Health-related risk of SARS-CoV-2 infection in chronic obstructive pulmonary disease patients: A systematic review

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1. INTRODUCTION

The global pandemic resulting from the increasing viral diseases has affected the health facilities around the world. Millions of individuals around the world are at serious risk of developing multiple viral infections. Several life-threatening diseases have emerged in recent times and one of them is Coronavirus Disease-19 (COVID-19) that is caused by a novel strain of coronavirus (SARS-CoV-2) [1,2]. COVID-19 is an emerging infective disease that primarily affects the respiratory system and has directly impacted the lives of millions of people worldwide [2]. A similar type of virus was previously identified, namely, the Severe Acute Respiratory Syndrome (SARS) virus in the year 2003, and the Middle East Respiratory Syndrome (MERS) coronavirus in the year 2012 [3,4]. Both of these viruses belong to the single-stranded RNA family responsible for respiratory syndrome in humans. The newly identified strain from the zoonotic origin (COVID-19) also belongs to the same family containing a positive sense of single-stranded RNA genome with similar clinical symptoms to MERS and SARS [5]. They are also responsible for causing significant human mortality as well as increasing the number of major public health issues worldwide. COVID-19 is a respiratory and systemic disease that can progress to severe hypoxemia in as many as 15–20% of suspected and confirmed cases requiring some form of ventilator support. The World Health Organization (WHO) has declared this a pandemic [6]. This disease outbreak has led to 102,083,344 cases globally and 2,209,195 deaths in 194 countries, till 11th Feb 2021 [7,8]. Chronic obstructive pulmonary disease is characterized by the progressive worsening in lung function capacity with an increase in the rate of exacerbations that drive a great deal of disease morbidity and death. Early detection of chronic obstructive pulmonary disease (COPD) is a prime concern to manage this disease but an increase in the number of viral disease and change in lifestyle has become one of the reasons for the progression of the disease. Worsening of symptoms with an increase in exacerbations resulting in admission to hospitals and severe infection are the significant events associated with COPD [7]. Several factors, such as obesity, age-related factor, and...
underlying health issues, have been identified to make a significant contribution to the worsening of COPD symptoms along with the viral infection as the primary cause, especially the new coronavirus. SARS-CoV-2 is the recently emerging virus epidemic that affects mainly the respiratory tract and lung functions [9]. As COPD and COVID-19, both are considered as a respiratory illness, so, some common symptoms which inter-relate the COVID-19 with COPD are coughing, shortness of breath along with an increase in the rate of exacerbation in severe cases. Other commonly reported symptoms include fatigue, gastrointestinal disturbance, anosmia, and sputum production [10]. Changes in local or systemic immune response, excessive mucus production, weakened host immunity, structural damage to the lungs, microbial imbalance, and usage of inhaled corticosteroids (ICS) inter-linked with cytokines can contribute to the risk of COVID-19 [11].

A hyperactivated immune response to the infection results in the development of fatal clinical signs accompanied with an excessive release of inflammatory cytokines, known as the cytokine storm. In both SARS and MERS infections, the cytokine storm has a negative impact on the host, resulting in severe consequences and multiple organ failure. Through trans-repression of gene transcription, corticosteroids decrease pro-inflammatory cytokine synthesis in a variety of cell types. ICS medication has been demonstrated to lower inflammatory cell counts in the lungs in investigations using bronchoscopy and sputum samples. While these anti-inflammatory actions protect against COPD exacerbations, corticosteroids may also enhance infection susceptibility through molecular pathways. ICS treatment was found to enhance the risk of pneumonia in COPD patients with chronic bacterial infection or low blood eosinophil counts in a recent longitudinal cohort study. The mechanism underlying the link between ICS and increased bacterial presence and pneumonia incidence has yet to be discovered [12,13]. This systematic review, which together with angiotensin-converting enzyme-2 (ACE-2), will explain the risk factors of COVID-19 in COPD patients along with the use of nebulizers with mesh to prevent transmission, and adherence to medication in the world’s current pandemic situation.

