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Review Article

Effects of Smoking on COVID-19 Management and Mortality: An Umbrella Review

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Introduction. Smoking status appears to lead to a poor prognosis in COVID-19 patients. However, findings from the studies conducted on this topic have not been consistent, and further exploration is required. *Methods*. The objective of this umbrella review was to examine the effects of smoking on COVID-19 management and mortality. Online databases that included PubMed, Embase, Scopus, and Web of Science were searched using relevant keywords up to July 27, 2022. Articles were restricted to the English language, and the PRISMA protocol was followed. *Results*. A total of 27 systematic reviews, published from 2020 to 2022, were included. Individual studies included in the systematic reviews ranged from 8 to 186, with various population sizes. The consensus from the majority of systematic reviews was that COVID-19 smoker patients experience greater disease severity, disease progression, hospitalization rate, hospital admission duration, mechanical ventilation, ICU admission, and mortality rate. *Conclusions*. COVID-19 patients with a history of smoking (current and former) are vulnerable to adverse hospital outcomes and worse COVID-19 progression. Effective preventive and supportive approaches are required to decrease the risk of COVID-19 morbidity and mortality in patients with a history of smoking.

1. Introduction

Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2)—the cause of coronavirus disease 2019 (COVID-19)—first emerged in December 2019 in Wuhan, China [1–4]. The World Health Organization (WHO) declared a global COVID-19 pandemic in March 2020 [5]. As of August 8th, 2022, COVID-19 has infected more than 581 million people and caused more than 6.4 million deaths worldwide [6]. SARS-Cov-2 is mainly an aerosol-born disease and infects new cases through respiratory droplet inhalation [7–9]. COVID-19 presents mostly with flu-like symptoms such as fever, chills, myalgia, dry cough, fatigue, back pain, headache, anorexia, diarrhea, anosmia (loss of smell sensation), and ageusia (loss of taste sensation) [10, 11]. However, 4–41% of total cases can be asymptomatic [10, 11]. Severe COVID-19 can cause acute respiratory distress syndrome (ARDS), which manifests with hypoxia, dyspnea, chest pain, altered consciousness, cyanosis, and eventual death. It mainly occurs among older adults (i.e., >65 years) and vulnerable populations including patients with chronic kidney, liver, or lung disease, diabetes mellitus, obesity, HIV infection, and smoking history [12].

Smokers are more predisposed to viral and bacterial pulmonary infections including influenza, tuberculosis, and bacterial pneumonia [13–16]. In the first months of the pandemic in 2020, it was reported that Chinese patients with severe COVID-19 were mostly COPD patients or current smokers [17]. In addition, one of the earliest systematic reviews concluded that smoking is negatively associated with COVID-19 progression and prognosis [18]. Some studies have reported higher expression of angiotensin-converting enzyme 2 (ACE-2), which is the main receptor of SARS-CoV-2, in the lower respiratory airways of current smokers and COPD patients compared to nonsmokers, and stated that smoking and COPD could contribute to a higher COVID-19 incidence and relatively poorer outcomes [19, 20]. Conversely, some studies have reported lower levels of ACE-2 among smokers compared to nonsmokers [21, 22], and one preliminary meta-analysis of five studies in China stated smoking may not be significantly associated with an increased risk of severe disease among COVID-19 patients [23].

There have been five other meta-analyses conducted where the findings support the hypothesis that COPD and current smoking status contribute to worse progression and poor outcomes among COVID-19 patients [24–28]. One of the meta-analyses specifically stated that smoking can have negative adverse impacts on disease severity and mortality among hospitalized COVID-19 patients, with more impact on nondiabetic younger patients [27]. In addition, another meta-analysis specified that both current smoking and previous history of smoking increase COVID-19 severity significantly, while previous history of smoking increases the mortality risk [28]. Now that almost three years has passed since the first report of SARS-CoV-2 in human population, and large sample-sized studies and more reliable data are available, further investigation of COVID-19 and smoking is warranted. The aim of this review was to examine the associations between COVID-19 and smoking status (current smoker or history of smoking), answer the controversial paradoxes, and fill the gaps in the literature.

2. Methods

The objective of this umbrella study was to explore the prevailing systematic review literature pertaining the associations between COVID-19 and smoking status (being a current smoker or having history of smoking) and effects of smoking on COVID-19 management and mortality. In order to substantiate the results, the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist was followed. Quality of studies was evaluated with the NIH quality assessment tool.

