Introduction

Coronavirus disease 19 (COVID-19) is caused by the beta-coronavirus severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The first case of the disease was found in China in early December 2019, and over time, it could spread around the world and cause a pandemic (1-5). As of December 23, 2021, there were 276,436,619 confirmed cases of the disease, resulting in 5,374,744 deaths (6). COVID-19 induces diverse symptoms in patients. The disease is asymptomatic in many patients, while it causes mild symptoms in some cases and advanced and severe symptoms in other patients, causing progressive lung involvement with respiratory failure that requires treatment and may lead to death (2,7,8). The virus is transmitted through the spread of respiratory droplets and physical and oral contact with feces (9).

Vaccination, social distancing observation (1 meter), the use of masks, ventilation, regular handwashing with soap and water, and the like can be applied to prevent the spread of this disease and reduce the transmission of the virus (10). Tobacco smoking damages the lungs of smokers, compromises the immune system, affects almost all parts of the body, and increases the chances of developing respiratory infections (e.g., viral infections) and severe diseases and thus hospitalization (4,7,11).

Pulmonary diseases (e.g., chronic obstructive pulmonary disease), cardiovascular disease (hypertension, atrial fibrillation, and ischemic heart disease), renal failure, cancer, diabetes, and obesity have all been linked to smoking, resulting in increased severity and mortality from COVID-19 (4,12).

The virus may threaten smokers more than others (11). Thus, the harm of smoking is greater during the COVID-19 pandemic (13).

Evidence suggests that smoking is associated with the severity and mortality of COVID-19, and smokers, among patients with COVID-19, are more likely to have adverse health outcomes. The reports of a link between smoking and COVID-19 may influence smokers (11,12).

Considering that smoking can have adverse effects on the systems of the body, the current study sought...
to evaluate the effects of smoking on the incidence, transmission, prognosis, and severity of the disease in patients with COVID-19.

Methods
In this review, Scopus, PubMed, and ScienceDirect databases and the Google Scholar search engine were searched using three keywords (in the title) derived from Mesh (COVID-19, smoking, and tobacco) while considering no time limit.

The inclusion criterion was in this review was the availability of the English version of the articles and their full texts. Articles in other languages were excluded from the review.

From 97 extracted articles, after reviewing the title and abstract, 62 cases were found to be related to the purpose of the study and thus were included in the study.

Effect of COVID-19 on Different Systems in the Body
The secondary side effects of COVID-19 are such high that 2.4% of the world's mortality rate is now due to COVID-19 infection and organ failure (14,15). The virus may damage various tissues and systems of the body, and the first and foremost part damage is related to the respiratory system and lungs of the affected person, followed by the cardiovascular system, nervous system, and other organs (14,16).

COVID-19 may affect various parts of the respiratory system, including the nervous, muscular, airway, and lung parts of the individual (17). The initial symptoms are similar to the flu and can have a mild to severe effect on the person’s lungs. Respiratory distress syndrome and pneumonia may occur in patients with severe symptoms (18).

The second organ affected by the virus is the cardiovascular system, and this effect can be measured with most biological biomarkers (15,18).

It is noteworthy that COVID-19 is a risk factor for diseases such as myocarditis, pericarditis, abnormal coagulation mechanisms, and the like. Early signs of the disease in patients with COVID-19 include chest pain, and elevated creatine kinase and troponin levels, which are associated with coronary artery occlusion. In rare cases, patients with COVID-19 have no specific signs or symptoms (16).

The gastrointestinal tract of patients with COVID-19 may be disturbed due to the overexpression of ACE2 receptors (even more than in the lungs). Gastrointestinal symptoms in these patients include abdominal pain, nausea, diarrhea, and vomiting (19).

Diarrhea is also a common and early symptom in COVID-19 patients, thus this symptom occurs in some patients even before respiratory symptoms (20).

Patients with COVID-19 may further express ACE2 genes on the brain and glial cells. In acute cases, the level of D-dimer and inflammatory proteins rise, and severe inflammation can lead to stroke and thromboembolism. According to evidence, neurological symptoms such as headache and neck pain have been observed in acute COVID-19 cases.

