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Review article

Smoking and COVID-19: What we know so far

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ABSTRACT

The ongoing COVID-19 pandemic has placed a spotlight on infectious diseases and their associations with host factors and underlying conditions. New data on the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) virus are entering the public domain at a rapid rate such that their distillation often lags behind. To minimise weak associations becoming perceived as established paradigms, it is imperative that methodologies and outputs from different studies are appropriately critiqued and compared. In this review, we examine recent data on a potential relationship between smoking and COVID-19. While the causal role of smoking has been firmly demonstrated in regard to lung cancer and chronic obstructive pulmonary disease, such associations have the benefit of decades' worth of multi-centre epidemiological and mechanistic data. From our analysis of the available studies to date, it appears that a relationship is emerging in regard to patients with a smoking history having a higher likelihood of developing more severe symptoms of COVID-19 disease than non-smokers. Data on whether COVID-19 has a greater incidence in smokers than non-smokers is thus far, contradictory and inconclusive. There is therefore a need for some caution to be exercised until further research has been conducted in a wider range of geographical settings with sufficient numbers of patients that have been carefully phenotyped in respect of smoking status and adequate statistical control for confounding factors.

1. Smoking and non-communicable airway disease

The World Health Organization (WHO) estimates there are approximately 1.1 billion daily smokers globally at present, which is projected to increase to 1.3 billion daily smokers globally by 2025 [1]. Tobacco smoke is a complex mixture of more than 5000 chemicals/carcinogens/toxins [2], and is one of the major sources of exposure to chemically-mediated diseases in humans, and perhaps in other living organisms [3]. Smoking is one of the risk factors for the development and worsening of multiple respiratory diseases, including infections [4,5]. In particular, tobacco smoking is one of the main contributors to respiratory diseases that include chronic obstructive pulmonary disease (COPD) and lung cancer [6,7]. Smoking is also an independent risk factor for community-acquired pneumonia (CAP) due to disruption in the repair of respiratory epithelium and reduced bacteria clearance from the airways [8,9]. Furthermore, epidemiological studies have highlighted the role of smoking in the establishment of active tuberculosis (TB), reduction in *anti*-TB immunity, and TB-related mortality [10–14]. The WHO presented worrying statistics that lung-related deaths due to smoking, including second-hand smoke, totaled 3.3 million in 2017 and included 1.5 million people dying from chronic respiratory diseases and 1.2 million deaths from cancer (tracheal, bronchus and lung) [15].

Smoke exposure results in infiltration of inflammatory cells into the mucosa, submucosa, and glandular tissue, which in turn induces the excess production of mucus, causes epithelial-cell hyperplasia, interrupts tissue repair, thickens the small airway walls, induces emphysema, and impairs lung function including gas exchange [16]. Inflammation and injury to the pulmonary epithelia are induced when the airways are exposed to inhaled particulates (e.g. cigarette smoke; CS) [16]. This leads to the activation of transforming growth factor–β

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(TGF-β) in the airway epithelium [16,17]. During this process, CS also interrupts the TGF-β signaling, which causes alveolar macrophages to release pro-inflammatory mediators, facilitating inflammation and fibrosis in the airway [16,18].

CS exposure also activates and stimulates production of various inflammatory mediators, such as interleukin (IL)-8, TNF-α, IFN-γ, and IL-1β from infiltrating immune cells. CS and these cytokines induce the release of reactive oxygen species (ROS) and reactive nitrogen species (RNS), which further amplify inflammation, leading to mucus hypersecretion and alveolar wall destruction [19,20]. The various ROS, along with the proteolytic enzymes, cause further tissue damage [21]. CS also induces the release of various mediators that activate the epidermal growth factor receptor (EGFR) [22,23]. This leads to metaplasia of normal pseudostratified epithelium into goblet cells because of the altered expression of mucins, whereby the COPD patient experiences abnormal sputum production and chronic cough [22,23].

CS-induced injury to airway epithelial cells also causes the release of various danger-associated molecular patterns. These signals are recognized by pattern recognition receptors (PRRs), such as Toll-like receptors 2 and 4 on epithelial cells, which trigger non-specific, inflammatory responses including the release of TNF-α, IL-1β and IL-8, and the influx and activation of macrophages, neutrophils, and dendritic cells at the inflammation site to commence the innate immune response [24,25].

