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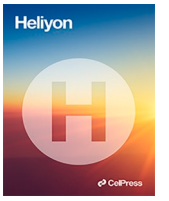

Review article

The predisposition of smokers to COVID-19 infection: A mini-review of global perspectives

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A B S T R A C T

Both SARS-CoV-2 and smoking tobacco adversely impact the respiratory system, damaging the airways and impairing lung function. While some studies have identified a positive association between smoking and increased susceptibility to COVID-19 infections, a few papers have concluded that smokers may be protected against such infections. Given these contradictory findings, there is an ongoing debate in the scientific community about whether or not smokers have a stronger predisposition towards COVID-19 infections. Through this mini-review, we aimed to study the relationship between tobacco smoking and COVID-19 infections by conducting a comprehensive literature search of peer reviewed articles that reported on the effects of smoking on COVID-19 susceptibility and were published globally over the past two years (January 2020–April 2022). Our search identified 31 articles that demonstrated a positive or strong relationship between smoking and COVID-19, while 13 articles had contrasting results. Additionally, we evaluated mechanistic studies suggesting that, among smokers, angiotensin-converting enzyme-2 genes are upregulated, facilitating easier binding of SARS-CoV-2, thereby increasing the risk of COVID-19 infection. In conclusion, the majority of studies in this area to date provide evidence of a strong relationship between smoking and COVID-19 infection; however, the strength of this association may vary across the smoking behaviors of differing populations. Future work could involve a meta-analysis of studies focusing on susceptibility to COVID-19 infection for different types of tobacco product smokers, which would result in a more comprehensive understanding of the predisposition of smokers towards COVID-19 infections.

1. Introduction

In December 2019, the city of Wuhan, China witnessed the emergence of a new virus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [1]. It took the virus only 48 days to infect over 1000 people, a significantly faster transmission rate compared to other similar viruses such as the 2002–2003 SARS-CoV and the 2012–2014 Middle East respiratory syndrome coronavirus (MERS-CoV) [2]. Within a short period of time, SARS-CoV-2 spread across China, and made its way across the globe, reaching nearly all countries by March 2020 [3]. As of October 24, 2022, with over 623, 893, 894 cases reported and close to 6,555,936 deaths reported globally, the COVID-19 (the disease caused by SARS-CoV-2) pandemic is still ongoing [4].

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Table 1
Studies evaluating the relationship between smoking and COVID-19 symptoms, hospitalization and death.