The virus can also enter the cerebrospinal fluid and cause encephalitis and meningitis. Of course, this complication is highly rare and occurs in special cases. In COVID-19 patients, the rupture of cerebral capillaries can be a sign of damage to the nervous system (21).

Moreover, the kidney system is affected by this virus. The prevalence of acute renal impairment in COVID-19 patients is nearly 7%. This damage is associated with symptoms such as proteinuria, hematuria, increased creatinine, and urea nitrogen in the blood.

The results of a study showed that proteinuria and hematuria increased the chances of admission to the intensive care unit (ICU) and the severity of the disease in COVID-19 patients. Old age and underlying diseases such as hypertension, diabetes, and heart diseases are the risk factors for acute kidney damage (22,23).

Effects of Tobacco on Different Body Systems
Cigarettes are composed of more than 7000 toxic chemicals, in which tobacco leaves are the main ingredient. First- and second-hand smoking affect the health, economy, community, and environment and will increase the risk of various diseases such as cancer, cardiovascular diseases, immune disorders, pneumonia, and the like (24). Some of the effects of smoking on different body systems are mentioned as follows.

Prolonged exposure to tobacco not only affects the respiratory tract and airway epithelial cells but also destroys their barrier-like function and ultimately blocks airflow by increasing goblet cell and submucosal glands and their secretions (25-27).

Tobacco reduces the production of antibodies against infectious antigens and increases the incidence, transmission, and severity of some viral infections in the respiratory tract. For example, subjects are more likely to develop diseases such as bronchitis, pneumonia, pneumococcus, and tuberculosis. Smokers are much more likely to develop lung cancer compared to non-smokers. Second-hand exposure to tobacco increases the risk of respiratory disease in adults and carries the risk of lung cancer, as well as sudden death in infants. Mothers smoking during pregnancy increase the risk of obstructive pulmonary disease and the development of lower respiratory system diseases in the first and second years of life in children (27).

Smoking affects the cardiovascular system and is involved in the development of atherosclerosis (28,29).

Nicotine increases blood pressure by affecting the body’s hemodynamics because it increases arginine vasopressin and catecholamines (epinephrine and norepinephrine),
along with increasing the activity of the angiotensin-aldosterone-renin system (28,30). Nicotine also causes an increase in the heart rate, myocardial contraction, and coronary artery stenosis, while it decreases coronary blood flow storage (30).

Tobacco use increases the risk of cardiovascular diseases (e.g., myocardial infarction and heart failure), enlarges the left ventricle, and decreases systolic function in both ventricles. Additionally, tobacco affects blood coagulation (31).

Aerosols in e-cigarettes also affect heart activity and blood circulation and increase heart rate, diastolic blood pressure, pulse wave velocity, and endothelial progenitor cells in the blood (32).

Oral microbiomes are found in the common form in the host body and include more than 600 species. These microbiomes may cause periodontal diseases and tooth decay under dysbiotic conditions, and traditional cigarettes are considered a risk factor for these diseases, but there is a limited number of studies that show the risk and role of e-cigarettes in these diseases (24).

The findings of a study demonstrated that tobacco is the most important risk factor for pancreatic diseases (33), and smoking also carries the risk of lips, mouth, esophagus, and pancreatic cancer (34). Cadmium and arsenic in cigarettes are carcinogenic and have been implicated in gastric ulcers, although arsenic is also effective in treating refractory proctitis. Cigarette can affect the microbial population of the gastrointestinal tract, but its mechanism is still unknown (35).

Smoking affects inflammatory bowel disease and causes the progression of Crohn’s disease, but it has a protective role for ulcerative colitis. However, this contradictory mechanism is still unknown (35,36).

The compounds in cigarettes (free radicals, cyanate, and carbon monoxide) have a toxic effect on neurons. Nicotine in tobacco influences the immune and inflammatory systems, as well as the function of the brain and spinal cord (central nervous system), and causes damage to cerebral blood vessels (26,37). Long-term use of nicotine increases cellular adaptation and thus causes permanent changes in neurons and neural networks. Severe nicotine consumption increases the excitability of dopamine-releasing neurons, but chronic use reduces dopamine release and nicotine receptor sensitivity, which is associated with nicotine withdrawal symptoms such as depression and sleep disorders (26,38).

