Coronavirus disease-19 risk factors

Koronavirüs hastalığı-19 risk faktörleri

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ABSTRACT

Coronavirus disease-19 (COVID-19) has spread around the world and been declared as a global pandemic by the World Health Organization. The disease has caused international social and economic impact, and high mortality. Quarantine and vaccination measures were used to control and prevent the disease. Several different types of vaccines have been developed against COVID-19, and novel drugs for COVID-19 are currently under development. Severity of disease can change depending on the predisposing conditions and risk factors. Many studies have been carried out to identify risk factors associated with the occurrence of the disease and severity of clinical manifestations, but different predisposing conditions and potential risk factors have been reported in these studies. Therefore, in this article, a review of studies was conducted to identify risk factors related to the COVID-19. The search was carried out in PubMed and publicly available preprints. Results of the literature review showed that age (>60 years old), male gender, Black and Hispanic race, obesity (body mass index > 30), underlying comorbidities such as chronic lung, kidney, liver, and heart diseases, diabetes, immunosuppression

ÖZET

Koronavirüs hastalığı (COVID-19) tüm dünyaya yayılmış ve Dünya Sağlık Örgütü tarafından küresel bir salgın olarak ilan edilmiştir. Hastalık uluslararası sosyal ve ekonomik etkiye ve yüksek ölüm oranına neden olmuştur. Hastalığı kontrol altına almak ve önlemek için karantina ve aşılama önlemleri kullanılmıştır. COVID-19'a karşı farklı aşı türleri geliştirilmiş olup tedavisi için de yeni ilaç geliştirme çalışmaları sürdürülmektedir. Hastalığın şiddeti predispozan koşullara ve risk faktörlerine bağlı olarak değişebilmektedir. Hastalığın ortaya çıkışı ve klinik belirtilerin şiddeti ile ilişkili risk faktörlerini belirlemek için birçok çalışma yapılmış ancak bu çalışmalarda farklı predispozan koşulların ve potansiyel risk faktörlerin ilişkili olduğu bildirilmiştir. Bu nedenle, bu makalede COVID-19 ile ilişkili risk faktörlerini belirlemek için yayınların incelemesi yapılmıştır. Yayın taraması, PubMed ve halka açık ön baskılarda gerçekleştirilmiştir. Literatür tarama sonuçları, yaş (>60 yaş), erkek cinsiyet, Siyah ve Hispanik ırk, obezite (vücut kütle indeksi >30), kronik akciğer, böbrek, karaciğer ve kalp hastalıkları, diyabet, immünsupresyon ve hipertansiyon gibi altta yatan komorbiditelerin, hastalığın oluşma riskini artıran ana

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and hypertension are the major factors increasing the risk of disease occurrence. It has been reported that the mortality rate due to SARS-CoV-2 infection was approximately three times higher in patients aged 41-60 years than in patients aged 18-40 years. Patients with active cancer are identified as at risk of severe forms of COVID-19. Severe outcomes of the disease are more common in pregnant women than non-pregnant women. Furthermore, smokers have a nearly two times higher risk of hospitalisation and have a six times higher risk of mortality than never-smokers. To establish a successful control program, it is important to determine the potential risk factors associated with the disease. Therefore, it is recommended to use risk assessment tools to develop effective public health strategies against pandemics.

Anahtar Kelimeler: COVID-19, SARS-CoV-2, pandemics, risk factors

faktörler olduğunu göstermiştir. Şiddetli akut solunum sendromu koronavirüs 2 (SARS-CoV-2) enfeksiyonuna bağlı ölüm oranının 41-60 yaş aralığındaki hastalarda, 18-40 yaş aralığındaki hastalardan yaklaşık üç kat daha fazla olduğu bildirilmiştir. Aktif kanseri olan hastalar, şiddetli COVID-19 formu riski altında olarak tanımlanmaktadır. Hamile kadınlarda, hamile olmayan kadınlara göre hastalığın şiddetli formu daha yaygındır. Ayrıca, sigara içenlerin hiç sigara içmeyenlere göre yaklaşık iki kat daha fazla hastaneye yatış riski ve altı kat daha yüksek ölüm riski bulunmaktadır. Başarılı bir kontrol programı oluşturmak için hastalık ile ilişkili potansiyel risk faktörlerinin belirlenmesi önemlidir. Bu nedenle, pandemilere karşı etkili halk sağlığı stratejilerini geliştirmek için risk değerlendirme araçlarının kullanılması önerilmektedir.