	Supporting studies	Study type (#articles)	Sample size	Nature of relationship with COVID-19
Positive relationship		**Smokers vs. non-smokers**		
	Vardavas and Nikitara 2020	Systematic review (5)	1549	Symptom prevalence RR = 1.4; 95% CI: 0.98–2.00
	Patanavanich and Glantz 2020	Meta analysis (19)	11,590	Disease progression OR = 1.91; 95% CI: 1.42–2.59
	Reddy et al., 2021	Systematic review (47)	32,849	RR = 1.35; 95% CI: 1.19–1.53
	Karanasos et al., 2020	Meta analysis (22)	6310	OR = 1.34; 95% CI: 1.07–1.65
	Almazeedi et al., 2020	Retrospective cohort study	1096	Hospitalization OR = 5.86; 95% CI: 1.40–24.47
	Emami et al., 2020	Meta analysis (10)	76,993	
	Soares et al., 2020	Cohort	10,713	Hospitalization OR = 5.12; 95% CI: 3.82–6.81
	Patanavanich and Glantz 2021	Meta analysis (46)	22,939	Disease progression OR 1.59, 95% CI 1.33–1.89 Mortality rate OR 1.19, 95% CI 1.02–1.39
	Paleiron et al., 2021	Cross-sectional	1769	OR = 2.84; 95% CI: 1.30–7.5
	Zheng et al., 2020	Meta analysis (13)	3027	OR = 2.51; 95% CI: 1.39–3.32
		Current and fomer smokers vs. non-smokers		
	Alqahtani et al., 2020	Meta analysis (15)	2473	RR = 1.45; 95% CI: 1.03–2.04 (current)
	Umnuaypornlert et al., 2021	Meta analysis (40)		Disease severity OR = 2.48; 95% CI: 1.64–3.77 (former) Disease severity OR = 1.58; 95% CI: 1.16–2.15 (current) Mortality rate OR = 2.48; 95% CI: 1.64–3.77 (former) Mortality rate OR = 1.35; 95% CI: 1.12–1.62 (current)
	Gülsen et al., 2020	Meta analysis (16)	11,322	OR = 1.51; 95% CI: 1.12–2.05 (current)
	Jackson et al., 2020	Cross-sectional	53,002	OR = 1.07; 95% CI: 1.01–1.15 (former) OR = 1.11; 95% CI: 1.03–1.20 (current)
	Hopkinson et al., 2021	Survey	2.4 million	Symptoms prevalence OR = 1.42, $p < 0.05$ Hospitalization rate OR = 2.11, $p < 0.05$
	Hamer et al., 2020	Cohort	3,87,109	RR = 1.34; 95% CI: 1.15–1.56 (former) RR = 1.45; 95% CI: 1.16–1.83 (current)
	Clift et al., 2021	Observational	4,21,469	Hospitalization rates OR = 1.80; 95% CI: 1.26–2.29 (current)
	Farsalinos et al., 2020	Review (18)	6515	OR = 1.53; p = 0.022 (current)
	Sanchez-Ramirez and Mackey 2020	13		OR = 3.46; 95% CI: 2.46–4.85 (former) OR = 1.98; 95% CI: 1.16–3.39 (current)
	Puebla Neira et al., 2021	Retrospective cohort study	10,216	Hospitalization rates OR 2.31; 95% CI 1.94–2.74 (former) Hospitalization rates OR = 0.68; 95% CI: 0.60–0.99 (current)
	Paleiron et al., 2021	Retrospective cohort study	1688	Symptoms prevalence OR = 0.98; 95% CI: 0.70–1.38 (former) symptoms prevalence OR = 0.59; 95% CI: 0.45–0.78 (current)
	Gao et al., 2022	Cohort	7,869,534	Hospitalization rates HR = 1.07; 95% CI:1.03–1.11 (former) Hospitalization rate HR = 0.36; 95% CI: 0.17 to 0.76 (current) Mortality rate HR = 1.17; 95% CI:1.10 to 1.24 (former) Mortality rate HR = 0.77; 95% CI:0.54 to 1.10 (current)
		Co-morbidities and smoking		
	Pranata et al., 2020	Meta analysis (21)	4603	Symptom prevalence OR = 1.65; 95% CI: 1.17–2.34
	Zhao et al., 2020	Systematic review (12)	2002	Symptom prevalence OR 1.98; 95% CI: 1.29–3.05
	Zhang et al., 2021	Meta analysis (109)	5,17,020	Mortality rate OR = 1.58; 95% CI: 1.38–1.81 Hospitalization rate OR = 1.73; 95% CI: 1.36–2.19
	Jayarajan et al., 2020	Prospective	59	Mortality rate OR = 1.58; 95% CI: 1.38–1.81
		Non-cigarette smoking		
	Gaiha et al., 2020	Survey	4351	OR 5.00; 95% CI: 1.82–13.96 (e-cig only) OR 7.00; 95% CI: 1.98–24.55 (e-cig + cig)
	Tattan-Birch et al., 2021	Survey	3179	OR = 1.34, 95% CI:1.04–1.73
	Jose et al., 2021	Cohort	69,264	OR = 0.67; 95% CI: 0.49–0.92; p = 0.013 (e-cig + cig)
	Duszynski et al., 2021	Cohort	8214	OR = 2.17; 95% CI: 1.26–3.72 (smokeless tobacco)
Negative relationship		**Smokers vs. non-smokers**		
	Hernández-Garduño 2020	Case-control	32,583	Females OR = 0.49; 95% CI: 0.31–0.78 Males OR = 0.64; 95% CI 0.51–0.81
	Parra-Bracamonte et al., 2020		3,31,298	Symptom prevalence OR = 1.175; 95% CI: 1.130–1.221
	Tsigaris and Teixeira da Silva 2020			Mortality rate p > 0.05
	de Lusignan et al., 2020	Cross-sectional		OR = 0.49; 95% CI: 0.34–0.71
	Lippi and Henry 2020	Meta analsysis (5)		OR = 1.69; 95% CI: 0.41–6.92

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Table 1 (*continued*)

	Supporting studies	Study type (#articles)	Sample size	Nature of relationship with COVID-19
	Farsalinos et al., 2021	Meta analsysis (20)	7162	Symptom prevalence OR 1.40; 95% CI 0.98–1.98 Mortality rate OR 1.86; 95% CI 0.88–3.94
	Duszynski et al., 2021	Cohort	8214	OR = 0.654; 95% CI: 0.32–1.35 (e-cig) OR = 0.49; 95% CI: 0.32–0.74 (cig)
	Jose et al., 2021	Cohort	69,264	OR = 0.93; 95% CI: 0.69–1.25; p = 0.628 (e-cig only)

Multiple variants and subvariants (including Alpha, Delta and Omicron) of SARS-CoV-2 have been identified over the past three years, each of which vary with regard to their transmissibility and infection severity [5,6]. With the virus constantly undergoing mutations to adapt to the changing environment and evade the immune system [7], the long-term impacts on the human body from this virus are still being studied extensively, but we know that the main organ system affected by this disease is the respiratory system [8]. COVID-19 infection often includes symptoms of the common cold, bronchitis, and pneumonia [9]. Associated fluid saturation of the lungs leads to difficulty in breathing and more severe cases may result in acute respiratory distress syndrome, and ultimately lung failure and death [10]. Additionally, sepsis, (when the infection spreads through the bloodstream) can also occur during a COVID-19 infection [11].