Nicotine is one of the products in tobacco that enters the body through active or passive smoking, causing nephropathy and reducing the activity of superoxide dismutase and renal catalase (34). Cigarettes and their metabolites are involved in kidney and bladder cancer (34,39). Plasma carcinoembryonic antigen is increased under the influence of smoking in people with non-neoplastic diseases. Furthermore, nicotine can cause kidney cancer by inhibiting the enzyme CYP2A6, which is involved in the activation of cancer genes. Cadmium is a nephrotoxic substance that is found in significant amounts in cigarettes, and constant overexposure to this substance increases the risk of immunoglobulin A mesangial glomerulonephritis. Smoking increases the risk of microalbuminuria and accelerates the development of persistent proteinuria, leading to the progression of diabetic nephropathy to end-stage renal disease (34).

**Effect of Smoking on the Transmission of COVID-19**

The COVID-19 pandemic has an impact on mental health, which leads to psychosocial problems, anxiety, and depression, and in turn, causes an increase in smoking cigarettes, nicotine products, and the like to reduce these problems. According to the World Health Organization (WHO), smoking increases the chances of virus transmission due to the increased contact of smokers’ hands with their mouths and considers smoking a risk factor for COVID-19 (40,41).

Group smoking in closed environments, following friendly discussion, drinking, and passing cigarettes to each other due to physical proximity, contact with others’ saliva, cough, sneezing, and increased smoke volume, releases much SARS-CoV-2-containing aerosols into the environment, causing the transmission of coronavirus and other respiratory infectious agents (42,43). These individuals take off their masks to smoke in public places. This has caused concerns among non-smokers who share the places (even if non-smokers wear masks). This is because the spread of the virus is effectively prevented only when both parties wear masks, and this is a true concern about the possibility of virus transmission through the exhalation of tobacco smoke (41).

Frequent hand-to-mouth contact and the mutual use of some tobacco devices such as pipes, water pipes, and e-cigarettes are common among smokers and, due to the virulence of the coronavirus, these behaviors will be associated with the possibility of transmitting COVID-19 (44,45).

Smokeless tobacco is widely consumed in South Asian countries in the sales centers. It is placed in the mouth (frequent contact of the hand with the mouth) using the fingers and constant chewing, which increases the secretion of the saliva and leads to spitting in public places. This is repeated several times during the day, resulting in the transmission of pathogenic agents such as SARS-CoV-2 (43,46).

Saliva droplets come in a variety of sizes, which determines the risk of the transmission of the virus to host cells. Large droplets (over 60 μm in diameter) settle rapidly, limiting the possibility of transmission to individuals close to the source of the aerosol. Small droplets (smaller than 10 μm in diameter) evaporate in the medium and may be carried within distances of less than
1 m (46). The average concentration of airborne particles with a diameter of ≤2.5 μm in smokers’ homes is almost ten times higher than in nonsmokers’ homes, indicating that members living in the smokers’ homes, especially in non-ventilated homes, are exposed to high concentrations of these particles (47). Family members are exposed to these particles considering the home quarantine during the pandemic and the presence of smokers in the home, and the issue that they do not usually wear masks at home (41).

Smokers are advised to follow health protocols such as social distancing, wearing face masks, and using proper devices when smoking at home or in public places to reduce the risk of transmission of the virus (41).

It should be noted that smokers are at higher risk for severe COVID-19 due to weakness and infection of the lungs and transmission of COVID-19 through saliva droplets and should be encouraged to quit smoking, especially in public places and groups (42).

### Relationship Between Smoking and Risk of COVID-19

According to the WHO, more than 8 million people die each year from smoking, and first-hand smoking is the main reason in this regard (48).

Smoking is a major risk factor for bacterial and viral respiratory infections, as well as non-communicable diseases such as cardiovascular diseases, cancer, and the like (49). However, some studies suggest that smoking is inversely related to the risk of COVID-19 (50-52).