Key Words: COVID-19, SARS-CoV-2, pandemi, risk faktörleri

INTRODUCTION

The first case of Coronavirus disease-19 (COVID-19) was reported in China at the end of 2019, and then it has spread rapidly across countries due to the global connectivity and transportation worldwide. On 11 March 2020, it was declared as a pandemic. A novel coronavirus, the causative agent of the COVID-19 named as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), belongs to the genus *Betacoronavirus* within the family *Coronaviridae* (1). The disease is characterised by fever, headache, fatigue, cough, myalgia, diarrhoea, and pneumonia. As of 18 March 2023, the total number of global confirmed cases and deaths were 760,360,956 and 6,873,477 deaths, respectively (2). The case fatality rate of disease ranged between 0.1% and 18.1% (3).

SARS-CoV-2 is mainly transmitted person to person via respiratory droplets and aerosols during sneezing and coughing. It has been reported that the proportion of asymptomatic COVID-19 cases could be as high as 81% (4). Asymptomatic carriers play role in the transmission of the disease. The severity of disease can change from person to person. Predisposing conditions and risk factors are associated with disease occurrence and severity of clinical manifestations (5).

Assessment of risk factors could be helpful for clinicians in identifying high risk patients. Furthermore, risk factors are important for developing effective health strategies against the next pandemic. Therefore, in this review available literature on risk factors related to COVID-19 was compiled (Table 1).

Table 1. The potential risk factors associated with severe outcomes of COVID-19

Strong associations	Weak associations	More studies needed to assess associations
Age (> 60 years old)	Chronic kidney disease	Ethnicity
Male gender	Smoking	Chronic liver disease
Chronic lung disease	Alcohol consumption	Allergy and asthma
Cardiovascular disease	Pregnancy	
Diabetes		
Cancer		
Obesity		

DEMOGRAPHIC FACTORS

Age and gender

The older age, especially >60 years, was frequently reported as a demographic factor associated with the severity of the disease (6,7). A study which was carried out in China found that mortality rates due to COVID-19 in patients ≤18 years, patients >18, ≤40 years, patients >40, ≤60 years, patients >60, ≤80 years and patients >80 years were 0.8%, 1.1%, 3.4%, 9.8% and 21.6%, respectively (8). Furthermore, a meta-analysis study reported that the risk of mortality and hospitalization due to SARS-CoV-2 infection increased per age year by 7.4% and 5.7%, respectively (9). Older age is associated with more comorbidities and weaker immune response (5). Furthermore, reduced levels of cells that express angiotensin-converting enzyme 2 (ACE-2) and lung progenitor cells in older adults may contribute to disease severity (10).

In terms of gender, males are more likely to susceptible to COVID-19 than females. The epidemiological studies reported that morbidity and mortality rates were higher among males than females (8,11,12). Furthermore, a meta-analysis study showed that male patients were required more intensive treatment unit admission than female patients (OR 2.84, 95% CI 2.06-3.92) (13). The differences in susceptibility to COVID-19 between males and females could be due to higher expression of ACE-2 in males, sex-based immunological differences, biology, genetics and behaviours (11).

Ethnicity

Ethnicity has been linked with higher SARS-CoV-2 infection rates (14). Studies which were carried out in the USA reported that Black and Latino patients had higher rates of hospital mortality than White patients (15,16). However, another study which was carried out in the USA found that ethnicity was not related to higher mortality in COVID-19 hospitalized patients (17). The ethnicity effect on the severity of the disease may be associated with social determinants of health such as employment, working conditions and housing (15).

PRE-EXISTING COMORBIDITIES

Chronic lung disease

Some early studies suggested that having a chronic lung disease is associated with high mortality and hospitalization rates due to SARS-CoV-2 infection (18, 19). A previous study which was carried out in China reported that rate of patients with chronic lung disease was highest in the critically ill group (20). However, a population cohort study reported that there was a lower risk of SARS-CoV-2 infection in patients who had COPD or interstitial lung disease (21). Severity of the disease in patients who had chronic lung disease could be explained by limited pulmonary reserve, restrictive ventilatory dysfunction and use of inhaled steroids (18,21).

