Tobacco Use and the Risk of Suffering from COVID-19

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Introduction

At present, global attention has been directed toward the disease of coronavirus (COVID-19), a respiratory infection lead by coronavirus 2 (severe acute respiratory syndrome coronavirus 2 [SARS-CoV-2]) [1] and resulting a respiratory syndrome in severe and acute condition. This illness case was detected first at the end of 2019, specifically December, in district of Wuhan, China; after which the virus spread rapidly over 27 countries [2]. By identifying the global impact, on January 30, 2020, the World Health Organization (WHO) stated that the outbreak of the disease was resulting from coronavirus was a global health emergency [3], [4]. It is reported that the disease caused the high mortality rate. This respiratory infection caused death above 2858 cases, and infected patients more than 83,652 cases globally. This COVID-19 led to the worst mortality rate in Wuhan [3].

The respiratory infections, such as mild-to-severe cold, were predominantly transferred by respiratory droplets, which were produced from individuals with respiratory diseases. These droplets are typically produced by the coughing and sneezing people and are transmitted to other people through direct or indirect contact [1]. On the other hand, the contagious nature of COVID-19 leads to the high fatalities among smokers in China, as well as following up references or primary articles. The search was conducted from April 23 to 24, 2020, adopting the use of several terms, such as "tobacco use" AND "COVID-19", "tobacco use" AND "SARS-CoV-2", "smokers" AND "COVID", "cigarette" AND "SARS-CoV-2", and "tobacco use" AND COVID-19 AND SARS-CoV-2.

CONCLUSION: Tobacco use among smokers and former smokers is significantly correlated to the decline in the status of the human immune system and worsen the disease prognosis. In addition, smoking status is associated with a greater likelihood of smokers being infected with SARS-CoV-2; a condition that can further develop into coronavirus disease.
and smokeless tobacco, the world needs to consider action to de-normalize the use of tobacco and highlight the issue of users’ and companies’ corporate social responsibility [7], [8], [9], [10]. Tobacco use has been widely acknowledged as being related to a range of negative health issues such as: (i) cardiovascular defects, (ii) respiratory diseases, (iii) cancer, and (iv) reproductive health, as well as other adverse impacts on health. However, the policy of public health for a smoke-free worldwide covers <20% of the world’s population [10].

The association between smoking activity and either transmission or fatality among confirmed COVID-19 patients has been given little attention [6]. The use of cigarettes and other nicotine delivery modes is open to debate: Whether or not tobacco use contributes to the high number of smokers who have been identified as COVID-19 cases. This review explores the matching evidence-based publications to provide arguments in an effort to respond to this important contemporary issue.

Methods

Study Design and Data Collection

Considering the limited amount of literature on COVID-19, proposing a systematic review was as irrelevant among the heterogeneous types of studies [11] as a theoretical qualitative meta-analysis [12]. Therefore, a narrative literature review is employed to obtain an argument to answers the polemic [13].

The analysis focused on compiling the relevant literature published in 2019–2020, from the beginning of the pandemic until April 23 and 24, 2020, when the search took place. The primary concern of the study is the relationship between tobacco use, either conventional cigarettes or smokeless ones (e-cigarettes), and the COVID-19 incident. A keyword search on EBSCOhost and ProQuest databases was performed to identify the articles, followed by a further search manually for other relevant publications. The search terms included “tobacco use,” “smokers,” “e-cigarette,” in combination with “COVID,” and “SARS-CoV-2.” Meanwhile, a manual search of various relevant journals, such as Tobacco Induced Diseases and the European Respiratory Journal, was included as the other reference list of original articles found with the equal search terms. The data collection identified 18 articles, consisting of seven journal articles and 11 academic-related reviews.

An evaluation of the methodological research context was excluded from the study as a systematic review of the papers was deemed inappropriate, due to the very limited number of publications focused on the target issue.

Ethical Consideration

There is no ethical clearance needed for the study as it used secondary data from several data bases.

Results

The review classifies two major domains describing the relationship between COVID-19 and cigarette or tobacco use among current and former smokers.