In their study on the effect of smoking on the SARS-CoV-2 infection, Prinelli et al examined 6857 patients with COVID-19 using online platforms. Based on their report, 63.2%, 21.3%, and 15.5% of patients had no history of smoking, had a history of smoking, and were current smokers, respectively. Their finding also showed that people with a history of active smoking are significantly younger than those who have quit smoking, which could be due to COVID-19 in patients with a history of smoking, as well as chronic and underlying diseases (51).

In another study in China (50), it was found that the incidence of COVID-19 is significantly lower in smokers compared to non-smokers (about a quarter). Conversely, the results of Zheng and Li represented that smoking (current smokers) does not reduce the risk of COVID-19 (53).

Nicotine in cigarettes and tobacco may affect ACE2 expression levels and interferes with the patient’s inflammatory process by reducing expression, leading to stronger host cell defense (50,54). Of course, economic and social status and the level of access to health services may affect the results of studies as well (50).

Animal studies also indicate that nicotine in cigarettes prevents acute respiratory distress syndrome (50).

Nicotine may inhibit the production of proinflammatory cytokines without inhibiting the production of anti-inflammatory cytokines, which could be important in the pathophysiology of COVID-19 (50).

In a study, gender was observed not to be significantly associated with the incidence of COVID-19, while the rate of experiencing smoking was significantly higher in men than women (55). In the meantime, in the study of Neira et al, the incidence rate of COVID-19 was significantly higher in women such that out of 3.9% of patients (398 subjects) with a history of active smoking, 60% were women (56).

### Effect of Tobacco on the Severity and Prognosis of COVID-19

Shortly after the onset of the COVID-19 pandemic, the WHO announced a higher risk of outcome in smokers compared to non-smokers (57). A study in China in early March 2020 stated that smoking is the most important risk factor for a poor prognosis of COVID-19 (58).

Conflicting data exist about the effect of tobacco on the prognosis of COVID-19. Some studies have suggested a positive association between smoking and the intensity of COVID-19 (8), while some others reported that smoking will have a protective effect on COVID-19 (59-62).

Weakening lung function and the immune system, tobacco and cigarettes aggravate the complications of COVID-19 (57,61). Although the results of a study indicated that tobacco had a slight effect on the lungs of COVID-19 patients and there was no significant difference between the smokers and nonsmokers, smoking may not increase the severity of the disease through the lungs. Nonetheless, it may exacerbate the symptoms of COVID-19 in subjects with a history of smoking by suppressing the immune system (8).

Tobacco upregulates the ACE2 receptor and may increase the severity of disease and death (40,63). The upregulation of this receptor also increases angiotensin II, resulting in microthrombosis, vascular endothelial destruction, and severe coagulopathy (7). COVID-19 increases the risk of stroke by clotting the blood. Moreover, tobacco and e-cigarettes are considered risk factors for stroke by lowering thrombomodulin levels; they exacerbate the complications of a stroke in subjects with COVID-19 (40).

According to a study conducted in a hospital in China, the duration of illness and hospital stay was shorter in smokers compared to non-smokers (8). Various studies showed that smoking has an effect on the outcome and prognosis of COVID-19. The severity of the disease, need for hospitalization and ICU admission, and the death rate are higher in smokers in comparison with non-smokers (58,59,62). The need for mechanical ventilation also increases in subjects with a history of smoking (40,63). Further, tobacco affects the treatment process and makes treatment challenging (40,61).

The results of a cohort study revealed that 39.3% of
smokers caught severe COVID-19 compared with 10.5% of non-smokers (8). In subjects with a history of smoking, the risk of severe symptoms was 1.4 times higher, and the need for an ICU, mechanical ventilation and the death rate were 2.4 times higher in subjects without a smoking history (40,61).

According to studies on patients with COVID-19, severe COVID-19 occurred in 32% and 15% of subjects with and without a history of smoking, respectively. In addition, 27% and 3% of smokers and non-smokers were more severely ill after 2 weeks in hospital, respectively. Based on the results of a systematic review and meta-analysis, 22% of current smokers and 46% of ex-smokers experienced severe side effects. Another meta-analysis reported that current smokers were 1.45 times more likely to have severe complications in comparison with never and former smokers (59). Tobacco also doubles the death rate (3). Hospitalization rates for current smokers and former smokers are 1.2 and 1.3 times higher than those of never smokers, respectively (57).