2. DATA SOURCE AND STUDY SELECTION

The systematic search was performed in electronic databases such as PubMed, LitCovid, COVID-Evidence, Clinical Trials, and Science Direct. The relevant search strategy and keywords (such as “Novel coronavirus” or “COVID-19” or “SARS-CoV-2”) were used to collect information on the novel coronavirus. Additional keywords (such as “COPD and COVID-19” or “Role of ACE-2 in SARS-CoV-2” or “COVID-19 and respiratory diseases”) were used to collect all useful information for this review. The additional search was carried on Google scholars and COPD medical literature. The search was carried out systematically for the screening of the related content [Figure 1]. Initially, a total of 372 publications were retrieved from different databases and 82 articles were deleted due to duplication. The remaining articles have been carefully reviewed in order to determine the eligibility and methods used. In the end, 30 articles were used which met the inclusion criteria and 16 more articles were referred for the present review work. The articles were thoroughly evaluated, and articles with improper methodology were excluded. The information from the articles on COVID-19 with COPD patients was selected as the main base for the review. Information on COPD patients infected with COVID-19 was collected and inclusion criteria were severity rate and admission to the intensive care unit. Information was extracted in a simplified form, with methodological details, research characteristics, subjects, patient details, and outcomes. All the collected data were combined and reviewed for health-related risk for COPD patients with COVID-19.

3. UNDERSTANDING SARS-COV-2 AND ITS PATHOPHYSIOLOGY

Three waves of human coronavirus infections have emerged in the last two decades, SARS-CoVin 2002, MERS in 2012, and the current SARS-CoV-2 in December 2019. The infection caused by any of these coronaviruses has pneumonia-like symptoms, such as dry cough and fever leading to respiratory failure and death in a few cases [14,15]. SARS and MERS triggered epidemics in various countries, whereas
SARS-CoV-2 having high transmission and infectivity rates resulted in a drastic rise in the number of infections across the globe, contributing to the development of this infection into a disease outbreak and pandemic like situation [1,16]. The SARS-CoV-2 incubation period ranges from 2 to 14 days, and asymptomatic transmission occurs before the initial diagnosis [17]. Virus transmission is believed to be primarily through coughing or sneezing.

The live-effective virus has been isolated from aerosols lasting up to 3 h, with an approximate half-life of 1.1 h. In addition, after 3 days of application on stainless steel and plastic surfaces the virus was found to be effective and viable. The genome of SARS-CoV-2 has also been found in the blood and stool of an infected person, and whether the virus can be transmitted by exposure to non-respiratory body fluids is not yet known [18]. Coronavirus pathophysiology will help us in understanding its infectivity and its viral entry into the cell [Figure 2]. The novel coronavirus is 26–32 KB large in size contains a single-stranded RNA genome. The genome of viral RNA is located within a nucleo-capsid, which is stored inside a viral membrane. This membrane/envelope consists of different proteins, one of which is a membrane protein, and the other one is envelope protein, both of which are primarily responsible for viral infection along with spike protein, which facilitates the entry of viral genome into host cells. The spike proteins play a significant role in the initiation of human infection, as well as in assessing the specificity of the host tissue and inducing an immune response from the host. The spike protein of coronavirus consists of two distinct subunits that facilitate the binding of the viral host. The spike protein domain S1 functions in viral binding and binding to the membrane of the host cell. To date, various receptors mostly on cellular membranes involved in the binding of the S1 subunit have been reported, such as the ACE-2, CD26, cyclophilins, and ezrin. The spike protein S2 domain is accountable for the convergence of the viral and host cell membranes, making it easier for the SARS-CoV-2 genome to enter the host cell. This mechanism involves interaction between the viral genome and the host genome, resulting in rapid replication of the viral cell [19]. Global research programs are currently in the process of using the spike protein S1 domain as a basis for vaccine development and therapeutic antiviral therapy.

The observed increase in binding efficiency of SARS-CoV-2 S-glycoprotein to the host receptor can be attributed to codon mutations in the protein sequence, resulting in a plausible increase in site-specific priming activity of proteases and cathepsins, resulting in SARS-highly-CoV-2’s contagious nature as compared to SARS and MERS [20]. The ubiquitous involvement of proprotein convertase family proteases, including as furin and furin-like serine proteases, in viral entrance and spread was investigated. These furin and furin-like proteases were found translocated through secretory routes to access viral S-protein and facilitate viral entrance to host cells, despite being synthesized in the endoplasmic reticulum and playing a role in viral biosynthesis.

