

Risk Factors for COVID-19

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SUMMARY

SARS-CoV-2 in bats was transmitted to humans at a live and wet animal market in China through the intermediate host, creating COVID-19. Viral, environmental and host factors play roles in virus infection and disease. The virus has high transmissibility and is rapidly transmitted to people through close contact and droplets from coughing, sneezing and talking loudly, as well as through contact with contaminated objects. As crowding is an environmental risk factor for con-

tamination, its transmission is high among patients and staff in hospital and also in elderly-care centers. It is more common in the elderly, in men, and subjects with diabetes mellitus, hypertension, cardiovascular disease, and malignancy.

Keywords: Host, risk factor, environment, crowding, COVID-19.

INTRODUCTION

In recent years, many changes in social, technological, and environmental conditions have led to the emergence of an unknown pneumonia caused by a new zoonotic virus called severe acute respiratory syndrome coronavirus-2 (SARS-CoV2) in Wuhan, China in late 2019. The highly contagious disease was then called COVID-19. The disease rapidly spread to other countries and became a serious public health threat throughout the world. Until 16 Oct. 2020, more than 39 millions persons have been infected and more than one million have died around the world [1]. Eventually, the disease has become the most important economic, political and social problem of

the world during the second decade of the 21st century.

SARS-CoV-2 has genes of open reading frame 1a (ORF1a) and ORF1b which encode non-structural proteins and also has genes for structural proteins including spike (S), envelope (E), membrane (M), and nucleocapsid (N) [2]. The genome of the virus has 96.2% and 79.5% sequence homology with the bat coronavirus RaTG13 strain and SARS-CoV, respectively [3]. It seems that the virus originated in bats and was able to infect humans after some mutations in the S and N genes [4]. The virus binds to its receptor on the host cell surface known as angiotensin-converting enzyme 2 (ACE2). The mechanism is mediated by S protein of the virus. The affinity of S protein to its receptor (human ACE2) in SARS-CoV-2 is much more than SARS-CoV [5]. The ACE2 is highly expressed on lung cells, especially alveolar epithelial cells, intestine, kidneys, stomach, esophagus, liver, bile ducts, and epithelial cells of the oral mucosa. Therefore, the cells can be appropriate targets for

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SARS-CoV-2 binding and the cells of the oral mucosa are proper site for spreading the virus after it has multiplied [6].

The virus causes different clinical pictures in infected people. In 80% of the cases, it is asymptomatic, or it causes mild upper respiratory tract symptoms. However, pneumonia along with fever, cough, dyspnea, and fatigue occurs in 20% of the patients, which progresses in some cases, leading to respiratory failure as well as multiple organ failure. In the symptomatic cases, the severity and outcome of the disease varies with age and other health conditions [7]. Hereditary and acquired factors play a role in host sensitivity as well as the disease severity. Risk factors are not the main cause of the disease, but they indicate correlation, meaning they can increase the risk of developing the disease. By identifying and evaluating the relevant factors and managing the proper strategies, the complications of the disease will be reduced by early diagnosis and treatment of the patients and the number of people recovering from COVID-19 will increase. In this study, we evaluated risk factors in order to identifying high-risk individuals and therefore help to make preventative decisions to reduce disease and mortality and control the COVID-19.

■ TRANSMISSION

Human intervention in nature, wildlife trade, and especially eating wild animals, made possible to transmit coronavirus from the animals to humans. In this way, the coronavirus in the bat, after being transmitted to the intermediated host and a small change in the transmission power of the virus was transmitted to humans [8]. The virus spread rapidly among humans in China and it spread from China to more than two hundred countries [9]. The spread of zoonotic viruses depends on the source of the pathogen, the number of infected people, the ease and rapidity of transmission of the infection, and the clinical severity of the disease. The reproduction number of SARS-CoV-2 is 3.28, so its transmissibility is higher than SARS-CoV and Middle East respiratory syndrome-coronavirus (MERS-CoV) [10]. The virus can be transmitted from animal to human, human to human, and from human to animal [3, 9, 11]. Droplets created during coughing and sneezing are the most important way for the transmission of the