The severity and duration of smoking also affect the severity of COVID-19. For example, the hospitalization duration increases by increasing the frequency and longevity of smoking. The consumption of more than 30 packs of cigarettes per year increases the hospitalization and death rates by 2.25 and 1.89 times, respectively. The severity of COVID-19 is also directly related to the increased number of years of smoking (57,64).

**Attitudes of Subjects About Smoking and Quitting at the Time of COVID-19**

The effects of the COVID-19 pandemic on tobacco addiction and quitting are complex and sometimes contradictory (65). COVID-19 may change the perception of smokers about the risk of smoking, smoking cessation, or smoking frequency (66). Several studies have identified smoking as a risk factor for hospitalized patients with COVID-19, who have a higher mortality rate (67).

Based on previous data, the likelihood of quitting smoking has doubled considering public awareness of the link between smoking and COVID-19. Therefore, it is necessary to make the public aware of the harmful effects of tobacco consumption during the epidemic and facilitate their access to tobacco-quitting services (13). Raising awareness, public education, and access restrictions can be effective in increasing interest, attempting to quit smoking, and preventing high stress (66,68).

COVID-19 affects smokers in a variety of ways and causes stress to them. Some of them smoked more and some less than before (69). During the COVID-19 pandemic, various factors such as psychological and financial stress due to job loss, and the like can also be the causes of increasing unhealthy coping behaviors (70). The stress of the COVID-19 pandemic may impair coping skills in people who tend to quit smoking (71), and about a quarter of smokers attribute increased smoking to the fear of the consequences of COVID-19 (72).

An appropriate preventive measure against the SARS-CoV-2 infection is smoking cessation (73,74). According to previous research, one-third of smokers were motivated to quit smoking due to the spread of the virus (11). According to a recent study, smoking cessation reduces the risks of COVID-19 (75). Although the relationship between smoking and the risk of the incidence and survival rate of COVID-19 has not yet been confirmed, evidence suggests that smoking quitters may increase in this period (76). Public health experts advise smokers to quit smoking to reduce the risk of SARS-CoV-2 and the complications of COVID-19, using effective and proven smoking cessation interventions (74).

Although efforts and interest in making smokers quit smoking have increased since the beginning of the pandemic, smokers are smoking more frequently in some countries (65). According to a survey in Serbia (72), for example, the COVID-19 pandemic caused 22.7% and 26.3% of smokers to increase their smoking frequency and quit because of health awareness, respectively.

In the United States and Turkey, motivation to quit smoking increased due to COVID-19 health concerns, and the rate of smoking represented a decline. In Poland, on the other hand, with the successful suppression of the initial spread of the disease, smoking was on the rise due to the increased stress caused by quarantine.

In countries such as Italy and Spain, which were especially affected by the rapid outbreak at the beginning of the pandemic, smokers reduced their smoking rate (72).

Some countries have taken strict tobacco control measures to prevent the spread of COVID-19. For example, the use of water pipes has been banned in public places in several Eastern Mediterranean countries. During the quarantine, the Indian government banned the sale of tobacco products to prevent its spread. The production, supply, and sale of tobacco or its import were also prohibited in Bangladesh, Botswana, and South Africa. Diversities between countries in terms of the impact of the pandemic on the smoking prevalence are probably influenced by differences in the severity of COVID-19 effects such as mortality (72).

**Conclusion**

The examination of the results of various studies showed that smoking and COVID-19 affect different systems of the body (including respiratory, heart and circulatory, gastrointestinal, nervous, urinary, and renal ones) and are interconnected in a way that smokers are less likely to develop COVID-19 disease, while transmission, severity, mortality, hospitalization, and treatment challenges are higher in smokers compared to non-smokers.

Therefore, considering the COVID-19 pandemic and its
dangerous effects on human health, as well as the negative effects of smoking on the prognosis of this disease, smoking cessation may improve respiratory function and reduce the complications of COVID-19. Accordingly, it is necessary for different countries to pay attention to this issue and take constructive policies and measures to control and reduce its consumption.

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Authors’ Contribution
All authors contributed to the study design, data collection, writing, and preparation of this study.

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