2. Smoking and respiratory infection

Cigarette smoking, including active, passive and third-hand smoke exposure, is an important risk factor for upper and lower respiratory tract infection [26,27]. A large meta-analysis of nine studies (n = 40, 685) reported that current smokers are five times more likely to develop influenza infection than non-smokers [28]. A history of smoking has also been significantly associated with increased risk of hospitalization due to influenza infection, particularly in the elderly [29]. Crucially, an association between second-hand smoke exposure and influenza-associated hospital admissions in children below 15 years of age has been reported [30]. This highlights that both active and passive smoking could substantially increase influenza infections in all age groups. Similarly, infections with human rhinoviruses (HRVs) are more pronounced in smoking or exposed individuals than those who are non-smokers [31]. HRVs are major viral pathogens that cause exacerbations of COPD and asthma. Venarske et al. have reported that asthma patients hospitalized for HRV-induced exacerbations are more likely to be current smokers than non-smokers (odds ratio: 11.2) [31].

There are multiple mechanisms through which smoking or exposure to cigarette smoke may increase the risk of viral infections. These include alterations in airway biology, such as activation of the epithelium and hallmark structural changes in the respiratory tract such as impaired mucociliary clearance, mucus hypersecretion, fibrosis and epithelial barrier dysfunction, as well as alterations in the immune response [28,32–35].

Cigarette smoke extract (CSE) has been shown to modulate chemokine production, with increased IL-8 and reduced IL-10 production, from human airway epithelial cells when stimulated experimentally with HRV [36]. This could potentially result in an altered immune cell profile in the airway lumen. Another study showed that HRV-treated bronchial epithelial cells exhibited a marked downregulation of the IFN–STAT-1 and SAP–JNK pathways and the suppression of CXCL10 and CCL5 production that accompanied increased viral RNA expression [37]. Importantly, CS has been shown to affect the cell-mediated immune response through elevated peripheral immune cell counts, CD4+/CD8+ cell ratio in the lungs, phagocytosis impairment, and Natural Killer cell dysfunction [38–41]. Moreover, CS is also known to disturb the humoral immunity, with lower immunoglobulin levels in serum but higher levels in the lungs, in both human and animal studies, which have been reviewed elsewhere [42]. Another potential mechanism by which CS increases the risk of viral infections could be upregulation of viral adhesion receptors in the respiratory tract. For instance, smoking has been shown to increase the expression of Intercellular Adhesion Molecule-1 (ICAM-1), which is a known receptor for HRV [43]. Crucially, blocking ICAM-1 with *anti*-ICAM-1 monoclonal antibody has been found to inhibit HRV-induced exacerbations of lung inflammation in an experimental mouse model [44].

3. Emergence of SARS-CoV-2 and the COVID-19 pandemic

Coronavirus disease 2019 (COVID-19) was first reported in December 2019 in Wuhan, China and is caused by a novel coronavirus named Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). On December 31, 2019, the WHO Country Office in China notified the WHO Western Pacific Regional Office of several cases of unusual pneumonia that occurred in Wuhan, China [45]. On January 11, 2020, China announced its first death from the virus [45]. However, at that time, no evidence was reported that the virus was spread by human-to-human transmission. Soon after, other countries including the United States of America reported confirmed cases of the virus [45]. On January 23, 2020 Wuhan city with a population of over 11 million was closed off by the Chinese authorities by which point, over 570 people had been infected and 17 had died [45]. WHO declared COVID-19 a pandemic on March 11, 2020 [45]. At the time of writing, more than 56.5 million worldwide cases of COVID-19 have been confirmed, with over 1.3 million deaths [46]. The United States of America is one of the countries hardest hit by the COVID-19 pandemic to date, with over 11.8 million cases and more than 256,000 deaths reported as of November 19, 2020 [46]. In a major spike in new COVID-19 cases, India became the nation with the world's second-highest share of cases (>8.9 million) with more than 131,000 casualties, surpassing Brazil (>5.9 million cases and >167,000 deaths) [46].