The first group of studies focused on chemical substances in cigarette or Electronic Nicotine Delivery Systems (ENDS). There are five studies [14], [15], [16], [17], [18], [19] exploring the effect of smoking in the human body that decreases the immune system’s effectiveness and therefore makes it vulnerable to hosting yet more infections. The following references are shown in Table 1:

Evidence from this group provides perspectives on: (a) The COVID-19 fatalities who were smokers, and (b) the number of patients who recovered, and the severity of organ injuries experienced by the patients, correlated with their COVID-19 prognosis.

The second group of studies employed the role of angiotensin-converting enzyme 2 (ACE2), which has a significant correlation with the lungs’ function. The risk of coronavirus infection among smokers is higher as the upregulation of ACE2 is the predisposing factor [20]. Seven studies emphasized how (ACE2) (Table 2), is correlated with the COVID-19 infections and how that led to more severe conditions in smokers; ultimately with fatal conclusions for many [1], [4], [6], [15], [20], [21], [22].

Discussion

Smokers are more susceptible to respiratory viruses, as the receptor of ACE2 could be “up-regulated” by smoking. ACE2 is known as the receptor or main binding sites of various respiratory infections [1], such as SARS-CoV, and the human respiratory coronavirus NL6386. The classification of smoking also includes the use of electronic devices and the heated model (IQOS device) [6].
The analysis of this study is presented in the two main themes, namely: (a) The role of smoking and other tobacco use devices in depressing the human immune system and (b) the increase of COVID-19 receptors among current and former smokers compared to non-smoking patients.

### Human immune system

The recent study on coronavirus infected patients portrayed a prognosis among 19 participants: Twelve smokers and seven former smokers [3]. Half of those current smoking groups died, indicating that...
COVID-19 risk is higher in the group of people with a constantly unhealthy behavior and lifestyle [18], [19]. In general, smoking behavior repressed the effective function of the human lung and provoked further inflammation. Particularly for those using the most recent electronic smoking devices, greater repression resulted than for those patients using conventional cigarettes due to the activity of immune and inflammation response genes in the smoker’s nasal cells [17]. The capacity of the innate immune system to curb viral replication is diminished by smoking effects, which downregulate CXCL-10, a chemokine that takes a role into macrophages, neutrophils, and natural killer cell recruitment [15].

A further review revealed that waterpipe use [14] and conventional smoking were associated with the adverse progression and detrimental prognosis of COVID-19 [16]. Smokers experience a higher risk of respiratory infection complications than non-smokers, as tobacco destroys ciliated epithelium and reduces lung protection by disrupting the ciliated epithelium’s function, which produces mucus and rapid clearance pathogens [15]. Besides, this unhealthy behavior was also associated with the adverse prognosis of acute respiratory distress syndrome [14].

In addition, smoking activities increase hand movements to the face repetitively; a habit which could potentially contribute a route for the viral entries [23]. The use of the waterpipe smoking apparatus was also recognized as increasing the risk of COVID-19 spreading with the nature of communal waterpipe smoking and sharing the apparatus’ mouthpiece, especially in social settings [14]. Furthermore, countries with considerable levels of COVID-19 outbreaks, such as China, South Korea, and Italy, were identified as countries with high populations of smokers [23].

**COVID-19 receptors**

Human ACE2 has a good binding affinity with SARS-CoV-2 spike proteins. Therefore, it is worth considering a suggestion that ACE2 is more efficiently recognized by SARS-CoV-2 correlated to the previous SARS-CoV, which leads to the latest virus transmission ability from person to person [2], [6], Table 2. Host cell entry and viral replication require ACE2 [4], [22]; thus its over-expression heightens the disease severity [2], [6], [15] resulting in the coronavirus using this receptor (epithelial cells) to gain entrance [20], [22] into the epithelial cells. ACE2 was “upregulated” in the smokers’ airway epithelium and it was reported that smokers have higher ACE2 gene expression compared to non-smokers [6] and, as such, have a significant correlation with lung function [20]. These findings indicate that smokers are more vulnerable to the SARS-CoV-2 infection and possibly COVID-19 [6]. Figure 1 illustrates the process of enhanced expression of ACE2 in lung tissue resection of chronic obstructive pulmonary disease (COPD) subjects and smokers with a healthy lung function. It is necessary to remind that ACE2 is absent from the non-smoking people’s samples [6].