2.1. Data Sources. An extensive search of four online databases was performed which included PubMed, Scopus, Embase, and Web of Science as data sources. Articles were restricted to the English language, and the search was conducted up to July 27, 2022. The following keywords and their combinations were used during the search:

(a) "COVID-19" OR "Novel coronavirus" OR "2019-nCoV" OR "SARS-CoV-2" OR "SARS- CoV2" [Title/Abstract]

(b) "Smoking" [Title/Abstract]

(c) "Systematic review" [Title/Abstract]

(d) [A] AND [B] AND [C]

2.2. Study Selection. In order to improve the study selection process, a two-step method was employed. The first step consisted of screening literature with regard to titles and abstracts. This was done by five researchers. The second step was performed by another five researchers, involving screening of full texts that were potentially eligible. Articles that met the inclusion criteria were advanced to the next step of data extraction. Articles were included if they had a systematic review nature and were peer-reviewed report on smoking and COVID-19. The exclusion criteria included studies lacking published data investigations, nonhuman research studies, duplications, abstracts with deficient full texts, editorial letters, conference abstracts, case series, and case reports.

2.3. Data Extraction. Data of publications having met the eligibility criteria and passing the second step of selection process was meticulously extracted and gathered in Table 1. Five researchers investigated the full texts and extracted these study requisites. Any duplicates were removed, and the accuracy of the extracted data was checked.

2.4. Quality and Risk of Bias Assessment. Study quality and risk of bias was assessed with the National Institute of Health (NIH) Quality Assessment (QA) Tools for Case Series Studies. Two independent reviewers rated the quality of the included studies. Table 2 shows the results of the study quality and risk of bias. The scoring strategy of this tool has been explained at the bottom of this table.

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Table 1: Characteristics of studied items in the included papers.

First author (reference)	Country	Year of publication	Type of study	Population	Age	Gender	Smoking history
Alghamdi, S.A. [29]	Saudi Arabia	2020	Systematic review and meta-analysis	146,793 patients (from 11 studies)	55.2 y (mean age)	Male:55.4%	Smokers: 11,973 Nonsmokers: 134,820
Baker, J [30]	USA	2022	Systematic review	39 studies (populations varied from 101 to 406,793)	N/A	N/A	Smokers were ranging from 1.95% to 81.1% of populations
Farsalinos, K [31]	Greece	2020	Systematic review and meta-analysis	6,515 patients (18 published studies) 10,631 patients (prepublications)	N/A	N/A	440 smokers (out of 6115 pts) 961 smokers (out of 10631 pts)
Gonzalez-Rubio, J [32]	Spain	2020	Systematic review and meta-analysis	5,023 pts (18 studies)	N/A	53.2% male	Current smokers: 7.7%
Grundy, E. J [33]	UK	2020	Review of reviews	Varies from 17 to 387,109 pts for each of the included studies in * studies (8 studies)	N/A	N/A	Patients divided in smokers, ex-smokers, and nonsmokers groups
Gulsen, A [34]	Turkey	2020	Systematic review and meta-analysis	10,797 patients (16 studies)	Mean age range: 38 to 62.2 y	N/A	Average smoking prevalence: 8.4% Range: 3.6 to 19.9%
Hou, H [35]	China	2021	Systematic review and meta-analysis	863,313 (73 articles)	N/A	N/A	Current smokers and former smokers
Kang, S [36]	China	2021	Systematic reviews	7041 (21 studies)	N/A	N/A	14.0% (984) had a history of smoking
Karanasos, A [27]	Greece	2020	Systematic review and meta-analysis	6310 patients (18 studies)	N/A	N/A	N/A
Kumar, R [37]	China (PRC), USA, and Europe	2021	Systematic review and meta-analysis	12037 (19 studies)	Age ranged from 23 to 91 years	55.68% male 42.76% females	N/A
Li, J [38]	China	2021	Systematic review and meta-analysis	2445 patients (12 studies)	N/A	N/A	N/A
Luo, S [39]	China	2022	Systematic review of Mendelian randomization studies	50 studies	N/A	N/A	Smoking include smoking initiation, smoking heaviness, and lifetime smoking
Mahamat-Saleh, Y [40]	France	2021	Systematic reviews and meta-analyses	186 studies 1,304,587 patients (210 447 deaths) (186 studies)	N/A	N/A	Former and current smoker

Table 1: Continued.