Chronic liver disease

When compared to patients who had no pre-existing liver diseases, patients with pre-existing liver diseases have a higher susceptibility to SARS-CoV-2 infection (12). It has been reported that chronic liver diseases are at increased risk because of immunosuppression and metabolic dysfunction (22). A study which was carried out in the United States found that patients with chronic liver disease had a higher mortality rate (12%) than those without liver disease (4%) (23). On the contrary, another study found that having a chronic liver disease was not related to increased risk of mortality (OR 2.33) and severe outcomes of infection (OR 0.96) (24). Further studies are required to improve our knowledge about the impacts of pre-existing liver diseases on the severity of the disease.

Chronic kidney diseases (CKD)

Previous studies found that there was an increased risk of severe clinical manifestations in patients with CKD (24-26). A previous study identified adverse effects such as mechanical ventilation, intensive treatment and acute respiratory distress syndrome for the CKD patients with a RR of 2.63 (95% CI 1.33-5.17) (27). Studies reported that hospitalization rates varied between OR 1.38 (95% CI 1.19-1.60) and OR 3.9 (95% CI 2.4-6.3) in patients with CKD and COVID-19 (25,28). CKD patients with COVID-19 have a higher risk because of the attenuated immune system activation, which increases the susceptibility to infections (29).

Cardiovascular disease

Epidemiological results suggest that cardiovascular diseases are considered to be risk factors for increased disease mortality (24,30). The Centers for Disease Control and Prevention (CDC) (31) reported that hypertension and cardiovascular diseases increase the risk of severe outcomes. Hypertension is highly prevalent among older adults. Therefore, older adults have been reported to be at higher risk (24).

It has been reported that there is a nearly 2.5-fold increase in the risk of severe outcomes for patients with hypertension (32,33).

The mechanism underlying the severe form of the disease in patients with cardiovascular diseases remains unclear. However, it has been suggested that high levels of ACE-2 expression on cardiomyocytes may play a role in virus mediated injury and viral susceptibility, and myocardial injury may lead to life-threatening arrhythmias and severity of the disease (30).

Antihypertensive drugs, such as angiotensin II receptor blockers (ARBs) and angiotensin-converting enzyme inhibitors (ACEIs), are frequently used for treatment of cardiovascular diseases. Therefore, it has proposed to use ARB and ACEI drugs in patients with hypertension who are at higher risk (34). However, it has been reported that COVID-19 positivity rates in patients with ACEIs/ARBs users were not significantly different from non-users (35).

Allergy and asthma

Some of the epidemiological studies reported that allergy and asthma were associated with severe outcomes of the disease (36, 37). However, a study which was carried out in England reported that allergic rhinitis and asthma (aged less than 65) have protective roles against COVID-19. Further studies are needed to improve our knowledge about the impacts of allergy and asthma on the severity of clinical manifestations.

Diabetes

Severe and fatal cases were observed in diabetic patients compared to non-diabetic patients (6,19). Several studies reported that diabetic patients had an almost two-fold greater risk for hospital admission (38-40).

The association between severity of the disease and diabetes can be explained by the immunosuppressive effects of hyperglycaemia and higher expression of ACE-2 in diabetic patients (41).

The upregulation of ACE-2 causes endothelial cell activation and chronic inflammation, which lead to dysfunction of the alveolar-capillary barrier (42).

Cancer

Patients with active cancer are identified as at risk of COVID-19 severity. It has been reported that COVID-19 patients with hematologic cancers have the highest mortality rates among cancer patients (43). Mortality rate was 21% among COVID-19 patients who had cancer and 7.8% in non-cancer patients (44,45). A study which was carried out in the United Kingdom involving 16,749 hospitalized patients, reported a higher risk of mortality for cancer patients, OR 1.13 (95% CI 1.02-1.24) (46). Another study found that cancer patients who were diagnosed less than one year ago had a 2-fold increased risk of severe outcomes (47). The high mortality rate among cancer patients could be related with comorbidities, age and gender. Generally, cancer is common in older age with coexisting chronic diseases. Type of cancer, chemotherapy and duration may influence the severity of COVID-19 (47).

Pregnancy

The CDC reported that severe COVID-19 outcomes are more common in pregnant women than non-pregnant women (48). A systematic review of 17 studies and 84 neonates reported adverse outcomes of the disease in pregnant women were preterm birth (21.3%), foetal distress (10.7%), low birth weight (<2500 g, 5.3%), neonatal death (1.2%), neonatal asphyxia (1.2%) and stillbirth (1.2%) (49).