A recent study found evidence for the presence of a furin-like cleavage site in SARS-spike CoV-2’s protein, which was not seen in other beta coronaviruses. It was previously shown that, when compared to less pathogenic influenza virus strains, highly pathogenic strains have a furin-like cleavage site that is replaced by a single basic residue cleavage site in less pathogenic viruses. Another group of researchers linked the presence of a furin site in the envelope protein to higher levels of plasminogen in COVID-19 patients with severe disease [19,21]. Further research focusing on site-specific binding studies could be a strategy for identifying potential druggable targets involving various proteases and specific peptide inhibitors. Aside from the aforementioned structural proteins, there are several non-structural proteins encoded by genes located within the viral RNA genome, namely non-structural protein (NSP)1 to NSP10 and NSP12 to NSP16 [22].

4. IS THERE A POTENTIAL RISK OF DEVELOPING SEVERE FORMS OF COVID-2019 IN COPD PATIENTS?

COVID-19 is reported as a global epidemic. Although many patients infected and confirmed with COVID-19 had moderate symptoms, just 20% of patients reported severe or extremely serious illness, with signs and symptoms of pneumonia, septic shock, respiratory failure, and organ damage. Importantly, a near-fatal rate of 1–2% occurred in people with severe underlying chronic conditions, such as COPD and cardiovascular disorders [17]. Despite this, the cause for specificity and severity is completely unknown. One possibility is ACE-2 receptor expression, the key receptor used by SARS-CoV-2 to penetrate the host mucosa and induce active infection. Other than the ACE-2 receptor, obesity has become one of the risk factors for worsening of symptoms in COVID-19 [21].

Figure 2: Viral entry of the SS-RNA genome of SARS-CoV-2 into the host cell and the steps involved in its replication [3,19,20].
The identified genomic sequence of the novel SARS-CoV-2 has a similarity of 79.6% with that of the SARS-CoV. In addition, the virus uses the same receptor that SARS-CoV uses to enter the host cell. As far as COVID-19 is concerned, the ACE-2 receptor, the identified target receptor responsible for SARS-CoV-2, was observed to increase in COPD patients [23]. However, early research findings of COVID-19 have not consistently reported significantly higher rates of serious illness in COPD patients [2]. As reported by the Centers for Disease Control and Prevention, the COVID-19 outbreak has put the patient with COPD and other co-morbidities at high risk. Although limited official data and published reports on COPD patients with COVID-19 are available, a recent report published in the European Respiratory Journal analyzed 1590 hospitalized cases in China and showed a low incidence of COVID-19 in COPD patients (24 cases) with a co-morbidity rate of 25.1%. Furthermore, after accounting for smoking status and age, COPD patients had a major effect on risk to adverse outcomes expressed by a hazard ratio (HR) of 2.681 (95% CI: 1.424–5.0480). As a risk factor, the rate of co-morbidity in COPD patients was second only to malignancy with a HR of 3.50 (95% CI: 1.60–7.64) [24].

A study was conducted at St Paul’s Hospital in Vancouver, Canada, in which all COPD patients with forced expiratory volume <70% or clear evidence of emphysema were selected. Research findings demonstrated a significant increase in the ACE-2 expression in epithelial cells in COPD patients compared to the normal group. Interestingly, the smoking status of COPD patients was also strongly associated with the level of ACE-2 expression. The study demonstrated a high level of ACE-2 in current smokers compared to non-smoking patients. Former patients with a history of smoking had levels of gene expression in-between those who never smoked and current smokers. Present smokers were at higher risk of severe complications and higher mortality compared to former smokers and non-smokers [25]. However, there is no complete evidence and data to summarize its role, but it seems to have a significant role to play in blood pressure and cardiovascular function. The role of ACE-2 in airways and its physiological function is mostly unknown, but the role of ACE-2 in mice has been shown to protect animals from a severe lung infection, prevent tissue damage in the airways, and sepsis [26]. Although the up-regulation of the ACE-2 enzyme may be helpful in protecting host cells from an acute lung injury, this may put COPD patients at higher risk of COVID-19, which uses this receptor to gain entry into epithelial cells of the lungs. Another study also indicated that there is a gradual increase in ACE-2 expression in bronchial epithelial cells in patients who are overweight [27]. Obesity is, therefore, one of the factors that result in an increase in the ACE-2 receptor in COPD patients and puts them at higher risk for infection with COVID-19. So those COPD patients with current smoking status, overweight, and exacerbations related to viruses are at high risk to COVID-19 and other viral respiratory infections [25].