virus. The particles spread through the mouth are transmitted from infected people to others during close contact [12]. There is also a possibility of transmission during recovery and incubation [13]. Since the virus can survive for several hours in aerosols, there is a possibility of transmission through them, especially indoors and in places without ventilation [14]. Due to the proliferation of the virus in the epithelial cells of the mouth and lower respiratory tract, it has been shedding for a long time. The condition increases in the prodromal phase and reaches a maximum on days 3-5 of the disease. In some patients, the time reaches up to 37 days [15]. Asymptomatic individuals appear to play a key role in the transmission process [16]. They are not aware of their infection and therefore are not under control, and on the other hand, the number of these people in the society is higher than the symptomatic ones. The virus survives on aluminum, plastic, and steel for a long time and has the ability to be transmitted through the contacts [14]. Social gatherings are one of the most important ways to spread the disease [17]. Therefore, in places such as prisons, elderly-care centers and homeless gatherings, schools and universities, stadiums are more likely to be transferred. In such centers, control and monitoring must be done more carefully to cut the transmission chain.

■ HOST RISK FACTORS

Risk factors are agents that increase the risk of disease or infection. The most important hosting factors for infection and COVID-19 are the following.

Older age

SARS-CoV-2 can infect all ages but it is much less common in people under 14 years old and it is often asymptomatic in young people [16, 18]. With age, COVID-19 increases so that aging becomes a risk factor for the disease [15, 19]. Middle-aged people are usually infected in the community, but older people are usually infected with coughing and sneezing from other infected family members and acquaintances or hospitalization [20]. The rate of the mortality is higher in the elderly people [11, 18, 19]. Aging adversely affects lung function and delays the activation of the acquired immune system as a result; the virus can become more replicable, producing more pro-inflammatory responses and increasing the risk of death [21].

Gender

Men are more sensitive to SARS-CoV-2 [19] so that the male sex is one of the risk factors for COVID-19 [7, 8, 15]. It seems that due to the fact that this disease is community-acquired and men are more out of the house due to working conditions and are more present in the community, in some countries such as Iran, therefore, they are more likely to become infected. Behavioral differences between men and women, especially in terms of health advices, as well as their less attention to the issue of social distancing, is an issue that should not be overlooked. A protein called A disintegrin and metalloprotease 17 (ADAM17) is more expressed in the lung and liver, which is involved in shedding surface proteins such as ACE2. Increasing ADAM17 enhances shedding and thus the amount of soluble ACE2, which is a means of blocking the entry of SARS-CoV-2 into cells. Estradiol, which is present in high concentration in women, increases the expression and activity of ADAM17, thus ultimately increasing the soluble ACE2 in women and can be one of the causes of reducing the prevalence of COVID-19 in women compared to men [22].

Diabetes

Diabetes is the most common metabolic disease in the world. It is a disease that weakens the immune system [7]. The number of people with diabetes in the world is increasing, especially in developing countries. Researchers have shown that diabetes increases the risk of COVID-19 [18, 19]. Diabetic patients are less responsive to treatment and have a higher risk of death (14% vs 31%) ($p=0.0051$) [15]. In diabetic patients, innate immunity is impaired due to elevated blood glucose levels, so glycosylation of cytokines disrupts the function of cytokines dependent on type I helper T lymphocytes (Th1). Pulmonary microangiopathy, tissue damage caused by oxidative stress in hyperglycemia, and pulmonary inflammation predispose the patients to COVID-19, as similarly occurs to patients susceptible to tuberculosis [23, 24].

Blood hypertension

Hypertension is often a genetic condition that is exacerbated by external stimuli such as lifestyle, diet and stress. With age, the blood pressure also rises, usually due to a disorder in blood vessels, such as atherosclerosis. Researchers have found

that COVID-19 and its mortality rate are high in these individuals [15, 18, 25]. Because SARS-CoV-2 enters cells through ACE2 receptors therefore, the virus was thought to be linked to the renin-angiotensin-aldosterone system (RAAS) via ACE2 [6]. Thus, medication with angiotensin-receptor blockers (ARBs) such as losartan may be associated with increased ACE2 expression in susceptibility to COVID-19. It seems that, high blood pressure is likely to increase COVID-19 mortality by affecting lung function and impairing oxygen delivery.