In contrast, the adverse health effects of smoking tobacco products have been studied in great detail over many decades and it is well-documented that tobacco use adversely affects the lungs [12,13]. In addition to restricting airflow, smoking inflames and irritates the lungs, causing mucus to build up and making the lungs more susceptible to a variety of bacterial and viral infections [14,15]. Tobacco smoking has also been shown to reduce the number of cilia in the lungs, causing chronic airflow limitation and reducing lung function [16,17]. These adverse health effects are not restricted to combustible traditional tobacco products alone. In a cross-sectional study that examined bronchoalveolar lavage and brushings from 73 subjects, electronic cigarette (e-cigarette) users exhibited lung inflammation and damage, but to a lesser degree than traditional smokers [18]. Other studies have demonstrated that smokers not only are 34% more likely to be infected with the flu when compared to non-smokers [19,20] but also carry a higher risk of hospital admittance [21].

Since both SARS-CoV-2 and tobacco smoking heavily affect the lungs, there is the potential that smoking could influence the transmission of COVID-19, or that a long-term smoker could be at a higher risk of acquiring the disease [15,16]. To date, it has been demonstrated that the rate of COVID-19 infection, disease progression, and mortality rates in people with underlying health conditions and comorbidities are higher compared to that of healthy individuals [22,23]. While the most common comorbidities studied with COVID-19 disease progression are hypertension, diabetes, obesity, chronic obstructive pulmonary disease (COPD), cardiovascular diseases (CVD), and malignancies, multiple studies have demonstrated a statistically significant positive relationship between smoking and COVID-19 prevalence, including a higher risk of severe illness due to COVID-19 among active smokers (Table 1). In contrast, other studies point toward a potential protective benefit of smoking with regard to COVID-19 infection (Table 1). While this debate is ongoing, the objective of this mini-review was to better understand the predisposition of smokers to COVID-19 infection globally by summarizing the published studies to date in this area.

2. Methods

A comprehensive literature search was conducted using Google Scholar and PubMed databases. All meta-analyses, retrospective studies, comments, scoping reviews, systematic reviews, clinical trials, and letters to editors on the effects of tobacco smoking on COVID-19 risk and COVID-19 patients were included. Included studies were published from around the world between January 2020 and April 2022, written in the English language, and reported in peer-reviewed journals.

The following key search terms were included when searching the above-mentioned databases: “smoking”, “tobacco”, “COVID-19”, “coronavirus”, “smoker”, “cigarette”, “pandemic”, “SARS-CoV-2”, “smokeless tobacco”, “hookah”, “water pipe”, and “electronic cigarettes” both individually and in conjunction with others. After reviewing the abstracts, articles focusing on either other smoking-related diseases, policy recommendations or social behavior surveys were excluded and a total of 33 relevant articles were ultimately included in this mini-review.

3. Results

3.1. Studies reporting a direct relationship between smoking and severe COVID-19 symptoms, diseases progression, and mortality

The first study that demonstrated a potential link between smoking and COVID-19 was a systematic review and meta-analysis of studies completed in China [24]. The study was published online on March 20, 2020, only a few days (March 11, 2020) after the World Health Organization (WHO) declared COVID-19 a global pandemic. This meta-analysis included five independently researched studies of which four were retrospective [15,25–27] and one was prospective [28]. Overall, the meta-analysis revealed that smokers were 1.4 times more likely to have severe symptoms of COVID-19 and were 2.4 times more likely to be admitted to an intensive care unit (ICU), need medical ventilation, or die compared to non-smokers. While the above study found that smokers were more likely to have severe symptoms of COVID-19, a second meta-analysis by Patanavanich and Glantz (2020) demonstrated a likelihood of COVID-19 disease

progression with smoking. This study included data available from 19 peer-reviewed papers (China (16), Korea (1), and the United States (U.S.) (2)) that were accessible from PubMed on April 6, 2020 [29]. This meta-analysis included a total of 11,590 individuals among which 731 COVID-19 patients (6.3%) had a history of smoking. Out of these smokers, 29.8% demonstrated disease progression as compared to 17.6% of non-smokers that experienced disease progression. The authors concluded that patients who are smokers were significantly more likely to experience disease progression and severe COVID-19 infection compared to nonsmokers (OR = 1.91; 95% CI: 1.42–2.59).