Common early symptoms of COVID-19 include high fever, sore throat, dry cough, body ache and fatigue [47]. The infection caused by SARS-CoV-2 virus initially targets key areas of the lungs and airways that usually allow the transfer of oxygen into the blood circulation [47,48]. Affected individuals with pre-existing chronic medical conditions, such as heart disease and diabetes, are considered to be at greater risk of acquiring severe forms of the infection [49,50]. During the COVID-19 pandemic, many health professionals are urging smokers to quit [51,52]. Moreover, in response to the pandemic, the Anti-smoking Centre of the National Cancer Institute of Milan and Bedfront Scientific Ltd has developed a portable carbon monoxide analyser known as "Smokerlyzer" which is used for smoking cessation assessment without the need for close contact with subjects [51], assisting health professionals in conducting assessments and the follow-up of smoking cessation programs [51,52]. Nevertheless, the risks associated with smoking and COVID-19 are somewhat unclear but a number of recent publications have reported that smokers were under-represented in hospitalized COVID-19 cases and even suggested that a potential protective effect for nicotine [53,54].

Based on the currently available data, this article focuses on and discusses the potential relationship between smoking and susceptibility to COVID-19 infection as well as severity of COVID-19 symptoms.

4. Evidence to date for an association between smoking and COVID-19

Smoking is well established as having an adverse impact on lung health. As outlined above, research has shown that smoking is detrimental to the immune response within the respiratory system, causing smokers to become more prone to infectious pathogens [55]. Previous studies have identified smoking as one of the risk factors associated with Middle East Respiratory Syndrome (MERS) infection and mortality [42,56]. A significantly increased risk of MERS-related mortality was reported in smokers when compared to non/never-smokers (relative risk:

Table 1
Summary of prospective and retrospective cohort studies for COVID-19.