Cardiovascular disease

Patients with cardiovascular disease are more sensitive to COVID-19 [15, 19, 25]. The reason may be related to the expression of the ACE2 in the myocytes and vascular fibroblasts [26]. The presence of the virus in cardiovascular cells can damage them and stimulate the infiltration of mononuclear inflammatory cells into the heart tissue and the inflammation will exacerbate the disease.

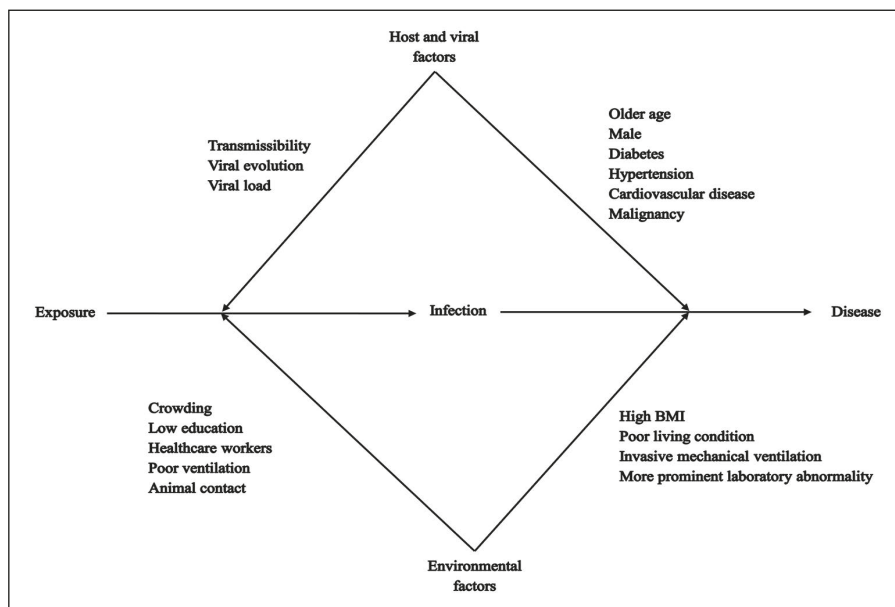
Malignancy

Cancer is the abnormal growth of cells that results from mutations in DNA, especially in damaged DNA repair genes, and a mutation in proto-oncogenes. Cancer patients are more susceptible to infection than non-cancerous individuals because the growth and proliferation of immune cells are weakened due to malignancy and therapeutic processes such as chemotherapy; therefore, an immunosuppressive state will be created in the body. Thus, cancer patients are more likely to develop COVID-19 than non-cancerous ones [7, 18, 19, 25]. In addition, the development of crisis state in cancer patients with COVID-19 is higher than in non-cancer individuals (8% vs 39%) ($p=0.0003$) [27].

Other host factors

Other factors can increase the risk of COVID-19 disease by weakening lung function, heart, circulation, excretion of waste products, as well as weakening the immune system. The following factors can be mentioned: chronic obstructive pulmonary disease (COPD), chronic renal disease, malnutrition, immunodeficiency, specific genotypes of interleukins and interferons, asthma, autoimmune diseases such as multiple sclerosis, rheumatoid arthritis and systemic lupus erythe-

Figure 1 - Risk factors for COVID-19.



matous, cerebrovascular disease and chronic liver disease, as shown in Figure 1 [18, 25].

■ ENVIRONMENTAL RISK FACTORS

Crowding

It seems that the most important way to transmit the SARS-CoV-2 is the presence of unprotected people in gatherings where there is a possibility of an infected person [17]. Therefore, the presence of a person in public vehicles such as buses, subways, trains and airplanes, if the social distancing is not observed, it will be a risk factor for contamination. Also, being in crowded shops, shrines, sports competitions and other crowded places can increase the risk of contamination.

Low education

Proper and adequate training is an important factor in cutting the transmission chain; therefore, people who do not have proper training in this field, they will transmit the virus unconsciously. For example, uneducated people who are trying to distribute disinfectants among the individuals can cause social gatherings or, health care workers (HCWs) with personal protective equipment (PPE) such as gown, masks and gloves that were present with the patients; they go to the hospital's administrative centers and contaminate the envi-

ronment and because the virus stays on the devices for a long time, they provide the possibility of infecting people [14].