First author (reference)	Country	Year of publication	Type of study	Population	Age	Gender	Smoking history
Mattey-Mora, PP [41]	USA	2022	Systematic reviews	1,002,006 patients (188,597 hospitalized patients) (40 study)	Mean age 44–68.8 years (from 11 study) Mean age 41–66.1 (from 11 study) 18 study not mentioned on age	N/A	Current/past smoking
Mesas, AE [42]	Spain	2020	Systematic review and meta-analysis	51,225 patients from 60 studies	Mean age range: 40-73 year	N/A	Current smokers and nonsmokers
Minh, LHN [43]	Japan	2021	Systematic review and meta-analysis	62,949 patients from 148 studies	N/A	N/A	Current smoker, external smoker, and never smoker
Patanavanich, R [44]	USA	2021	Systematic review and meta-analysis	22,939 patients from 46 studies	N/A	N/A	Current smokers, ex-smokers, and nonsmokers
Patanavanich, R [45]	Thailand	2022	Systematic review and meta-analysis	35,193 patients from 34 articles	Mean age 63.5 years	N/A	Current smokers, former smokers, and never smokers
Plasencia-Urizarri, TM [46]	Cuba	2020	Systematic review and meta-analysis	99,817 patients from 13 studies	N/A	N/A	Smokers and nonsmokers
Pranata, R [47]	Indonesia	2020	Systematic review and meta-analysis	4603 patients from 21 studies	>17 years	N/A	Current smokers, former smokers, and nonsmokers
Reddy, RK [28]	UK	2020	Systematic review and meta-analysis	32 849 hospitalized COVID-19 patients from 47 studies	N/A	N/A	8417 (25.6%) patients with a smoking history, comprising 1501 current smokers, 5676 former smokers, and 1240 unspecified smokers
Sanchez-Ramirez, DC [48]	Canada	2020	Systematic review and meta-analysis	13,184 COVID-19 patients from 22 studies	N/A	55% males	Current smokers, former smokers, and nonsmokers
Taylor, EH [49]	South Africa	2021	Systematic review and meta-analysis	44,305 patients from 58 studies	Mean age of 61.8 (60.7–63.0) years	68.9% males	Smokers and nonsmokers
Umnuaypornlert, A [50]	Thailand	2021	Systematic review and meta-analysis	369287 patients from 40 studies	Mean age 54.10 years	N/A	Current smokers, former smokers, and nonsmokers
Vardavas, C.I [18]	USA	2020	Sys review	Ranged from 41 to 1099 (5 studies)	N/A	N/A	Current smokers, former smokers, and nonsmokers
Zhang, H [51]	USA, China	2021	Sys review and meta-analysis	517020 pts(109 studies)	N/A	N/A	Patients divided to current smokers, former smokers, and never smoking group
Zhang, T [52]	China	2020	Sys review, meta-analysis and metaregression	Varies from 21 to 476 (16 studies)	Mean or median age varies from 39 to70.7y	Male is the dominant sex in 11 studies	Current smokers, former smokers, and nonsmokers

Table 2: Quality ratings of included studies based on NIH quality assessment (QA) tool for case series studies.