Similarly, Karanasos et al. (2020) conducted a meta-analysis that included 22 studies of which 17 reported on severity, four on morbidity, and one on both [30]. The analysis included 6310 patients from both the U.S. and China and found that smoking increased the risk of a more severe response to COVID-19 (OR = 1.34; 95% CI: 1.07–1.65). This meta-analysis also demonstrated an increased risk in the severity of COVID-19 patients among smokers but failed to show an increase in the mortality rate. Another retrospective cohort study conducted in Kuwait examined 1096 patients, screened for risk factors that affected admission to ICUs, and also found a significant association between hospital admission and smoking (OR = 5.86; 95% CI: 1.40–24.47; $p = 0.015$) [31]. In addition, the authors calculated mortality risk and found a significant association (OR: 10.09; 95% CI: 1.22–83.40; $p = 0.032$) among smokers. Furthermore, two more studies evaluated the relationship between smoking and the risk of hospitalization and death from COVID-19 among 10,713 and 3403 patients diagnosed with COVID-19 respectively [32,33]. While the Soares et al. (2020) study concluded that smoking was one of the comorbidities strongly associated with hospitalizations ($p = 0.053$), the Emami et al. (2020) meta-analysis of 10 articles noted smoking as a prevalent underlying cause among patients hospitalized for COVID-19.

Subsequently, a meta-analysis of 46 peer-reviewed papers with a total of 22,939 COVID-19 patients, demonstrated an increased risk of COVID-19 disease progression among ever smokers (current and former smokers) (OR = 1.59; 95% CI: 1.33–1.89) [34]. In addition, the authors found that smoking was associated with an increased risk of mortality from COVID-19 (OR = 1.19; 95% CI:1.02–1.39) and disease progression among younger adults. In contrast, a cross-sectional observational study of 1769 sailors found that older adults (>50 years old) were at a significantly higher risk of COVID-19 symptoms compared to adults <50 years old (OR = 2.84; 95% CI: 1.30–7.5) [35]. Another meta-analysis of 13 studies including 3027 patients demonstrated that older males (>65 years old) and smokers were at a higher risk of COVID-19 disease progression (males >65 years old, OR = 6.06, 95% CI: 3.98–9.22; current smokers, OR = 2.51, 95% CI: 1.39–3.32) [36]. Additionally, a multi-center observational study from Malaysia included 5899 COVID-19 patients and showed that even though the ever-smokers were at a higher risk of having COVID-19 complications (respiratory distress syndrome, renal and liver injury), there was no significant difference between disease outcomes when compared to non-smokers [37].

3.2. The predisposition of current vs. former smokers to COVID-19 symptoms, disease progression, hospitalization, and mortality

As the pandemic progressed, a few studies evaluated the effect of COVID-19 among current smokers, former smokers, and non-smokers. For example, a review article by Alqahatani et al. (2020) analyzed 15 studies from China that examined 2473 confirmed cases of COVID-19 among current smokers [38]. The authors observed that current smokers were 1.45 times more likely to have severe symptoms from COVID-19 compared to former smokers or people who have never smoked (RR = 1.45, 95% CI: 1.03–2.04). Current smokers also had a higher mortality rate (38.5%). Similarly, in a systematic review and meta-analysis of 40 articles, Umnuaypornlert et al. (2021) found that both current and former smokers experienced statistically significantly greater COVID-19 severity (OR = 1.58; 95% CI: 1.16–2.15; and OR = 2.48; 95% CI: 1.64–3.77; respectively) and an increased risk of death (OR = 1.35; 95% CI: 1.12–1.62; and OR = 2.58; 95% CI: 2.15–3.09; respectively) compared to non-smokers [39].

To evaluate the association between the history of smoking and the severity of COVID-19 symptoms, a meta-analysis of 16 articles was then performed [40]. While a significant association was found between a history of smoking and severe COVID-19 cases (OR = 2.17; 95% CI: 1.37–3.46; $p < 0.001$), non-smokers (10.7%) had less severe COVID-19 symptoms compared to active smokers (21.2%). The cross-sectional study on sailors mentioned above found similar results with active smokers (OR = 0.59; 95% CI: 0.45–0.78; $p < 0.001$) characterized by a significantly higher COVID-19 prevalence when compared to former smokers (OR = 0.98; 95% CI: 0.70–1.38; $p = 0.93$) [35]. A systematic review article including 47 studies (China (32), U.S. (10), Italy (2), U.K. (1), and International (2)) focused on the effects of smoking on COVID-19 [41]. Studies included in this review paper reported hospitalization and mortality rates for COVID-19 patients from early December 2019 to early June 2020. The overall meta-analysis in this review article (n = 32,849 study participants) demonstrated an increased risk of COVID-19 among smokers (RR = 1.35; 95% CI: 1.19–1.53). This study also demonstrated that a history of smoking was associated with an increased risk of mortality among patients (RR = 1.26; 95% CI: 1.20–1.32). Current smokers were found to be at a significantly higher risk of severe COVID-19 infection (RR = 1.80; 95% CI: 1.14–2.85). Similar to the above-mentioned study by Vardavas and Nikitara (2020), the authors also observed an association between severe or critical cases of COVID-19 and smoking, in-hospital mortality, and disease progression ($p < 0.05$) [24]. In contrast, a retrospective cohort study from the U.S. involving 10,216 patients showed significantly more hospitalization rates from COVID-19 among former smokers (OR 2.31; 95% CI 1.94–2.74) when compared to current smokers (OR = 0.68; 95% CI: 0.60–0.99) [42].