Study Design	Number of Patients	Selection Criteria	Major Outcome(s)	Smoking status	Reference
Retrospective multicentre cohort study	1099 patients with confirmed COVID-19 and admitted in 552 hospitals in 30 provinces, autonomous regions and municipalities in mainland China till January 29, 2020	All participants had laboratory confirmed test for SARS-CoV-2 nucleic acid via RT-PCR or high throughput sequencing assay of nasal and pharyngeal swab	926 patients were categorized as non-severe group; while 173 were categorized as severe group. Within non-severe group, 1 patient died (0.1%); 7 patients recovered (0.8%); and 875 patients remained hospitalized (94.5%). Whereas, within severe group, 14 patients died (8.1%); 2 patients recovered (1.2%); and 154 patients remained hospitalized (89.0%).	Within non-severe group (n = 926), there were 793 patients who never smoked (86.9%); 12 patients were former smokers (1.3%); and 108 were current smokers (11.8%). Whereas, within severe group (n = 173), there are 134 patients who never smoked (77.9%); 9 patients were former smokers (5.2%); 29 patients were current smokers (16.9%).	[47]
Retrospective multicentre cohort study	78 patients with confirmed COVID-19 admitted in three tertiary hospitals in Wuhan from December 30, 2019 till January 15, 2020	All participants confirmed positive for SARS-CoV-2 nucleic acid via RT-PCR assay of their respiratory specimen; and had been hospitalized for over 2 weeks, died while hospitalized, or had recovered and been discharged	11 patients (14%) showed disease exacerbations; 67 patients showed improvement and stabilization (85.9%); 2 patients died (2.5%)	There were 5 patients reported with history of smoking. Two of them demonstrated improvement after hospitalization (3.0% of n = 67); and 3 of them (27.3% of n = 11) showed disease exacerbation.	[58]
Retrospective study	140 patients with confirmed COVID-19 hospitalized in Wuhan, China from January 16, 2020 till 3/2/2020	All participants had laboratory confirmed test for SARS-CoV-2 nucleic acid via RT-PCR assay of pharyngeal swab	140 patients were categorized into non-severe group and severe group according to their oxygenation index, pulse oximeter oxygen saturation and presence of respiratory distress. There were 82 patients in non-severe group (58.6%) and 58 patients in severe group (41.4%).	In non-severe population, 3 patients were former smokers (3.7%) and 79 patients never smoked (96.3%). Whereas, in severe group, 4 patients were former smokers (6.9%); 2 patients were current smokers (3.4%) and 52 (89.7%) never smoked.	[59]
Retrospective multicentre cohort study	191 patients with laboratory confirmed COVID-19 admitted to JinYinTan Hospital and Wuhan Pulmonary Hospital in Wuhan, China	All participants were more than 18 years old and had laboratory confirmed test for SARS-CoV-2 nucleic acid via RT-PCR or next-generation sequencing assay of respiratory specimen	137 patients demonstrated improvement and were discharged (71.7%); and 54 patients died (28.3%).	There were 11 patients reported as current smokers. Among them, 6 patients survived COVID-19 disease (4.4%); whereas 5 patients died (3.6%).	[60]
Prospective study	41 confirmed COVID-19 patients hospitalized in Wuhan from December 16, 2019 till January 2, 2020	All participants confirmed with SARS-CoV-2 infection via RT-PCR and next generation sequencing of respiratory specimens	28 patients recovered (68%); 6 patients died (15%); 7 patients remained in hospital as of January 22, 2020 (17%)	Three patients identified as current smokers and not admitted to ICU.	[94]
Prospective study	393 patients with confirmed COVID-19 and admitted to two hospital in Manhattan, New York, USA between March 3, 2020 till March 27, 2020	All participants had laboratory confirmed test for SARS-CoV-2 nucleic acid via RT-PCR assay of nasopharyngeal swab	40 patients died (10.2%); 260 patients were discharged from hospital (66.2%); and 93 patients remained hospitalized (23.6%)	There were 20 patients identified as current smokers (5.1%). Six of them required invasive mechanical ventilation and 14 did not need invasive mechanical ventilation	[95]
Retrospective Cohort Study	799 patients with laboratory confirmed COVID-19 and admitted to Tongji Hospital in Wuhan, China	All participants had laboratory confirmed test for SARS-CoV-2 nucleic acid via RT-PCR assay of their throat swab	161 patients demonstrated recovery (20.2%); 525 patients remained hospitalized (65.7%); and 113 patients died (74.1%)	There were 19 patients with smoking history in the participants' pool (7%). Within the recovered population, there were 9 patients with a smoking history (8%); 7 of them being current smokers (6%) and 2 former smokers (2%). Whereas, within the population who died, there were 19 patients with a smoking history (7%); 12 of them were current smokers (4%) and 7 were former smokers (3%)	[96]
Retrospective single centre study	155 patients with confirmed COVID-19 and hospitalized at ZhongNan Hospital of Wuhan University, China from January 1, 2020 till February 5, 2020	All participants had laboratory confirmed test for SARS-CoV-2 nucleic acid via RT-PCR assay of their throat swab	70 patients showed improvement after receiving treatment (45.2%); and 85 patients did not show signs of improvement despite the treatment (54.8%)	Six patients were identified as current smokers; 2 of them showed improvement after receiving treatment and 4 did not respond well to the provided treatment	[97]
Retrospective multicentre study	645 patients with confirmed COVID-19 and admitted to hospitals in ZheJiang province, China	All participants had laboratory confirmed test for SARS-CoV-2 nucleic acid via RT-PCR assay of their throat swab and also examined via chest CT and radiographic examination	72 patients presented with normal CT and radiographic results (11.2%). 573 patients were presented with abnormal chest CT and radiographic imaging (88.8%)	Forty One patients were identified as current smokers; 4 patients had normal imaging results and 37 patients had abnormal imaging findings.	[98]

2·55 [95%CI: 1·1–5·9]), although the data were based on only eight smokers [57]. As both MERS-CoV and SARS-CoV-2 belong to the same Coronaviridae family, there is increasing attention on the potential for smoking to predispose individuals to SARS-CoV-2 infection or a worsened COVID-19 prognosis.

A retrospective cohort study was conducted on 78 COVID-19 patients admitted to three hospitals in Wuhan, China between December 30, 2019 and January 15, 2020 [58]. The investigators reported that a

significantly higher proportion of patients with a history of smoking exhibited a rapid deterioration in health during their admission compared to non-smokers (27% versus 3%, $p = 0{\cdot}018$), suggesting that smoking may have a harmful effect on COVID-19 prognosis [58]. Multivariate logistic regression analysis supported a significant association between history of smoking and severe disease progression (OR 14·3 [95% CI: 1·58–25·0]) [58] (Table 1).