Occupational risks

COVID-19 is an occupational disease that first infected people who worked or visited the seafood and wet animal market in Wuhan. Due to the ability of the virus to spread rapidly and patients refer to medical centers, it can be said that the most sensitive people to get the disease are HCWs. Of the 138 patients admitted to COVID-19 in Zhongnan Hospital, Wuhan, China, 40 patients (29%) were from HCWs [25]. Although HCWs use some safety methods, they are at risk for SARS-CoV-2 and the less they pay attention to safety precautions, the more likely they are to be infected. Procedures that have the potential to produce aerosols and droplets could be a potential source of contamination, the most important of which is tracheal intubation [7]. Other contaminant procedures include airway suction, non-invasive ventilation, manual ventilation, tracheotomy, cardiopulmonary resuscitation, and manipulation of oxygen masks in people with COVID-19 [28]. Other dangerous jobs in the cities include sweepers who are at risk of contamination during the disposal of contaminated waste, and taxi and bus drivers are at risk of contact with asymptomatic people.

Poor ventilation

There is no specific vaccine or treatment for this infection, and asymptomatic people can infect others therefore, places where the air conditioning is poor can infect people [16]. Thus, proper ventilation in hospitals, clinics, offices and banks is essential, and wherever there is a gathering of people, there should be airflow.

Animal contact

The virus is transmitted from bat to human through the intermediate host [8]. It can be present in human feces and infect other animals [11]. By examining the presence of antibodies in cat, dog, monkey, cattle and sheep, it is possible to determine how many animals that have been in contact with humans are infected. These animals may be able to act as bats as reservoirs and infect villagers and veterinarians who are most in direct contact with the animals.

Other environmental factors

Other environmental factors that can cause COVID-19 as well as its severe form include poor hygiene, prisons, nursing homes, dormitories, poor living conditions, unemployment, high body mass index (BMI), stress, taking the subway, eating in a restaurant, and more prominent laboratory abnormality, as shown in Figure 1.

■ VIRAL RISK FACTORS

Identifying viral risk factors helps target strategies for rapid diagnosis and treatment.

Transmissibility

The primary reservoir of the virus, number of the infected people, and the transmission route are important factors in the virus transmission. SARS-CoV-2 is more transmissible and its R_0 is 3.28. Surviving in aerosols, it infects a significant number of people [10, 14]. The virus is easily transmitted between family members, acquaintances, and those with friendly contact with asymptomatic infected individuals and patients as a cluster [20]. The virus is also transmitted during the incubation period [13]. In addition, it remains for a significant time on teflon, glass, surgical gloves, and steel [14].

Viral evolution

The mortality rate from COVID-19 varies from country to country [1]. By examining the se-

quence of separated strains in different regions, mutations are seen in these strains. They are higher in ORFs, 1a, S, 8, N and RNA-dependent-RNA polymerase (RdRp) [29]. The mutations affect virus replication, its transmission, immune responses, virus virulence, drug resistance, and adaptation to new hosts [30]. In addition, with the emergence of new strains, due to the mutation, there will be a possibility of invasion of the new strain and the chance of damaging children and adolescents. It could possibly infect people who have been infected before because their lungs are damaged, so there will be a chance that the disease will be severe and possible to die, thus delaying the production of a vaccine that can respond to all strains.

Viral load

SARS-CoV-2 and its receptor, ACE2, are present in the cells of the lower respiratory tract and the epithelial cells of the mouth and tongue and multiply in these cells [6]. The virus has viral shedding for a long time, even up to 37 days [15]. The virus load in an asymptomatic patient is similar to that in symptomatic patients, but the number is about four times higher in asymptomatic individuals than in symptomatic patients; therefore, they can infect a significant number of people [16]. The high number of viruses entering the body increases the innate immune response. It causes severe inflammation and cytokine storm that can endanger the patient's life, as shown in Figure 1 [22].

■ CONCLUSIONS

It can be concluded that timely diagnosis and isolation of patients with COVID-19 and quarantine of infected individuals is the most important method to reduce the prevalence of COVID-19. Viral and environmental factors such as crowding, low education, health care workers and poor ventilation are important risk factors for infection and in the elderly, men, and those with underlying diseases, the severe form of the disease is high. Therefore, identifying high-risk individuals and preventing their infection can reduce mortality.

Conflict of interest

No potential conflict of interest relevant to this article was reported.

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