Similar to the above-mentioned research articles, several studies from the U.K. found a significant association between current smoking and COVID-19 symptoms. First, a cross-sectional survey of 53,002 people in the U.K. found that current smoking is associated with an increased risk of COVID-19 infection [43]. In the survey, 25.7% were ex-smokers and 15.2% were current smokers. Former smokers (OR = 1.07; 95% CI: 1.01–1.15) and current smokers (OR = 1.11; 95% CI: 1.03–1.20) had a higher prevalence of COVID-19 when compared to non-smokers. Another study from the U.K. evaluated the risk of COVID-19 among tobacco smokers via the Zoe COVID-19 Symptom Study app used by over 2.4 million people [44]. The results showed that current smokers (11%) were not only more prone to report COVID-19 related symptoms (OR = 1.14, $p < 0.05$) but also had a higher symptom burden (greater number of symptoms) (OR = 1.42, $p < 0.05$) and were more frequently admitted into the hospital (OR = 2.11, $p < 0.05$) when compared to

non-smokers. Another cohort study from England evaluated the effects of smoking among 387,109 participants via a questionnaire survey [45]. The authors found that current smoking increased the relative risk of COVID-19 1.45 times (95% CI:1.16–1.83) when compared to never smoking, while past smoking increased the relative risk of COVID-19 1.34 times (95% CI: 1.15–1.56) compared to never smoking [45]. A fourth study from the U.K. examined 1649 COVID-19 patients, 968 hospitalizations, and 444 COVID-19-related deaths [46]. Mendelian randomization analyses revealed current smokers to be at a higher odds of COVID-19-related hospitalization (OR = 1.80, 95% CI: 1.26–2.29) when compared to non-smokers. Additionally, a higher number of cigarettes smoked per day was also positively correlated with a higher risk of all infection outcomes (OR = 2.51, 95% CI: 1.20–5.24). Finally, a large cohort study from England including 7,869,534 participants evaluated the risk of current and former smokers to hospitalization and mortality from COVID-19 [47]. The authors found that while all smokers had a higher risk for all-cause mortality when compared to non-smokers, current smokers were at a reduced risk of severe COVID-19 symptoms compared to former smokers who were at a higher risk of hospitalization (hazard ratio (HR) = 1.07 (95% CI, 1.03–1.11)) and death (HR 1.17 (1.10–1.24)).

In addition, a literature review by Farsalinos et al. (2020) of 18 relevant studies (China (15); U.S. (2); South Korea (1)) was performed to examine the relationship between adverse outcomes of COVID-19 and smoking [48]. The overall review included 6515 patients with a smoking prevalence of 6.8%. Results from this study found that current smokers were 1.53 times more likely to experience adverse effects from a COVID-19 infection than non-smokers ($p = 0.022$). However, current smokers were 0.42 times less likely to have an adverse outcome than former smokers ($p = 0.003$). Similarly, 13 additional studies demonstrated that current smoking was more prevalent among COVID-19 patients exhibiting severe COVID-19 outcomes compared to patients experiencing non-severe outcomes [49]. Former smokers (OR 3.46; 95% CI: 2.46–4.85) and current smokers (OR 1.98; 95% CI: 1.16–3.39) also had significantly higher odds of severe COVID-19 outcomes.

3.3. Additional risk factors and co-morbidities beyond smoking impact COVID-19 symptoms, disease progression, hospitalization, and mortality

While the data from the above-mentioned articles indicate that current smoking causes a higher rate of infection from COVID-19 when compared to former smoking, there have been additional studies demonstrating that other factors may also play a significant role in exacerbating the symptoms of COVID-19. For example, a few meta-analyses have evaluated the effects of COPD and smoking on patients with COVID-19. One such meta-analysis (comprising 21 peer-reviewed articles) included 4603 patients and found that smokers have a 1.65 times higher risk of severe COVID-19 when compared to non-smokers (OR = 1.65; 95% CI: 1.17–2.34) [50]. In addition, the meta-analysis found that COPD was also associated with an increased risk of severe COVID-19 (OR = 4.62; 95% CI: 2.49–8.56). Another systematic review and meta-analysis by Zhao et al. (2020) included 12 Chinese studies and also analyzed the impact of COPD and smoking history on COVID-19 infection [51]. This study evaluated a total of 2002 patients, but only 7 of the 12 studies included reported the smoking history of the individuals. A compilation of the data found that while smoking increases the risk of severe COVID-19 infection by about a factor of 2 (OR = 1.98; 95% CI: 1.29–3.05), COPD was closely linked to the development of severe COVID-19 (OR = 4.38; 95% CI: 2.34–8.20). However, when one of the studies that had the largest sample size (that seemed to heavily impact their results) was removed, the impact of smoking on COVID-19 severity became statistically insignificant. The authors concluded that although their overall data indicated that smoking and COPD increases the severity of COVID-19 infection, there were limitations in the studies and further data is required to generate more conclusive results.