The viral processes and human immune response are essential biological processes related to genes associated with ACE2 [21]. CS induces the ACE2 expression patterns in the lower respiratory tract [20], and its elevation was revealed in intrapulmonary airways and oral epithelial cells among smokers [21]. ACE2 expression was observed to be significantly reduced after a long period of smoking inactivity; an outcome that even led some patients to quit their smoking habit [21]. This condition is identified to promote a further attention relating to people using waterpipe smoking [24], as well as those who switched to the electronic cigarettes and “heat-not-burn” IQOS devices [25]. Thus, both conventional and the most recent smoking devices present high risks of their users suffering from serious lung infection [25].

Another study described more detail regarding ACE2 gene expression in the airways among smokers; a level which is significantly higher compared to former smokers and non-smoking groups (smokers=2.77±0.91, former smokers=2.00±1.23, and non-smokers=1.78±0.39) [20]. This susceptibility to the bacterial and viral infection in the lung is higher among
### Table 2: The role of angiotensin-converting enzyme 2 on COVID-19 cases

<table>
<thead>
<tr>
<th>S. No.</th>
<th>Authors/Year</th>
<th>Title</th>
<th>Purposes</th>
<th>Research Design, population, and instrument</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Zhang et al. (2020)</td>
<td>Angiotensin-converting enzyme 2 as a severe acute respiratory syndrome coronavirus 2 receptor: molecular mechanisms and potential therapeutic target. Sars-cov-2 and coronavirus disease 2019: What we know so far: Pathogens</td>
<td>Review the rationale for angiotensin-converting enzyme 2 receptor as a specific target</td>
<td>Research design: Literature review Sample: selected 35 articles Instrument: biochemical interaction studies and crystal structure analysis</td>
<td>The human Angiotensin-converting enzyme 2 is proven to have strong binding affinity with severe acute respiratory syndrome coronavirus 2 spike protein.</td>
</tr>
<tr>
<td>2</td>
<td>Rabi et al. (2020)</td>
<td>Smoking Upregulates Angiotensin-Converting Enzyme 2 Receptor: A potential adhesion site for novel coronavirus severe acute respiratory syndrome coronavirus 2 (COVID-19).</td>
<td>A summary of current knowledge regarding the novel coronavirus and the disease it causes</td>
<td>Research design: Literature review Sample: Studies of 82 articles related to Covid-19 Instrument:-</td>
<td>The findings among smokers that Angiotensin-converting enzyme 2 gene expression was increasing significantly</td>
</tr>
<tr>
<td>5</td>
<td>Leung et al. (2020)</td>
<td>Smoking Upregulates Angiotensin-Converting Enzyme 2 Receptor: A potential adhesion site for novel coronavirus severe acute respiratory syndrome coronavirus 2 (COVID-19).</td>
<td>Determined whether patients with chronic obstructive pulmonary disease have increased expression of Angiotensin-converting enzyme 2 in bronchial epithelial cells in lower respiratory tract</td>
<td>Research design: Mixed method Sample: Patients undergoing bronchoscopy at St. Paul’s Hospital, Vancouver, Canada, which were required to be 19 years of age or older Instruments: Cytological brushing using RNeasy Mini Kit (Qiagen, Hilden, Germany); FastQC; RSEM (RNA-Seq by Expectation Maximisation); Limma; voom; the Cornell Dataset; British Columbia Cancer Agency cohort; the Bond Polymer Refine Red Detection kit on a Leica Bond Autostainer; Krasul-Watts with Dunn’s Multiple Comparisons tests</td>
<td>Smoking expressed gene levels of the participants airway was significantly correlated with current smoking status. This higher gene expression was found among smokers compared to non-smokers samples.</td>
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<td>6</td>
<td>Wang et al. (2020)</td>
<td>Susceptibility analysis of COVID-19 in Smokers Based on Angiotensin-converting enzyme 2</td>