First author (# of ref)	*Question									Rating by reviewers	
	1	2	3	4	5	6	7	8	9	# 1	# 2
Alghamdi, S.A. [29]	Yes	Yes	N/A	Yes	N/A	Yes	N/A	Yes	Yes	Good	Good
Baker, J [30]	Yes	Yes	N/A	Yes	N/A	Yes	N/A	Yes	Yes	Good	Good
Farsalinos, K [31]	No	Yes	N/A	Yes	N/A	Yes	N/A	Yes	Yes	Good	Fair
Gonzalez-Rubio, J [32]	No	Yes	N/A	Yes	N/A	No	N/A	No	Yes	Fair	Poor
Grundy, E. J [33]	Yes	Yes	N/A	Yes	N/A	No	N/A	No	Yes	Fair	Fair
Gulsen, A [34]	Yes	Yes	N/A	Yes	N/A	Yes	N/A	Yes	Yes	Good	Good
Hou, H [35]	Yes	Yes	N/A	Yes	N/A	Yes	N/A	Yes	Yes	Good	Good
Kang, S [36]	No	No	N/A	Yes	N/A	No	N/A	Yes	Yes	Fair	Fair
Karanasos, A [27]	Yes	Yes	N/A	Yes	N/A	Yes	N/A	Yes	Yes	Good	Good
Kumar, R [37]	Yes	No	N/A	Yes	N/A	Yes	N/A	No	Yes	Fair	Good
Li, J [38]	No	Yes	N/A	No	N/A	No	N/A	Yes	No	Poor	Poor
Luo, S [39]	Yes	Yes	N/A	Yes	N/A	No	N/A	No	No	Fair	Poor
Mahamat-Saleh, Y [40]	Yes	Yes	N/A	Yes	N/A	Yes	N/A	No	Yes	Good	Good
Mattey-Mora, PP [41]	No	Yes	N/A	Yes	N/A	No	N/A	No	No	Poor	Fair
Mesas, AE [42]	Yes	Yes	N/A	Yes	N/A	No	N/A	Yes	Yes	Fair	Good
Minh, LHN [43]	Yes	Yes	N/A	Yes	N/A	Yes	N/A	Yes	Yes	Good	Good
Patanavanich, R [44]	Yes	Yes	N/A	Yes	N/A	Yes	N/A	Yes	Yes	Good	Good
Patanavanich, R [45]	Yes	Yes	N/A	Yes	N/A	Yes	N/A	Yes	Yes	Good	Good
Plasencia-Urizarri, TM [46]	Yes	No	N/A	Yes	N/A	Yes	N/A	Yes	No	Fair	Poor
Pranata, R [47]	Yes	No	N/A	Yes	N/A	No	N/A	Yes	Yes	Good	Good
Reddy, RK [28]	Yes	Yes	N/A	Yes	N/A	Yes	N/A	Yes	Yes	Good	Good
Sanchez-Ramirez, DC [48]	Yes	Yes	N/A	Yes	N/A	Yes	N/A	Yes	Yes	Good	Good
Taylor, EH [49]	No	Yes	N/A	Yes	N/A	No	N/A	Yes	Yes	Good	Fair
Umnuaypornlert, A [50]	Yes	Yes	N/A	Yes	N/A	Yes	N/A	Yes	Yes	Good	Good
Vardavas, C.I [18]	No	Yes	N/A	Yes	N/A	Yes	N/A	Yes	Yes	Good	Good
Zhang, H [51]	Yes	Yes	N/A	Yes	N/A	Yes	N/A	Yes	Yes	Good	Good
Zhang, T [52]	No	Yes	N/A	Yes	N/A	No	N/A	Yes	Yes	Fair	Good

Note: NIH: National Institutes of Health; CD: cannot determine; NR: not reported; NA: not applicable. *The NIH quality assessment tool for case series studies (https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools) contains nine questions: 1 = Was the study question or objective clearly stated?, 2 = Was the study population clearly and fully described, including a case definition?, 3 = Were the cases consecutive?, 4 = Were the subjects comparable?, 5 = Was the intervention clearly described?, 6 = Were the outcome measures clearly defined, valid, reliable, and implemented consistently across all study participants?, 7 = Was the length of follow-up adequate?, 8 = Were the statistical methods well-described?, 9 = Were the results well-described? (source: National Heart, Lung, and Blood Institute; National Institutes of Health; U.S. Department of Health and Human Services) https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools.

3. Results

The database search yielded 113 potential studies (after duplicates removed), and following the screening, a total of 27 articles met the eligibility criteria (Figure 1). The included systematic reviews were published between 2020 and 2022. One study included was designed as reviews of reviews [33].

Included studies were from China, the USA, Spain, Greece, Thailand, Canada, Indonesia, Japan, and other countries. China (7 studies) and the USA (5 studies) were the countries most represented. The 27 systematic reviews included a wide range of studies (i.e., 8 to 186 studies) with different populations (from 17 to 1,304,587 patients among mentioned populations). Males were the dominant population in 6 studies [29, 32, 37, 48, 49]. Table 1 shows the characteristics of the studies.

Smoking history was categorized as smokers and non-smokers in some studies [46, 49], while most studies evaluated the smoking status as current and former smokers with comparisons between these groups [18, 40–42, 47]. One study represented smokers based on smoking heaviness, lifetime smoking, and smoking initiation [39].

Most of the studies concluded that smoker's with COVID-19 had a worse outcome and higher mortality rate [27, 30, 34, 36]. Evaluating the hospital admission rate, most of the studies showed increased risk of hospital admissions in smokers [18, 29, 30], while one study showed that smokers had lower risk of hospital admission [33].

