finally, pneumonia caused by COVID-19 could be proposed as the mechanism of viral infection-induced exacerbation in COPD patients. On the one hand, pneumonia is frequently present in COVID-19 patients, symptomatic or asymptomatic, observed during the advanced progression [74]. On the other hand, pneumonia significantly contributes to longer hospitalization of patients with COPD along with their need for artificial respiration [75]. This is also concerning for COPD patients because the use of inhaled corticosteroids (ICS) could lead to the increasing risk of pneumonia [76].

Symptoms and Clinical Features of Patients with COPD Exacerbation and COVID-19

COPD patients might not aware of the SARS-CoV-2 infection, especially during its early stage that is only present with mild symptoms. Nonetheless, lung function degradation could occur immediately on the progression into the next stage. Based on a study in the United Kingdom, COVID-19 symptoms among the COPD patients, other than the cough and breathlessness occupying 60% of the population, included diarrhea, vomiting, fatigue, nausea, confusion, pains, muscle aches, headaches, dysgeusia, and anosmia [48]. It is challenging in COPD patients to early detect the infection as they could have shown the same symptom before the infection. A preliminary observation, as of April 2020,

suggested that COPD patients were less likely to be tested for COVID-19 even when the mild COVID-19 symptoms had already been observed [77]. Hence, it is recommended to suspect the COPD patients for COVID-19 who have symptoms of an exacerbation, along with gastrointestinal, fever, dysgeusia, or anosmia complaints.

It is important to note that false-negative results for COVID-19 in RT-PCR tests have been found after confirmed using computed tomographic (CT), for which positive results were found later after serial testing [78]. Hence, patients with COPD presenting with fever, respiratory symptoms, or other COVID-19-related symptoms should undergo a series of tests for infection possibility (Figure 2). Clinicians should also keep in mind on the presence of coinfection by other pathogens [79]. Recurrence of COVID-19 symptoms is more likely in patients with underlying diseases or undergoing immunosuppressive therapies [80]. It implies the importance of repeat testing on the patients who have been recovered from COVID-19.

Regarding the use of chest radiography for COVID-19 diagnosis, it should be noted that its use on during early stage of infection is not reliable [81]. However, patients with moderate-to-severe COVID-19 symptoms could be indicated by abnormalities under chest radiography, where bilateral pneumonia is found in the most cases [82]. In asymptomatic COVID-19 cases, occurrence of pneumonia could be indicated by CT screening [83]. COVID-19 patients who have COPD tend to have higher local patchy shadowing, ground-glass opacities, and interstitial abnormalities on CT images than those who do not [84]. Pulmonary manifestations from SARS-CoV-2 infection might also be observed using point-of-care lung ultrasound [85].

Countermeasures for COVID-19 transmission risk during the diagnosis or treatment should be considered by either patients or clinicians. Face masks are useful in preventing the transmission of COVID-19 through droplets or aerosols [86]. The use of any face masks would not affect ventilation, even in patients with severely limited airflow [87]. Bronchoscopy on patients with COVID-19 positive should be postponed until the negative results obtained, where in emergency cases, a disposable bronchoscope is recommended [88]. SARS-CoV-2 transmission could occur when spirometry and pulmonary function tests were performed. Instead, peak expiratory flow accompanied by validated patient questionnaires could be performed for routine assessment of COPD patients. Indeed, the assessment could not replace spirometry, as the results from the assessment were not correlated with that of spirometry, leading to inability distinguishing obstructive and restrictive lung function disorders [89]. In such cases, remote diagnosis using personal electronic portable spirometer could be employed [90].