Although there is no evidence of vertical transmission, detection of SARS-CoV-2 in neonates has been reported (49-51). During the first trimester of pregnancy, high expression of ACE-2 in the placenta makes this trimester the most susceptible period for COVID-19 (52). Furthermore, it has been reported that intrauterine transmission of SARS-CoV-2 seems to occur in the last trimester of gestation (50). First and third trimesters of pregnancy are characterized as pro-inflammatory phases that are suitable for the virus activity; therefore, there is a higher risk for occurrence of the disease in the first and third trimesters than the second trimester (53). Further studies are required to determine whether the SARS-CoV-2 can cross the placenta and cause infection in foetal tissues.

LIFESTYLE

Obesity

Obesity is identified as a risk factor for hospitalization due to COVID-19 (54, 55). A study which was carried out in France found that severe obesity (body mass index (BMI) > 35) and obesity (BMI > 30) rates were 28.2% and 47.6% of the 124 COVID-19 patients, respectively (56). Furthermore, males who were obese had a higher risk og having severe COVID-19 (57). Obesity was also found to be a risk factor for respiratory diseases in humans, such as H1N1 influenza virus infection (58). Effects of the obesity in severity of the disease might be related to inflammation, which effects lung parenchyma and bronchi, and raised cytokines such as interleukin 6, which may cause impaired immune response (59).

Smoking

Smoking increases the risk of respiratory diseases. However, there are inconsistent reports on the relationship between smoking and severe outcomes of the disease. Some early studies suggested that there was no relation between smoking and severe illness. A population-based study in the United Kingdom found that there was no association between SARS-CoV-2 related mortality and smoking (60,61). It has been reported that nicotine may inhibit virus entry into cells by downregulating the ACE-2 receptors and have a pharmacological effect in COVID-19 (62).

On the contrary, a large, population-based study reported that the SARS-CoV-2 related mortality rate was increased among smokers (14,63). It has been reported that current smokers had a nearly two times (OR 1.80, 95% CI 1.26-2.29) higher risk of

hospitalisation and had a six times (OR 5.91, 95% CI 3.66-9.54) higher risk of mortality than never-smokers. Smoking is identified as at risk of COVID-19 severity because it damages the lungs and immune system, causing a decreased ability to fight the disease (64).

Alcohol consumption

Alcohol consumption can increase the risk of acute respiratory distress syndrome (ARDS) (OR 1.89; 95% CI 1.45-2.48) through alcohol-induced oxidative stress, interference of alveolar macrophage function and alveolar epithelium dysfunction (65). Chronic ethanol abuse increases the risk of developing ARDS because it damages the respiratory ciliated cells and immune system due to reduced T lymphocytes numbers and decreased natural killer cells function (66).

It has been reported that drinkers had a lower risk of COVID-19 compared to non-drinkers if they were drinking below the guideline levels (67). A study in the United Kingdom found that consumption of champagne, fortified wine, red wine and white wine had protective effect against the disease, but consumption of cider, spirits and beer increased the COVID-19 risk. They also did not find an association between COVID-19 mortality and subtypes of alcoholic beverages, amount and frequency (68). Alcoholic beverages have phenolic compounds, which have antioxidant properties. The concentration of phenolic compounds is highest in red wine, whereas it is lowest in spirits (69). Phenolic compounds have inhibitory effects against viruses such as influenza virus and other respiratory viruses (70). Therefore, it has been suggested that phenolic compounds have beneficial effects on SARS-CoV-2 infection (68).

CONCLUSION

In conclusion, SARS-CoV-2 induces mild to severe disease, and severity of disease can change from person to person depending on the predisposing conditions and risk factors. Severe outcomes of the disease are more common in elderly males (> 60 years old) with obesity and/or comorbidities (such as cardiovascular diseases, diabetes and cancer). Thus, additional care for this population may be required. An adequate, well-balanced diet and vaccination may be protective against the disease in this population. Furthermore, during pandemics, clinicians should pay more attention to the management of weight gain in patients with obesity.

The population aged 60 and over in the world is rising over the years, so the number of individuals susceptible to the severe form of the disease is increasing. Therefore, specific measures to support older people must be implemented during an outbreak, including access to medical services, social support, and essential supplies in quarantine. Furthermore, the vaccine needs to be made more accessible for older people.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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