Another retrospective cohort study conducted in the early stages of the COVID-19 outbreak on 140 confirmed COVID-19 patients admitted to No. 7 Hospital of Wuhan between 16 January and February 3, 2020, found that smoking was associated with more severe forms of the disease [59]. Other factors that related to progression of COVID-19 included older age, a higher body temperature at admission, higher respiratory rate, reduced albumin and elevated C-reactive protein levels [58]. A study involving a larger cohort of 1099 patients with COVID-19 across 30 provinces, autonomous regions, and municipalities in mainland China through to January 29, 2020 determined that a greater proportion of current and former smokers were among severe cases of COVID-19 (16·9 and 5·2%, respectively) than among non-severe cases (11·8 and 1·3%, respectively) [47]. Additionally, of COVID-19 patients who were admitted to an ICU, needed mechanical ventilation, or died, 25.8% were current smokers and 7.6% were former smokers as compared to 11.8% and 1.6% of patients, respectively, without these adverse outcomes.

In a study of 191 COVID-19 in-patients from Jinyintan Hospital and Wuhan Pulmonary Hospital, in which 54 patients died during hospitalization and 137 were discharged, the proportion of smokers was found to be modestly higher in non-survivors of COVID-19 than in survivors of the disease (9% vs 4%, $p = 0{\cdot}2$) [60]. Furthermore, Hu et al. found a statistically significant association between smoking status and severity of disease amongst 323 hospitalized COVID-19 patients in Wuhan, China (OR 3·46 [95% CI: 1·18–10·2]) [61]. A multivariate analysis by Yu et al. identified an association between smoking and the exacerbation of pneumonia in COVID-19 patients after treatment, with a significant OR of 16·1 (95% CI: 1·3–204·2) [62]. Besides, Alqahtani and his team reported, based on a meta-analysis of 15 studies that included 2473 confirmed COVID-19 patients, that active smokers with COVID-19 had a higher mortality rate, and were more likely to have severe complications, compared to non-smokers [63].

One of the largest cohort studies conducted to date from the UK reported an increased risk for in-hospital COVID-19 death in ex-smokers compared to never-smokers (HR 1·8 [95% CI 1·7–1·9]) when adjusted for age and sex [64]. This association was found to be significant even after adjustment for additional risk factors, such as body mass index, chronic respiratory diseases, diabetes, hypertension, and chronic heart disease (fully adjusted HR 1·25 [95% CI 1·18–1·33]). In addition, current smoking was found to be associated with a higher risk of COVID-19 mortality (age and sex adjusted HR 1·25 [95% CI 1·12–1·40]), which however decreased to 0·88 (0·79–0·99) when fully adjusted. They reported that the decrease in risk was largely driven by the adjustment for chronic respiratory disease, which is strongly associated with tobacco smoking.

Two preliminary meta-analyses by Zhao et al. and Zheng et al. that analyzed data from 7 to 5 studies totaling 1726 and 1980 patients, respectively, found a statistically significant association between smoking and severity of COVID-19 (OR 2·0 [95% CI: 1·3-3·1] and 2·0 [95% CI: 1·3-3·2], respectively). Furthermore, a recent meta-analysis that included 11,590 COVID-19 patients across 19 studies reported disease progression in 29·8% of patients with a history of smoking, compared with 17·6% of nonsmoking patients ($p < 0.001$) [65]. Moreover, a statistically significant association was found between smoking and COVID-19 progression (OR 1·91 [95% CI: 1·42–2·59]) [66,67].

5. Evidence to date against an association between smoking and COVID-19

While most of the studies to date have indicated an association between smoking and a worsening of COVID-19 symptoms, there are reports that have suggested an inverse relationship between smoking and COVID-19. In particular, smoking prevalence among patients hospitalized with COVID-19 has been reported to be lower than the smoking prevalence in the general population. Using hospital data from NHS England and APHP Pitié- Salpêtrière Hospital from France, Williamson et al. and Miyara et al. reported a slight protective effect against death from COVID-19 in current smokers [64,68]. Two meta-analyses have published the pooled prevalence of smokers among hospitalized COVID-19 patients across China. Emani et al. and Farsalinos et al. analyzed data for 2986 and 5960 patients and found a pooled prevalence of 7·6% (95% CI: 3·8% −12·4%) and 6·5% (95% CI: 1·4% - 12·6%), respectively, which is approximately one-quarter the smoking prevalence of the general population in China [69,70]. Recently, Petrilli et al. showed that both current and former smoking status were associated with a reduced risk of hospitalization due to COVID-19 (OR 0.59 [95% CI: 0.43–0.81] and 0.69 [95% CI: 0.56–0.85], respectively) [71]. However, the authors also found that an unknown smoking status was associated with a higher hospitalization risk (OR 1.43 [95% CI: 1.16–1.75]) which may indicate difficulty in establishing the smoking status of patients [71].