Data from seven different studies are combined in Table 1, which includes 50 COPD patients out of 3,112 reported with COVID in their analysis.

Findings suggest that 66% (33/50) patients reported as severe compared to 34% (17/50) non-severe [Figure 3]. This shows that COPD patients are at a higher risk of more severe COVID-19 compared to patients without COPD [2,24,28-32]. Information from three different studies, including 29 confirmed cases of COVID-19 in COPD patients, shows a mortality rate of 58.62% (17/29) compared to a mortality rate of 24.23% (134/553) in non-COPD patients [10,33,34].

Table 1: Refractory patients’ profile from seven different study protocols.

<table>
<thead>
<tr>
<th>Study outcome</th>
<th>Total patients</th>
<th>Severe cases out of total</th>
<th>Number of COPD patients</th>
<th>Refractory patients with COPD</th>
<th>Reference number</th>
</tr>
</thead>
<tbody>
<tr>
<td>41 cases registered with confirmed COVID-19 were admitted to hospital from 16 December 2019 to 2 January 2020 (local health authority) and caused serious respiratory illness requiring ICU admission and high mortality.</td>
<td>1590</td>
<td>254</td>
<td>24</td>
<td>15</td>
<td>Guan et al. [24]</td>
</tr>
<tr>
<td>The presence of comorbidities such as hypertension, COPD, malignancy, cardiovascular disease, diabetes, cerebrovascular disease, kidney diseases, and immunodeficiency) increases the risk of health-related outcomes. From the total hospitalized patients, 399 patients were having above listed comorbidities, and 1191 patients were without any underlying disease.</td>
<td>1099</td>
<td>173</td>
<td>12</td>
<td>6</td>
<td>Guan et al. [28]</td>
</tr>
<tr>
<td>173 patients were classified as serious cases according to the guidelines by the American Thoracic Society for Community Acquired Pneumonia with severe respiratory illness and 926 as non-severe cases of COVID-19.</td>
<td>155</td>
<td>85</td>
<td>5</td>
<td>4</td>
<td>Mo et al. [29]</td>
</tr>
<tr>
<td>Patients with underlying comorbidities (severe patients) were kept on oxygen support (n=102) and ventilator support (n=36).</td>
<td>62</td>
<td>33</td>
<td>1</td>
<td>1</td>
<td>Xu et al. [30]</td>
</tr>
<tr>
<td>The symptoms were relatively mild and only one patient had ARDS and was admitted to ICU.</td>
<td>140</td>
<td>58</td>
<td>2</td>
<td>2</td>
<td>Zhang et al. [31]</td>
</tr>
<tr>
<td>58 severe patients were reported by the Chinese National Health Committee according to the SARS-CoV-2 diagnostic and treatment guideline. Of all the patients admitted, only 2 had COPD. 82 were non-severe.</td>
<td>25</td>
<td>9</td>
<td>5</td>
<td>4</td>
<td>Li et al. [32]</td>
</tr>
</tbody>
</table>

COPD: Chronic obstructive pulmonary disease, ARDS: Acute respiratory distress syndrome, ICU: Intensive care unit.
Following standard protocol, oxygen therapy should be given. Studies have shown that corticosteroids can affect innate immune system to delayed clearance of the virus from the body. In general, the use of ICS in COPD patients is linked with an increased incidence of respiratory tract infections. A systematic review of 43 randomised controlled trials of inhaled fluticasone (n = 21,247) and budesonide (n = 10,150) in COPD patients found that ICS may increase the risk of non-fatal serious adverse pneumonia events (requiring hospital admission) by 62% (OR 1.62, 95% CI: 1.00–2.62) to 78% (OR 1.78, 95% CI: 1.50–2.12) but not mortality, and this appears to be a drug-specific [36]. In COPD patients, the use of ICS is associated with an increased incidence of pneumonia but not with a change in respiratory virus detection [37]. In vitro studies have shown that corticosteroids can affect innate immune function against the virus, and the use of ICS has led directly to delayed clearance of the virus from the body. In general, the use of steroids results in a low eosinophilic count that can disable the body’s immune system to fight against any kind of disease. However, the use of ICS reduces the symptoms and exacerbation rates in COPD patients. If patients with severe symptoms of COPD stop taking ICS or decrease their ICS dose inappropriately in response to immunosuppressive concerns and concerns about the progression of COVID-19, they may be at serious risk of exacerbation. About 40–60% of COPD exacerbations are caused by viral diseases, including newly identified coronavirus strain [38,39]. Thus, the use of ICS must reduce the risk of exacerbation in COPD patients or alter the resulting inflammatory response of the immune system and lung damage.