The majority of studies found that smoking was associated with increased risk for mechanical ventilation [18, 29, 30]; however, there was one study showing no association between

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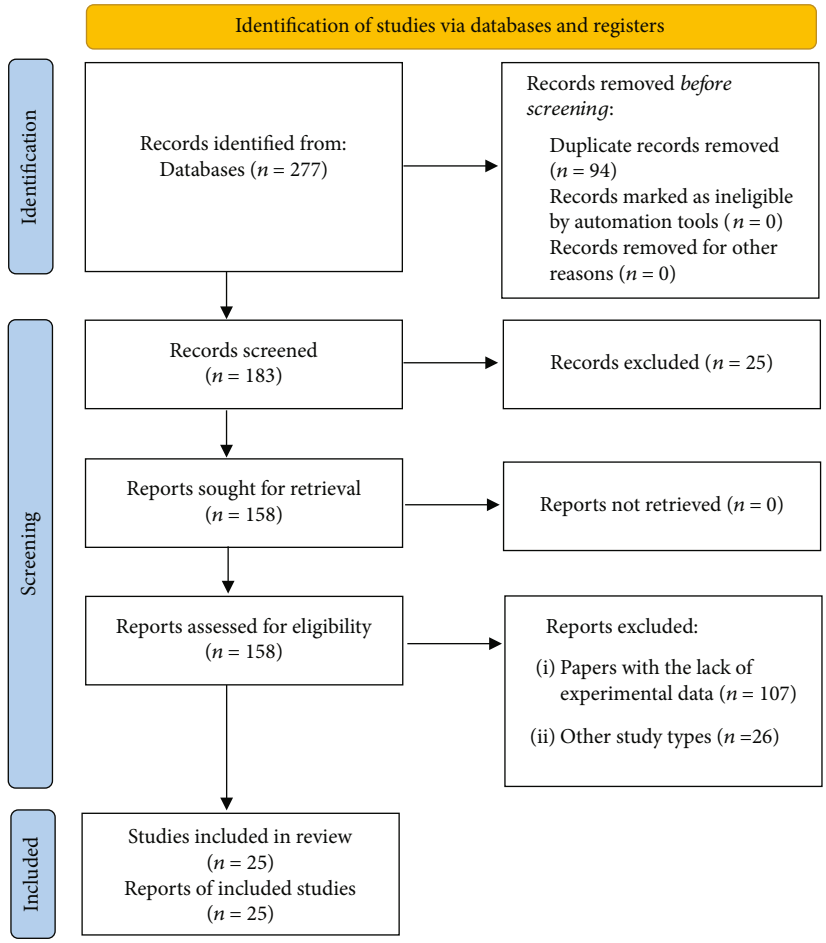

Figure 1: PRISMA 2020 flow diagram of study retrieval process.

smoking status and risk of mechanical ventilation [51]. These results are shown in Table 3.

4. Discussions

According to the NIH's LitCovid database, more than 291,000 articles related to COVID-19 have been published to date, which shows the explosion of research in this field. This incredible amount of research has increased the information on different aspects of the disease. However, knowledge is still lacking in some areas with further research required to better understand COVID-19 and its effects. This umbrella review is aimed at organizing and updating the existing body of literature on the effects of smoking on COVID-19.

The overall findings support the hypothesis of increased severity of disease in COVID-19 smoker patients. Specifically, smoking is linked to more advanced COVID-19 outcomes, as manifested by the necessity for ICU admission, mechanical ventilation, and COVID-19-related death. Nevertheless, only a few studies demonstrated no significant link between smoking and COVID-19-related mortality [30] and mechanical ventilation [51]. Additionally, only one study found no link between smoking and an increased risk of death from COVID-19 [27]. Notably, a study in England, that investigated approximately 17 million patient documents, discovered that increased COVID-19-related mortality linked to smoking no longer remained significant after adjustment for the presence of preexisting chronic pulmonary disease. This suggests that smoking-induced comorbidities may be the cause of the overall death toll among COVID-19 smoker patients [53]. The results emphasize the need for further research elucidating the mechanisms by which smoking increases the incidence of unfavorable outcomes in COVID-19 patients.

Various potentially harmful compounds are present in tobacco products. Moreover, further chemicals are formed during aerosolization as a result of combustion or heating. Previous studies have demonstrated that pulmonary epithelium and vascular endothelium are both damaged by harmful compounds in cigarette smoke. The mucociliary clearance and epithelial barrier are compromised by damage to epithelial cells. Additionally, injured cells release modified molecules that activate specific lung receptors, activating acquired and innate immune responses [54]. Through a variety of mechanisms including the direct effect of nicotine, reperfusion injury after carbon monoxide-induced hypoxia, and particulate matter's abundance, tobacco smoke ingredients cause oxidative stress [55, 56].