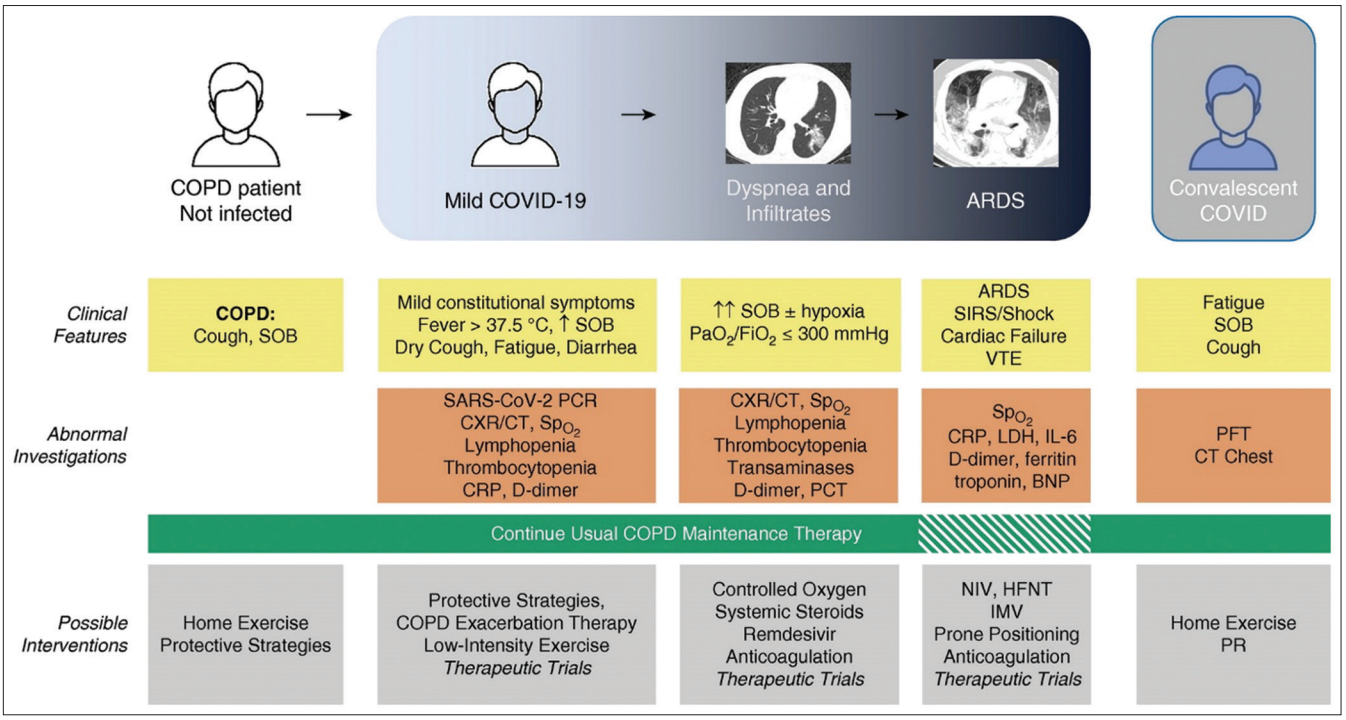

Figure 2: Clinical features and abnormal investigations shared among COPD patients infected with SARS-CoV-2, along with possible interventions. COVID-19 = coronavirus disease; COPD = chronic obstructive pulmonary disease; SOB = shortness of breath; ARDS = acute respiratory distress syndrome; SIRS = systemic inflammatory response syndrome; VTE = venous thromboembolism; CXR = chest radiograph; CT = computed tomography; SpO_2 = peripheral oxygen saturation; CRP = C-reactive protein; LDH = lactate dehydrogenase; PCT = procalcitonin; BNP = brain natriuretic peptide; PFT = pulmonary function tests; NIV = non-invasive ventilation; HFNT = high-flow nasal therapy; IMV = invasive mechanical ventilation; PR = pulmonary rehabilitation; reproduced under the terms of Creative Commons Attribution Non-Commercial No Derivatives License 4.0 citing [28]

Management of COPD Exacerbations during COVID-19

There is no particular different treatment for COPD exacerbation during COPID-19 pandemic. Severity of the underlying COPD exacerbation determines the type of treatment given to the patients. In fact, there are more than 80% of cases of exacerbation which could be managed on the patient without hospitalization, accompanied by pharmacological therapy such as bronchodilators, corticosteroids, and antibiotics [91]. In mild and non-infectious exacerbations, patients could be treated at home with a maintenance dosage of bronchodilators [92]. The bronchodilators might include short-acting beta-2-agonists, where combination with short-acting anticholinergics could be given when required [93]. Moderate level of exacerbations requires increased dosage of bronchodilators along with 5 days dosage oral corticosteroids [94].