Data on the overall or differential effects of ICS on COVID-19 are still lacking, though a recent in vitro study suggested not only their safety but also a COVID-19 preventive effect. Another study discovered that ciclesonide and mometasone inhibited SARS-CoV-2 replication by targeting viral NSP-15. Similarly, another in vitro study of budesonide and bronchodilators (glycopyrronium and formoterol) revealed inhibitory effects on coronavirus human coronavirus-229E (HCoV-229E) replication and cytokine production in human respiratory epithelial cells. As a result, there is no reason to suspect a direct pathological relationship between ICS use and COVID-19 [40].

So, it is strongly recommended to discourage its use in COPD individuals who are not frequent exacerbators, particularly those with low blood eosinophilic counts.

There is evidence that suggests that taking ICS may be effective in preventing viral infections, particularly those caused by a coronavirus. A combination of formoterol and glycopyrronium with budesonide, in the treatment of respiratory epithelial cells in vitro, has shown inhibitory actions on the replication of HCoV-229E strain and cytokine development [41]. A recent study in China found no benefit of using ICS and also demonstrated no risk of corticosteroids use while treating COVID-19 patients with COPD based on previous SARS experience. However, they also conclude that ICS should not be used outside the clinical trial for the treatment of COVID-19 induced lung injury [42].

5. USE OF ICS: AN IMMUNOSUPPRESSIVE AGENT

The current epidemic scenario caused by the novel COVID-19 raised a significant issue with the use of ICS in COPD patients. ICS is widely used for the treatment of COPD in combination with other long-acting bronchodilators. ICS is considered to be an immunosuppressive agent. ICS is absorbed into the systemic circulation from the lungs, has relatively low side effect when given in low concentration, but have systemic side effects when given at high concentration to COPD patients and increases the risk of developing pneumonia. A number of observations have been made about its effects on viral infections and exacerbation levels that are important to the COVID-19 pandemic when considering the use of ICS [35]. The use of ICS in COPD is linked with an increased incidence of respiratory tract infections.

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6. PRECAUTION AND MANAGEMENT STRATEGY FOR COPD PATIENTS

COPD patients should take the necessary safety precautions because they are at an increased risk of developing a more severe infection than others. Clinical management also sets out measures for the prevention and control of infections, as well as supporting treatment, including additional oxygen and ventilator support where necessary. National Institute for Health and Care Excellence and the Global Initiative for Chronic Obstructive Lung Disease (GOLD) initiative has proposed new guidelines for COPD patients who tested positive for the new infection with COVID-19 [43,44]. GOLD and WHO are actively working together to reduce the risk of COVID-19 infection in COPD patients. GOLD also reported that there is no evidence available to date to discontinue the use of ICS or oral corticosteroids in COPD patients during the outbreak of this disease. Precautionary measures for COPD patients as well as for patients with other respiratory conditions are as follows:

- When there are signs of a viral infection of COVID-19, and when patients have a history of travel from the red zone in the past 40 days, they should quarantine at home for the next 14 days.
- People with symptoms of COVID-19 should stop visiting family members before the quarantine period is over.
- Patients with COPD should continue their daily therapy and contact their physician for any health-related queries.
- Following standard protocol, oxygen therapy should be given when needed.
- Constant monitoring of patients and storage of medicines and other essential supplies that can last for several weeks.
- Stop non-essential journeys and stay at home safely.
- It is advised to take the COVID-19 test if any family member has symptoms of coronavirus infection.