<td>Determine whether cigarette smoking is a susceptibility factor for COVID-19</td>
<td>Research design: Statistical analysis Sample: The samples in GSE8994 were obtained from intrapulmonary always from normal smoking and non-smoking volunteers (including 34 current smokers, 23 never smokers, and 18 former smokers). The overall design of GSE17913 involved oral biopsy from 40 current smokers and 40 age- and gender-matched never smokers. We also extracted 55 samples from 14 different groups in the GSE18344 dataset, including a sham group (sham) and exposure group. The mice in the exposure group were continuously exposed to cigarette smoke (750 μg total particulate matter/L) for 2, 3, or 4 h/day (our low, medium, and high dose groups, respectively) Instruments: Three datasets (GSE994, GSE17913, and GSE18344), were downloaded from the Gene Expression Omnibus (GEO) database</td>
<td>Genes associated with Angiotensin-converting enzyme 2 were enriched in important biological processes such as viral processes and immune response. Elevated Angiotensin-converting enzyme 2 was found in intrapulmonary always (GSE8994) and oral epithelial cells (GSE17913) of smokers but not those of non-smokers or former smokers. Significant dose- and time-dependent relationships between current smokers and angiotensin-converting enzyme 2 expression were observed in mouse lung tissues, and long periods without smoking were found to significantly reduce angiotensin-converting enzyme 2 expression.</td>
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<td>7</td>
<td>Zhou et al. (2020)</td>
<td>A pneumonia outbreak associated with a new coronavirus of probable bat origin</td>
<td>Report the identification and characterization of a new coronavirus (2019-nCoV), which caused an epidemic of acute respiratory disease in humans in Wuhan, China</td>
<td>Research design: 4PCR-based detection method Sample: Seven patients with severe pneumonia Instrument: High Pure Viral RNA kit (Roche); anti-SARS-CoV IgG and IgM ELISA kits; Lopidiforme 3000; BGI MGESE/D0000 and Illumina MiSeq 3000 sequencers; DNAStar; MAFFT (v. 7.307); PAL2NAL (v. 14); Clustal Omega (v. 1.2.4); RAXML (v. 0.9.0)</td>
<td>This study shows that 2019-nCoV is 96% identical at the whole-genome level to a bat coronavirus. Pairwise protein sequence analysis of seven conserved non-structural proteins domains show that this virus belongs to the species of SARS-CoV. In addition, 2019-nCoV virus isolated from the bronchoalveolar lavage fluid of a critically ill patient could be neutralized by sera from several patients. Notably, this study confirmed that 2019-nCoV uses the same cell entry receptors—angiotensin converting enzyme II—as severe acute respiratory syndrome coronavirus.</td>
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smokers due to the damage caused by their smoking habit [6]. The SARS-CoV has the 80% homology with SARS-CoV-2 and is using the cell entry receptor, ACE2 [26]. A current research explored the possibility of two other receptors, namely, DC-SIGN and L-SIGN, finding that the DC-SIGN has higher gene expression among the lungs of former smokers [26].

Conclusion

As tobacco use is positively correlated with the presence of ACE2, a molecule for novel adhesion on SAR-CoV-2, and which can reduce human immunity towards new infection, it is essential to collect all data on the status of smoking and confirmed cases of COVID-19. The potential of coronavirus exacerbations and deceased cases need to be further investigated by taking into account tobacco use; including water pipes, ENDS, and “heat-not-burn” devices, IQOS. Furthermore, as this pandemic affects the global population, a comprehensive policy decision regulating the use, distribution, and advertisement, as well as the promotion and sponsorship activities of cigarette and other tobacco-related products should be prioritized, based on the WHO Framework Convention on Tobacco Control.

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