The angiotensin II conversion enzyme-2 (ACE2) receptor, which is abundant in mucosal respiratory epithelial cells,

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Table 3: Description of the findings reported in the eligible studies.

First author (reference)	Effect of smoking on COVID-19							
	Disease progression	Disease severity	Outcome	Hospital admission	Increase hospitalization	ICU admission	Mechanical ventilation	Other findings
Alghamdi, S.A. [29]	More in smokers	More in smokers	Increased mortality and worse overall outcome in smokers	More admission in smokers	N/A	Increased in smokers	More in smokers	Smokers are more prone to have a severe disease and increased mortality rate
Baker, J [30]	More in tobacco users	More in tobacco users	-Increased mortality in tobacco users (17 studies) -Decreased mortality (1 study) No association between mortality and tobacco use (14 studies)	Higher admission rate in tobacco use	Longer hospital stay in tobacco users	Higher in tobacco users	Increased risk in tobacco use	Adverse outcome and higher mortality rate and more severe disease found in tobacco users
Farsalinos, K [31]	N/A	N/A	Worse outcome in current smoker, but still less than former smokers	Interesting finding of lower admission rate between smokers	N/A	N/A	N/A	More negative outcome among current smoker but les probability of hospital admission But overall, smoking in not protective against COVID infection
Gonzalez-Rubio, J [32]	N/A	N/A	N/A	Lower in smokers	N/A	N/A	N/A	Lower hospital admission in smokers
Grundy, E. J [33]	Higher risk of progression in smokers	Sever disease in smokers	Adverse outcome in smokers	More in smokers	N/A	N/A	N/A	Smokers have greater risk of severe disease
Gulsen, A [34]	N/A	Sever disease in smokers	Increased mortality in smokers	N/A	N/A	Higher risk of ICU admission	N/A	Risk of severe COVID is increased with both current smoking and previous history of smoking
Hou, H [35]	N/A	N/A	Mortality is significantly higher in former smokers compared to current smokers	N/A	N/A	N/A	N/A	Significant increase in mortality rate in smokers(especially in former smokers compared to current smokers)
Kang, S [36]	Increase rate of disease progression	Smoking increase disease severity	Smoking increase mortality	N/A	Smoking increases hospitalized	N/A	N/A	N/A

Table 3: Continued.

First author (reference)	Effect of smoking on COVID-19							
	Disease progression	Disease severity	Outcome	Hospital admission	Increase hospitalization	ICU admission	Mechanical ventilation	Other findings
Karanasos, A [27]	N/A	Increased severity	Increased mortality	N/A	Smoking increases the risk of hospitalized	N/A	N/A	Association of smoking with severity was not significant (10 studies with 4152 patients)
Kumar, R [37]	N/A	Significant association with severity	N/A	N/A	N/A	N/A	N/A	
Li, J [38]	N/A	Significantly associated with severe COVID-19	N/A	N/A	N/A	Significantly associated with severe (ICU) COVID-19	N/A	
Luo, S [39]	N/A	Strong associations with smoking	Strong associations with smoking	N/A	Strong associations with smoking	N/A	N/A	
Mahamat-Saleh, Y [40]	N/A	N/A	Increased absolute risk of death	The absolute risk of COVID-19 death increased by 7%	N/A	N/A	N/A	In this study show risk of death increase in ever smoker 28% current 29% and former 25%
Mattey-Mora, PP [41]	N/A	N/A	N/A	N/A	Smoking increases hospitalized	N/A	N/A	
Mesas, AE [42]	N/A	N/A	Higher in-hospital mortality risk in smokers	N/A	N/A	N/A	N/A	N/A
Minh, LHN [43]	More in smokers	Higher risk of severity in smokers	Higher death risk in smokers	N/A	N/A	N/A	N/A	N/A
Patanavanich, R [44]	Higher disease progression in those with a history of smoking	N/A	Increased risk of death from COVID-19	N/A	N/A	N/A	N/A	N/A

Table 3: Continued.