Other studies have assessed additional risk factors such as diabetes and hypertension, along with smoking status. For example, a meta-analysis of 109 articles involving 517,020 COVID-19 patients provided evidence of a statistically significant relationship between smoking and COVID-19 severity using a random-effects model, controlling for age, gender, and other risk factors (OR = 1.55; 95% CI: 1.41–1.71) [52]. Additionally, the authors observed a statistically significant association between smoking and the risk of admission to an ICU (OR = 1.73, 95% CI: 1.36–2.19), increased mortality (OR = 1.58, 95% CI: 1.38–1.81), and critical disease composite endpoints (e.g., acute respiratory distress syndrome, invasive ventilation or death) (OR = 1.61, 95% CI: 1.35–1.93). The study also found that other covariates that significantly affect the association between smoking status and severe COVID-19 were age ($p = 0.004$), hypertension ($p = 0.007$), diabetes ($p = 0.029$), and COPD ($p = 0.001$).

3.4. Impact of smoking non-cigarette products on COVID-19 symptom severity

In addition to cigarette smoking, a few studies have evaluated the impacts of non-cigarette products (like hookah and e-cigarettes) and nicotine replacement therapy (NRT) on COVID-19; however, no conclusive associations have been observed [53]. In the review by Kashyap et al. (2020), smoking tobacco was associated with an increase in the severity of, but not the prevalence of, COVID-19 infection [53]. The authors also suggested that smoking leads to increased lung inflammation which may be a cause of increased morbidity and mortality associated with COVID-19. Similarly, a representative population survey by Tattan-Birch et al. (2021) found that current and past smoking increased the prevalence of COVID-19 infection [54]. The survey included 3179 participants and examined factors including smoking status, e-cigarette use, and NRT. The odds of smokers (20.9% of the study sample) self-reporting COVID-19 were significantly higher (OR = 1.34, 95% CI:1.04–1.73) when compared with never smokers (14.5%). However, the survey found no significant relationship between COVID-19 and e-cigarette use or NRT. A limitation of the study was information bias since participants were self-reporting COVID-19 symptoms. Another cohort study from the U.S. included 69,264 patients who self-reported to be either e-cigarette, traditional cigarette, or dual users [55]. While the authors found no statistically significantly higher susceptibility to COVID-19 associated with smoking e-cigarettes (OR = 0.93; 95% CI: 0.69–1.25), smoking cigarettes or both products seemed to decrease the risk of COVID-19 (OR = 0.43, 95% CI: 0.35–0.53; and OR = 0.67, 95% CI: 0.49–0.92, respectively). A second

community-based cohort study from the U.S. studied 8214 participants with self-reported tobacco use [56]. While smoking cigarettes or e-cigarettes was inversely related to COVID-19 infection rates (OR = 0.49, 95% CI: 0.32–0.74; and OR = 0.654, 95% CI: 0.32–1.35, respectively), using smokeless tobacco was positively associated with COVID-19 infection rates (OR = 2.17; 95% CI: 1.26–3.72).

In contrast to the above-mentioned work, a study by Gaiha et al. (2020) postulated that the youth e-cigarette epidemic is directly related to the COVID-19 pandemic and sought to understand a possible link between youth smokers and COVID-19 in the U.S [57]. Surveying 4351 people between the ages of 13–24, the authors revealed that youth who used e-cigarettes exclusively were five times more likely to be diagnosed with COVID-19 than their non-vaping peers (OR 5.00, 95% CI: 1.82–13.96). Additionally, youth who ever smoked both e-cigarettes and traditional cigarettes (dual users) were seven times more likely (OR 7.00, 95% CI: 1.98–24.55) to develop COVID-19 symptoms. The study also examined the impact of more frequent cigarette use and found that youth who were dual users in the past 30 days were 6.8 times more likely to have a COVID-19 infection (OR 6.8, 95% CI: 2.40–19.55) and were also 4.7 times more likely to develop symptoms (OR 4.7, 95% CI: 3.07–7.16). A limitation of the study was that COVID-19 hospitalization or the severity of symptoms was not included.