Two preliminary systematic reviews investigated the effects of smoking on severity of COVID-19 and reported a negative association. A meta-analysis of 1399 patients with confirmed COVID-19 found no significant association between smoking and COVID-19 disease severity (OR 1·69 [95% CI 0·41–6·92]), despite a trend towards higher risk [72]. Guo later cited issues in the data collection that may have affected the meta-analysis and concluded that an updated meta-analysis suggested that active smoking is significantly associated with the risk of severe COVID-19 [73]. On the other hand, Vardavas and Nikitara did not find a significant association between smoking and severity of the disease upon analysis of five studies (RR 1·4 [95% CI: 0·98–2·00]) [74]. However, they did report a statistically significant association between smoking status and the primary end-points of mortality, admission to ICU, or ventilator use (RR 2·4 [95% CI: 1·43–4·04]) [74].

A follow-up study also documented that COVID-19 disease prevalence and progression was not directly correlated with smoking status [75]. Some researchers are questioning the validity of these studies, highlighting flaws in the statistical analyses [76] and potential bias with regard to the smoker populations selected in the analyses [77]. Lo and Lasnier have underscored the inappropriateness of using null hypothesis significance testing to conclude an absence of smoking effect on COVID-19 progression, and recommended the use of an estimation approach as a more clinically informative statistical approach for interpreting the OR results [76]. In addition, some studies have not made statistical adjustments for confounders such as age, gender and co-morbidities.

While data on the association between smoking and COVID-19 is mixed, the available evidence suggests that smoking is associated with increased severity of disease and mortality in hospitalized COVID-19 patients. One of the challenges for studies on COVID-19 is to have sufficient sample sizes to allow adjustment for confounding risk factors, such as hypertension and chronic respiratory diseases, which are closely associated with tobacco smoking. Thus, well-designed population-based studies are needed to determine the risk of SARS-CoV-2 infection, as well as the risk of hospitalization with COVID-19 among smokers.

6. Angiotensin-converting enzyme as a potential therapeutic target

Angiotensin-converting-enzyme (ACE)-II has attracted worldwide attention in relation to COVID-19 [4]. Constitutively expressed in the respiratory tract, myocardium, and gastrointestinal tract, ACE-II is a type II transmembrane metallocarboxypeptidase that metabolizes angiotensin II into multiple metabolites, such as angiotensin-(1–9) and angiotensin-(1–7) [78,79]. In human respiration, ACE-II is expressed on

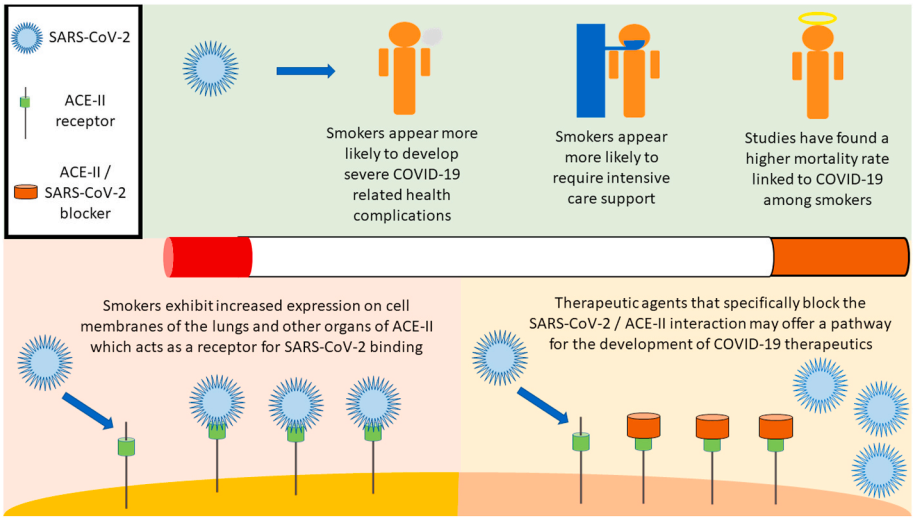

Fig. 1. Summary of the current knowledge on smoking and COVID-19. Recent available data indicate that individuals with a smoking history are more likely to acquire more severe COVID-19 outcomes, including intensive care unit admission and in-hospital mortality, than non-smokers. Moreover, research findings also indicate that smokers exhibit increased expression ACE-II receptors, which acts as a binding site for SARS-CoV-2 virus. Hence, therapeutic agents targeting SARS-CoV-2/ACE-II interaction may offer a path for the development of COVID-19 treatments.