First author (reference)	Effect of smoking on COVID-19							
	Disease progression	Disease severity	Outcome	Hospital admission	Increase hospitalization	ICU admission	Mechanical ventilation	Other findings
Patanavanich, R [45]	N/A	N/A	Higher risk of death in current and former smokers compared to never smokers	N/A	N/A	N/A	N/A	The risk for COVID-19 death in current smokers does not vary by age, but significantly drops by age in former smokers
Plasencia-Urizarri, TM [46]	N/A	Higher risk for severe clinical presentations in smokers	N/A	N/A	N/A	N/A	N/A	N/A
Pranata, R [47]	N/A	N/A	Increased risk of composite poor outcome in smoker	N/A	N/A	N/A	N/A	Current smokers were at higher risk of composite poor outcomes than former/nonsmokers
Reddy, RK [28]	Increased risk of disease progression in patients with a smoking history	Increased risk of severe COVID-19 in current smokers	Increased in-hospital mortality in patients with a smoking history	N/A	N/A	N/A	Increased need for mechanical ventilation in patients with a smoking history	N/A
Sanchez-Ramirez, DC [48]	N/A	N/A	Higher rate of severe outcome in current and former smokers	N/A	N/A	N/A	N/A	N/A
Taylor, EH [49]	N/A	N/A	Higher ICU mortality rate in smokers	N/A	N/A	N/A	N/A	N/A
Umnuaypornlert, A [50]	N/A	Increased risk of disease severity in current and former smokers	Increased mortality in current and former smokers	N/A	N/A	N/A	N/A	N/A
Vardavas, C.I [18]	Smokers are more prone to have negative progression and severe symptoms	Smokers have severe disease	Higher mortality rate and adverse outcome was seen in smokers	More in smokers	N/A	Higher risk of ICU admission in smoker group	Higher risk of MV in smokers	There is an association between smoking and higher mortality and adverse outcome

Table 3: Continued.

First author (reference)	Effect of smoking on COVID-19							
	Disease progression	Disease severity	Outcome	Hospital admission	Increase hospitalization	ICU admission	Mechanical ventilation	Other findings
Zhang, H [51]	N/A	Smoking was associated with severe COVID	Smokers have higher mortality rate	N/A	N/A	Higher risk of ICU admission was seen among smokers	No relationship was found between MV and smoking	Severe disease was more associated with former smoking compared to current smoking
Zhang, T [52]	Former smokers have more symptoms and severe disease	Former smokers are more prevalent in severe COVID group	Higher mortality rate is seen in severe cases (including former smokers)	N/A	N/A	N/A	N/A	Smoking is among the risk factors for severe COVID infection and complications

has been associated with COVID-19 infection. It is probably the most reasonable explanation for the potential increased risk of death among smokers. Infection by the host-virus binding to the ACE2 receptors is likely a critical stage in SARS-CoV-2 infection [57–59]. Smokers have significantly higher levels of pulmonary ACE2 gene expression compared to nonsmokers [60]. Tobacco use can cause oxidative stress and inflammation in the lungs, making smokers more susceptible to bacterial or viral diseases [58, 61]. Oxidative stress reduces epithelial permeability, which may have substantial consequences for smokers with COVID-19 disease [62, 63]. Likewise, smoking leads to cardiovascular disease, chronic lung illness, diabetes, and other comorbidities that are related to worse outcomes in patients with COVID-19 infection [64].

On the contrary, there is evidence demonstrating that smoking may exert positive effects on COVID-19 disease severity, mediated by nicotine [51]. It is important to keep in mind that specific cigarette ingredients, like nicotine, may affect ACE2 differently from entire cigarettes [65]. The underlying mechanism might be attributed to the evidence showing nicotine might decrease tumor necrosis factor (TNF) expression in airway epithelial cells [66]. Moreover, nicotine may act as an agonist of the cholinergic anti-inflammatory pathway, which regulates the immune response and inflammatory reaction [67, 68].

Factors responsible for higher susceptibility of smokers to COVID-19 are briefly discussed here to better understand the mechanisms about how smoking can affect the human body:

(i) Smoking causes significant pathological changes including the mucosal epithelial barrier and an increase in the permeability of epithelial cells, which makes smokers more prone to be defeated against the virus invasion [69]

(ii) Angiotensin-converting enzyme 2 (ACE 2) is defined as the principal receptor for SARS-CoV-2 virus to enter the host cell. ACE 2 expression is upregulated in the small airway epithelium of smokers, so the virus tends to invade host cells more easily. This upregulated receptor expression is one of the negative influences of oxidative stress due to smoking [20]

(iii) Smoking can reduce the function of the immune system by causing a reduction in the number of CD4 + T cell (also named T helper cell, which activates macrophage or B cell), inhibiting the production of interleukin-22 (which moderates lung inflammation) and also, by promoting the secretion of catecholamines (which will weaken the immune system) [70, 71]