Along with bronchodilators, corticosteroids are the mainstay of COPD exacerbation management [28]. Employing systemic corticosteroids could improve the recovery time, oxygenation, as well as pulmonary function and reduce the risk of early relapse, treatment failure, and hospitalization duration [95], [96]. During the primary care, 30 mg prednisolone should be given for 7 days [91], where its administration through oral route has been found as effective as the intravenous route [97]. Nonetheless, as also supported by the World Health Organization, a published review suggested to avoid the use of systemic corticosteroids for patients with mild-to-moderate COVID-19 [98]. Either inhaled or oral corticosteroids use in COPD treatment is suggested to be restricted for no longer than 3 months since it could lead to possible adrenal insufficiency [99]. Indeed, several studies show the protective effect of systemic corticosteroids for critically ill patients with ARDS or septic shock (where cytokine storm occurs) [100], [101]. Unfortunately, a study in the UK already reported the insignificance of the protective effect of inhaled corticosteroids toward COVID-19-related mortality [102].

If the exacerbations are caused by bacterial or viral infection, antibiotics treatment might be recommended [29]. Nonetheless, antibiotics for COPD exacerbation management restricted and should only be given when patients possess at least two of the three cardinal symptoms (elevated sputum volume, sputum purulence, and dyspnea) [28], [103]. Patients undergoing mechanical ventilation might also require antibiotics [28]. Preferability of antibiotics use in COPD exacerbations should be considered during the pandemic because of the increased bacterial coinfection prevalence in severe COVID-19 [104]. Moreover, patients with COPD and SARS-CoV-2 infection have been reported to be more susceptible against bacterial or fungal coinfections [84]. Indeed, in mild COVID-19 cases, the bacterial coinfection is not common [105]. Hence, according to the World Health Organization guidelines, patients with mild COVID-19 should only receive broad-spectrum antibiotics when clinical suspicion of bacterial infection is present [106].

Administration of mucolytics and anti-inflammatory agents, including the most common N-acetylcysteine (NAC), is also a part of COPD exacerbation management [107]. Mucus hypersecretion has been recognized as a sign of illness exacerbation along with infiltration of inflammatory cells [108], [109]. Furthermore, mucolytics in COPD exacerbation management may disrupt intramolecular interactions of the mucous gel. Once the mucus and remaining sputum are cleared, it allows the accessibility of inhaled drugs to peripheral airways [107]. In particular, NAC has been reported to improve the quality of life of patients with underlying COPD exacerbation [110]. Based on a meta-analysis, NAC is consistently proven to reduce the occurrence of COPD exacerbations with low adverse side effect [111]. Decrease on oxidative biomarkers and improvement on oxidative stress balance on the administration of NAC were observed in COPD patients [110]. Moreover, anti-inflammatory and antioxidant effects from NAC are not only beneficial for COPD patients [112] but also for COVID-19 patients [113]. As a thiol donor, NAC is also a blocker for pulmonary ACE2 reducing the penetrating ability of SARS-CoV-2 into host cells [113], [114].

Conclusion

Impacts of COVID-19 could be experienced worse, along with higher probability of being admitted to intensive care and mortality rate, in patients with underlying COPD than those without. Susceptibility to COVID-19 is increased by the alteration of ACE2 expression in COPD patients, though it still requires further investigation. Exacerbations of COPD could be triggered or worsened by COVID-19 because of the dysregulation of biological parameters. Pneumonia, commonly occur in severe SARS-CoV-2 infection, is also a triggering factor for COPD exacerbation contributing to more days of hospitalization. Despite its difficulty, early detection of SARS-CoV-2 in patients with underlying COPD is mandatory to prevent further pulmonary function deterioration.

At present, main treatment of COPD exacerbation during COVID-19 pandemic has no significant change. When COPD patients do not develop COVID-19, they could be treated at home along with protective strategies. In general, the management of COPD exacerbations includes therapies with bronchodilators, corticosteroids, and antibiotics. In the presence of SARS-CoV-2 infection, systemic corticosteroids should be carefully prescribed

because of possible adrenal insufficiency, leading to higher susceptibility against COVID-19. Moreover, inhaled corticosteroids potentially contribute to the increasing risk of pneumonia. It is recommended to administer systemic corticosteroids by considering the severity of the COVID-19. In addition, antibiotics are recommended when patients develop COVID-19 to prevent bacterial coinfection. Management of COPD exacerbation through the administration of NAC is potential for treating COVID-19 which requires further investigation. More changes in the management of COPD exacerbation in patient with COVID-19 are expected in the future as more studies will unveil the correlation of both diseases.

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