the surface of type-II pneumocytes [80]. It plays an essential role in regulating blood pressure and cardiac function, but its role in the respiratory system remains more obscure [81,82].

While a recent study showed that there is no significant correlation between ACE-II genetic polymorphism with COVID-19 infection, several studies demonstrated that its receptor does play a key role in the infiltration of coronavirus [83–86]. Coronavirus contains large type-I transmembrane spike glycoproteins, which contain 2 distinct domains, S1 and S2 [83]. S1 domain shares a similar homolog to the ACE-II receptor binding site, while the S2 domain facilitates fusion between cell and virus membrane [83,84]. Studies have shown that such characteristics appeared in several coronavirus family members, including SARS-CoV, NL63, and SARS-CoV-2 [83–85]. Recent studies demonstrated that SARS-CoV-2 has a significantly higher affinity in binding with the ACE-II receptor; hence, it is more likely to bind and infect human cells than other coronaviruses [80,87]. Importantly, studies have shown that smokers have increased expression of the ACE-II receptor, compared to non-smokers [4,88,89]. Similar events were also observed and reported in recent RNA expression profiling for patients with confirmed COVID-19 [90]. Collectively, this information suggests that smokers may be more vulnerable to SARS-CoV-2 infection due to elevated expression in ACE-II receptors.

Should elevated ACE-II expression be confirmed as a factor that increases the vulnerability of smokers to COVID-19 disease, therapeutic targeting of ACE-II may present new pathways in the treatment of COVID-19, particularly in smokers, as shown in Fig. 1. In recent work that utilised human recombinant soluble ACE-II (HRS-ACE-II), Monteil et al. reported that this approach was able to reduce SARS-CoV-2 recovery by a factor of 1000–5000 in kidney organoids under *in vitro* conditions, suggesting that HRS-ACE-II could potentially inhibit the invasion of host cells by SARS-CoV-2 [91]. HRS-ACE-II is currently undergoing a phase 2 clinical trial as a therapeutic agent for COVID-19 (NCT04335136), and hence, its efficacy in the treatment of COVID-19 patients, with and without a smoking history, remain to be determined [92].

Because angiotensin-converting enzyme inhibitors (ACEIs) reduce the biosynthesis ACE-II enzymes allowing greater number of free ACE-II receptors, there were initial concerns about the potential of an increased risk of COVID-19 mortality or severity among patients taking these drugs for cardiovascular conditions. Nonetheless, authorities including the Cardiac Society of Australia and New Zealand (CSANZ) recommends the continuation of ACEIs in patients with hypertension, heart failure and other cardiovascular related diseases, as discontinuation of these life-saving medications could potentially be harmful [93].

7. Summary of smoking and COVID-19 data and what we can say thus far

While we are still in the early stages of establishing the pathogenesis of COVID-19, several studies have implicated an association between tobacco smoking and poorer disease prognoses in COVID-19 patients. Further research will be required to validate these initial findings and also establish the mechanisms underlying the presentation of more severe symptoms of COVID-19 in smokers. In addition, clear evidence of a higher susceptibility to SARS-CoV-2 infection due to smoking has not been established to date and this will need to be carefully examined in future epidemiological studies. A role for the ACE-II receptor during infection of host tissues by SARS-CoV-2 has been proposed but exactly how this fits into initiation or progression of COVID-19 in smokers has not been demonstrated. Until then, clinical treatments for COVID-19 that target ACE-II are premature, except in those who require the medication for management of comorbidities. In conclusion, more extensive research is required to interrogate the potential role of tobacco smoking in SARS-CoV-2 infection and in the development of COVID-19 symptoms, as well as the validation of new therapeutic targets. This will require substantial ongoing investment in the global research capacity to obtain answers and solutions to the COVID-19 pandemic.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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