3.5. Relationship between angiotensin-converting enzyme-2 (ACE-2), smoking, and COVID-19 infection

The pathophysiology of SARS-CoV-2 demonstrates that the angiotensin-converting enzyme-2 (ACE-2) is the cell receptor for this virus [30]. Potentially, different factors that cause an increased expression of the ACE-2 enzyme on the alveolar epithelial cells, similar to the effect of smoking, may result in a higher susceptibility to and greater severity of COVID-19 infection [58,59]. Chronic exposure to NO_2 from smoking can cause an increase in ACE-2 expression in the alveolar epithelial cells, suggesting that smoking likely increases the risk of COVID-19, as well as the severity of and mortality from the infection. Another study summarized the mechanism of receptor-ligand function and its relationship to the behavior of SARS-CoV-2 infection among smokers [60]. These authors reported that tobacco smokers are 1.4 times more likely to develop severe symptoms of COVID-19 infection and have a 2.4 times higher mortality rate. The authors explain that the upregulation of the ACE-2 gene not only increases the risk of COVID-19 infection but also can lead to cytokine storms causing lung injury in COVID-19 patients. Additionally, the authors observed a 100-fold increase in ACE-2 activity following increased exposure to NO_2 from tobacco smoking, which could help explain the higher prevalence of COVID-19 among smokers.

A cross-sectional study that examined the impact of smoking on COPD also evaluated the expression of the ACE-2 gene [61]. The study found that current smokers were characterized by a significantly increased expression of the ACE-2 gene, but former smokers revealed no increase in ACE-2 gene expression. The authors concluded that active cigarette smoking upregulated ACE-2 expression, which may increase the risk of severe COVID-19 infection. Another review encompassing data from Iran, China, Italy, and South Korea showed that the SARS-CoV-2 virus has a 10–20 times higher affinity for the ACE-2 receptors than previous SARS-CoV viruses [62]. Additionally, the study also reported that men have higher smoking rates and COVID-19 infection rates than women, indicating that gender is a potential confounder of the relationship between smoking and COVID-19 infection. While the findings of this review reiterated that smoking causes the ACE-2 receptor to be upregulated, leading to higher infection rates for smokers, the authors warn that this upregulation in ACE-2 receptors not only increases the risk of infection but also the transmission of the virus. Lastly, this paper reported that users of e-cigarettes and "heat-not-burn" devices are just as likely to have these increased risks of an upregulated ACE-2 receptor. Similar to previous studies, in an evaluation of ACE-2 expression in SARS-CoV-2 infections, Li et al. (2020) and Russo et al. (2020) also found a higher expression of ACE-2 among smokers, likely leading to a greater risk of SARS-CoV-2 [63,64]. The above-mentioned studies reinforce the idea that smoking upregulates ACE-2 and facilitates easier binding to the SARS-CoV-2 virus, suggesting that long-term smokers are at a greater risk of COVID-19 infection.

3.6. Studies supporting the inverse relationship between smoking and COVID-19 prevalence

In contrast to all of the above-mentioned studies, multiple studies across different countries have demonstrated an inverse relationship between smoking tobacco and developing COVID-19 symptoms. A case-control study from Mexico included 32,583 patients (12,304 COVID-19 positive cases and 20,279 COVID-19 negative controls) of which 2.3% of cases were smokers and 4.3% of controls had a history of smoking [65]. This study not only concluded that active smokers had a decreased likelihood of developing COVID-19 (females, adjusted OR = 0.49, 95% CI: 0.31–0.78; males, adjusted OR = 0.64, 95% CI 0.51–0.81) but also suggested that nicotine in tobacco might have a therapeutic effect. Similarly, a study with 331,298 patients in Mexico studied the clinical characteristics affecting the mortality of patients with COVID-19 [66]. According to their multivariate logistic regression model, smoking was not statistically significantly associated with mortality risk or development of COVID-19 symptoms. However, the authors suggested that their multivariate analysis might have been influenced by the sex of the patient.

Similar to the results from the study by Hernández-Garduño (2020), Tsigaris and Silva (2020) also reported a negative relationship ($p > 0.05$) between COVID-19 mortality and smoking and suggested that nicotine may provide some protection from the infection [11]. Comparing 38 European nations, the authors found that countries with higher smoking rates had fewer COVID-19 cases per million people than countries with lower rates of smoking after controlling for confounding variables including economic activity and COVID-19 prevention measures in different countries. With the highest smoking rate (43.4%) among the countries analyzed, Greece had only 280 COVID-19 positive cases per million people, the lowest level of all countries analyzed. Moreover, while the average smoking prevalence among the five countries with the highest smoking rates was 39.5%, they only had an average of 1084 COVID-19 cases per million and 29 COVID-19 deaths per million people. This was substantially lower when compared to the five countries with the lowest smoking rate, which had an average smoking prevalence of 18.6% but had 2754 COVID-19 cases per million people and 133

COVID-19 mortalities per million people. However, the study did not find a statistically significant ($p = 0.626$) relationship between COVID-19 mortality rates and smoking.