In COPD patients, most of the treatment regimens require inhalers and inhalation device to reduce the symptoms. Pressurized metered-dose inhalers (pMDIs) and Dry powder inhalers for aerosol drug delivery are some of the best approaches for patients with mild to moderate symptoms, instead of using nebulizers. Use of nebulizers with a high flow nasal cannula or mouthpiece if DPI or pMDI raises cough or if the individual has an acute respiratory failure [44,45]. When administering aerosolised medicines, add filters to nebulizers as there is a high risk of being infected with COVID-19. Do not use a pMDIs.
or jet nebulizer for delivery of aerosols to COVID-19 patients who are dependent on ventilators. Use nebulizers with mesh for patients with COPD who are on ventilator support with COVID-19. If a mesh nebulizer is used, attach a filter to the other end of the mouthpiece to prevent the release of aerosols into the environment. The most important goal during the management of COPD is to prevent its exacerbation. Treatment of COVID-19 patients varies from that for pulmonary diseases that need aerosol therapy. Even so, it is important to presume that all patients may be affected during the pandemic, so a good personal hygiene practice and adequate precaution for the administration of aerosols must be implemented. Apart from following a basic hygiene, it is also advised for COPD patients to not withdraw or miss their routine medications, which should include the administration of systemic steroids that form an important part of their routine treatment.

7. IMPLICATIONS FOR POLICY AND PRACTICE

The summary of the data of this review is confined by the available information, particularly the lack of knowledge on how the newly emerging coronavirus increases the potential risk to patients with COPD. However, the finding indicates that the incidence of COVID-19 infection in patients with COPD is less so far due to fewer data available, but the risk of severity is high. So, self-management and advanced care planning are, therefore, the main focus for COPD patients. Additional data are needed to implement the use of ICS in COPD patients infected with COVID-19. A dual dose inhaler with the long-acting muscarinic antagonist and long-acting beta-agonist should be recommended for patients with mild to moderate symptoms and the addition of ICS under close monitoring for COPD patients with a severe condition. The use of pMDIs or jet nebulizer is not recommended in patients who are on ventilator support. It is strictly advised to COPD patients to adhere to their treatment regimen for better health-related outcomes and use a mesh with nebulizers to prevent the transmission of COVID-19 to other health care workers.

8. CONCLUSION AND FUTURE DIRECTIONS

Based on the findings of the search carried out and the available evidence from the study seen in this analysis, COPD individuals are at significantly increased risk with newly emerging COVID-19 when compared to non-COPD patients. Patients with COPD are recommended to take more preventive measures to avoid future SARS-CoV-2 exposure and contact with reported or suspected cases. The rise in ACE-2 expression in the respiratory tract of patients with COPD may also contribute to an increased risk of severe COVID-19. More evidence and data are still needed to promote the advancement of effective treatment and the use of ICS for COPD patients with COVID-19. Health professionals should be aware that there is no evidence supporting the removal of ICS in patients diagnosed with such infections, and doing so can be risky. COPD patients who are stable while using ICS should then continue their therapy. In fact, respiratory failure is the leading cause of death in a group of patients with severe COPD and requires ICU care. However, the rise in the mortality rate in COPD patients in the current epidemic may be due to the limited availability of respiratory support systems and ventilators in the COVID-19 management program, which depends on the critical care services available in each hospital or region.

Overall, considering the increased risks of nebulizers for a COPD patient being infected with COVID-19 use of nebulizers can be refrained unless during hospitalization. Treatment should instead include the standard methods such as the use of systemic steroids for severely infected or hospitalized patients. For the others, a basic treatment with the routine steroids will help counter the virus from developing severe symptoms. Apart from the routine pharmacotherapy, vaccination (influenza and pneumococcal), and rehabilitation should be encouraged to prevent infections and its associated hospitalizations.

9. AUTHORS' CONTRIBUTIONS

All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; agreed to submit to the current journal; gave final approval of the version to be published; and agreed to be accountable for all aspects of the work. All the authors are eligible to be an author as per the International Committee of Medical Journal Editors (ICMJE) requirements/guidelines.

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12. ETHICAL APPROVALS

This study does not involve experiments on animals or human subjects.

13. DATA AVAILABILITY

Data sharing is not applicable to this article as no new data were created or analysed in this study.

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