(iv) The most serious complication of COVID-19 disease is acute respiratory distress syndrome (ARDS), as a result of the cytokine storm. In this situation, large amounts of proinflammatory cytokines and chemokines such as IP-10, IL-6, TNF-α, IFN-γ, IL-2, IL-7, and GM-CSF are released and entail severe immune system response which eventually causes lung inflammation and damage. In former smokers, the expression of IL-6, TNF-α, and other proinflammatory factors are increased [72]

Although most of the reviewed articles support the hypothesis that nicotine, the main component of cigarettes, increases the odds of developing severe illness of COVID-19, it is unknown whether the harm is related to nicotine or other toxic ingredients in cigarettes. Even some articles indicate that nicotine may have anti-inflammatory effects. Nicotine has been found to prevent acute lung damage and restrain the expression of tumor necrosis factor (TNF), which plays role in the inflammatory response [66]. Furthermore, nicotine is an agonist of the cholinergic anti-inflammatory pathway that modulates immune and inflammatory reaction [51, 73].

There have been a few original research studies comparing former and current smokers. The lung may heal when someone quits smoking, which may bias the findings if former smokers are part of the exposed group since one study found that the death rate among former smokers reduces with age [44, 45]. As a result, the frequency of smokers may have been underestimated, and some former smokers may have been incorrectly classified as nonsmokers [51]. As a result, only a few systematic reviews compared the features of these two groups. Three studies found that current smokers had lower risks of an adverse outcome than former smokers [31, 35, 51]. This might be because former smokers are more likely to be older, smoked for a longer period than current smokers, or because they have concomitant conditions such as asthma or COPD as a result of smoking [51]. Another factor might be that current smokers reported their status less than former smokers. [50], although a study found that current smokers had a greater likelihood of adverse outcomes than former smokers and nonsmokers [47].

Overall, compared with nonsmokers, smokers have higher risks of severe forms of the disease and hospitalization, and mortality [18, 39, 74]. On the contrary, the severity of COVID-19 was not associated with current or former smoking but with the comorbidities caused by smoking [75, 76]. In this study, the incidence of infection by SARS CoV-2 virus in smokers and nonsmokers cannot be evaluated clearly due to the lack of data at this present time.

5. Conclusion

There is strong evidence that smoking increases the risks of disease severity/progression, hospitalization, and mortality among COVID-19 patients. Encouraging smokers to quit using, early initiation of treatment after the onset of symptoms, timely vaccination, and promoting other preventive behaviors by public health providers can control the possibility of these people getting the infection and a better prognosis. Vaccination of smokers should be done completely among the priority groups.

Data Availability

The authors stated that all information provided in this article could be shared.

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Additional Points

Implications. (i) There is strong evidence that smoking increases the risks of disease severity/progression, hospitalization, and mortality among COVID-19 patients. (ii) Encouraging smokers to quit using, early initiation of treatment after the onset of symptoms, timely vaccination, and promoting other preventive behaviors by public health providers can control the possibility of these people getting the infection and a better prognosis. (iii) Vaccination of smokers should be done completely among the priority groups.

Disclosure

The present study was conducted in collaboration with the Khalkhal University of Medical Sciences, Iranian Institute for Reduction of High-Risk Behaviors, Tehran University of Medical Sciences, and the University of Sydney.

Conflicts of Interest

The authors declare that there is no conflict of interest regarding the publication of this manuscript.

Authors' Contributions

Esmaeil Mehraeen and SeyedAhmad SeyedAlinaghi are responsible for the conception and design of the study; Amir Masoud Afsahi and Ramin Shahidi for the acquisition of data; Esmaeil Mehraeen, Shaghayegh Kianzad, Zahra Pashaei, Maryam Mirahmad, Pooria Asili, Hengameh Mojdeganlou, Armin Razi, Paniz Mojdeganlou, Iman Amiri Fard, Sara Mahdiabadi, Arian Afzalian, Mohsen Dashti, Afsaneh Ghasemzadeh, Zohal Parmoon, and Hajar Badri for the drafting of the article; SeyedAhmad SeyedAlinaghi, Daniel Hackett, and Amir Masoud Afsahi for revising it critically for important intellectual content; and SeyedAhmad SeyedAlinaghi, Esmaeil Mehraeen, and Daniel Hackett for the final approval of the version to be submitted.

Supplementary Materials

Supplementary table 1: description of the findings reported in the eligible studies. *(Supplementary Materials)*

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