Two cross-sectional studies evaluating the correlation between active smokers and COVID-19 positivity rates showed similar results [67,68]. The first study included 340 inpatients and 130 outpatients with a smoking rate of 4.1% and 6.1%, respectively [67]. The authors concluded that in comparison to the smoking rate among the general population (25.4%), the smoking prevalence in symptomatic COVID-19 patients was lower. The second study collected data from a primary care network in the U.K. to analyze the effect of several clinical risk factors, including smoking, on COVID-19 [68]. The study found that while active smokers had a positive COVID-19 test rate of approximately 6% less than that of non-smokers (adjusted OR = 0.49; 95% CI: 0.34–0.71), ex-smokers had a positive test rate of 0.6% less than that of non-smokers (adjusted OR = 0.87; 95% CI: 0.69–1.10). Despite these results, the authors concluded that more research is necessary before any conclusions about the impact (or lack thereof) of smoking on COVID-19 can be made.

A meta-analysis of five studies from China was published corroborating the previous negative relationship between smoking and COVID-19 infections [69]. This analysis found no significant relationship between smoking and COVID-19 (OR = 1.69; 95% CI: 0.41–6.92; and $p = 0.254$). An interesting point to note here is that, while this study analyzed the same five studies as Vardavas et al. (2020), the authors came to a different conclusion. This perhaps demonstrates the impact that limited data have on study findings and indicates that more research is needed to come to a definitive conclusion. Another meta-analysis of 7162 patients was performed using 20 studies from China and 2 from the U.S [70]. The authors found no significant association between smoking and COVID-19 disease severity (OR 1.40, 95% CI 0.98–1.98) and mortality (OR 1.86, 95% CI 0.88–3.94). Lastly, after reviewing 12 peer-reviewed articles from different regions of the world, Tajlil et al. (2020) observed a statistically significantly ($p < 0.001$) lower proportion of COVID-19 patients with a smoking history compared to what was expected, given the population averages of the geographic areas studied [71].

3.7. Controversies regarding the true nature of the relationship between smoking and COVID-19 prevalence and symptoms

A spatial epidemiological approach utilizing World Health Organization (WHO) data from 175 countries showed that the prevalence of smokers significantly explained global variation in COVID-19 outbreaks [72]. Nevertheless, controversies have arisen within the scientific community regarding the true relationship between smoking tobacco and developing COVID-19 symptoms. For example, Carmona-Bayonas et al. (2020) performed a Bayesian statistical analysis of the data from the review article by Lippi and Henry (2020) [69,73]. Lippi and Henry (2020) claimed that their data showed that smoking had no relationship with COVID-19 symptoms. However, Carmona-Bayonas et al. (2020) argued that this was an example of "absence of evidence is not evidence of absence." Furthermore, in the Bayesian analysis performed, the authors found that active smoking increases the severity of COVID-19 infection (OR = 1.79; 95% CI: 0.86–4.13). Similarly, Guo et al. (2020) also dissected the analysis performed by Lippi and Henry (2020) and claimed that their conclusion was incorrect [69,74]. Guo first asserts that the figures that Lippi and Henry used in their statistical analysis were not consistent with the results of the studies that they analyzed. Performing an updated meta-analysis, Guo et al. (2020) found that the pooled OR was 2.20 (95% CI: 1.31–3.67; $p = 0.003$) and not 1.69 (95% CI: 0.41–6.92; $p = 0.254$) as suggested by Lippi and Henry (2020). This provided evidence that Lippi and Henry's (2020) conclusion that smoking does not increase the prevalence of COVID-19 may be based on an inaccurate analysis. Subsequently, multiple myths concerning the topic of smokers being potentially protected against SARS-CoV-2 have evolved, and subsequent articles discussing the flaws in these interpretations have also been published [75,76]. The authors of these rebukes shed light on the methodical limitations of some of the articles that demonstrate an inverse relationship between smoking and COVID-19 complications.

4. Conclusions

Overall, the majority of the papers cited in this mini-review (31 articles) found a positive relationship between smoking tobacco (or active smokers) and COVID-19 infection, while 13 articles reported contrasting results. The papers reviewed included data concerning the impact of smoking on the risk of being infected by SARS-CoV-2 and the severity of the disease once infected. Differentiating the type of tobacco products used, some data indicated that e-cigarettes may increase susceptibility to COVID-19 but to a lesser extent than traditional smoking.

Overall, given the multitude of factors that might be responsible for exacerbating COVID-19 symptoms, there remains much to be researched. However, as evidenced by this literature review, the great majority of papers to date evaluating the associations between smoking and COVID-19 indicate that smoking may worsen COVID-19 infection and increase transmission. Moreover, some studies that have demonstrated a protective relationship between smoking and COVID-19 have later been shown to have methodological issues, suggesting that the findings from these studies should be viewed with caution.

Ethics approval

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Author contribution statement

SC, SK, and ZM conducted the literature review, summarized the findings, and wrote the first draft of the manuscript. SC and LM edited and critically revised the manuscript. SC and ARS conceived the manuscript idea, supervised the process, edited the manuscript, and approved the final version. SC served as the corresponding author.

Data availability statement

No data was used for the research described in the article.

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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