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High risk individuals in COVID-19 pandemic; an updated review

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Abstract

In December 2019, cases of pneumonia with an unknown pathogen were reporting in Wuhan city, China. The World Health Organization (WHO) recognized it as a pandemic, on March 11, 2020. The most frequent site of involvement is the respiratory system. The most common symptoms include cough, fatigue and fever. In some cases, neurological, respiratory and gastrointestinal complications can lead to death. Inflammatory cytokines can play a major role in pathogen damage. Due to the pandemic of COVID-19 and its severe complications, it is critical to identify the high-risk groups. Since this disease has a rapid transmission, following the instructions announced by the WHO, prevention is vital, especially in people with risk factors for disease complications and mortality. According to the latest reports by CDC (Center for Disease Control and Prevention), older age and having some medical conditions such as smoking, obesity (BMI ≥30 kg/m^2), chronic obstructive pulmonary disease (COPD), heart disease, cancer, solid organ transplant, type 2 diabetes mellitus, chronic renal failure, and sickle cell anemia in younger adults are known disease severity risk factor.

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Introduction

In December 2019, cases of pneumonia with an unknown pathogen were reporting in Wuhan city, Hubei province, China. After extensive research, the pathogen was sequenced and identified as a novel coronavirus (1), which was then named SARS-Cov2 and the disease was finally called COVID-19 (2-7). This virus is a single-stranded RNA virus, which is enveloped and belongs to the Coronaviridae family (8).

The disease rapidly spread in other parts of the world (9). Therefore, in January 2020, cases occurred in Japan, South Korea, Thailand, and then many other countries (5). The World Health Organization (WHO), recognized it as a pandemic, on March 11, 2020 (6). By the end of May 2020, over 5.9 million infected people and 300 000 victims were reported (7).

According to electron microscopy findings, coronaviruses, the largest known RNA viruses, are divided into four subfamilies (alpha, beta, gamma, and delta). Seven types are pathogenic for humans, which cause mild to severe respiratory diseases, ranging from seasonal cold-like illness to severe cases leading to acute respiratory distress syndrome (ADRS) or failure of some other organs (6-11). The new coronavirus is a beta type one (10). Other types of beta-coronaviruses can cause an acute respiratory syndrome and were highly pathogenic, including Middle East respiratory syndrome coronavirus (MERS-CoV) and Severe acute respiratory syndrome coronavirus (SARS-CoV), emerged in 2013 and 2002, respectively(7-13). The genome sequence dissimilarity between the novel coronavirus and the other previous types, denotes that SARS-Cov-2 is a new pathogen for humans (1).

The most frequent site of involvement is the respiratory system, which can lead the patient to be hospitalized in the intensive care

Key point
According to the latest reports by CDC (Center for Disease Control and Prevention), older age and having some medical conditions such as smoking, obesity (BMI ≥30 kg/m^2), chronic obstructive pulmonary disease (COPD), heart disease, cancer, solid organ transplant, type 2 diabetes mellitus, chronic renal failure, and sickle cell anemia in younger adults are known disease severity risk factor.

unit (12). The most common symptoms include cough, fatigue and fever. Diarrhea and headache are also reported, but patients may be asymptomatic or have mild symptoms (13). Other symptoms reported are muscle aches, sore throat, taste and smell disorders, and decreased level of consciousness (14). About 2 to 14 days after exposure to the virus, symptoms appear. In some cases, neurological, respiratory and gastrointestinal complications can lead to death (8). In addition to pulmonary involvements, other organs such as the heart, kidney, gastrointestinal, and central nervous system may be involved and the risk of thromboembolism is also increased with life-threatening consequences (14).

Since this disease is pandemic and highly contagious (6), identifying high-risk groups with higher mortality is essential. In this study, we review major risk factors for COVID-19.

Materials and Methods

Articles related to this topic were searched in EBSCO, Medline/PubMed, Scopus, Web of Science, Embase, Directory of Open Access Journals (DOAJ) and Google Scholar, using the following keywords or their combinations; COVID-19, SARS-Cov2, COVID-19 severity, COVID-19 risk factors, diabetes, obesity, pregnancy, cancer, chronic renal failure and angiotensin-converting enzyme 2.

Mechanism of viral pathogenesis

Each virus needs a receptor at the host cell surface for the successful entry. Human angiotensin 2 converting enzyme (ACE-2) receptor presents in various tissues such as the heart, lung, small intestine, kidney, thyroid, and the adipose tissue (13). Through one of the viral surface proteins, spike protein, the virus joins the receptor (5). The expression of the receptor, according to cell studies, is lower in women than in men(10). ACE-2 receptor is present in epithelial cells of lung tissue (type 2 pneumocyte) at high quantities. Other receptors for the virus entrance include CD209 L, CD209, and CD 147 (14).

Inflammatory cytokines production, such as interleukin-6 is induced after virus entry into the host cell. The predominant attendance of CD4 and GM-CSF (granulocyte-macrophage colony-stimulating factor) positive T cells in the blood is a feature in severe cases. GM-CSF positive Th1 and CD14 and CD16 positive monocytes, enter the lung tissue and cause tissue damage (15).

The innate immune system is the host's first defense against infectious diseases; However, an excessive immune response causes tissue injury, and inflammatory cytokines can play a major role in pathogen damage. Overproduction of these cytokines attracts neutrophils and monocytes into the tissues, a common mechanism in diseases caused by SARS and MERS viruses. ADRS is the result of non-specific inflammatory cells infiltration and overproduction of chemokines [such as IFNγ-induced protein 10, chemokine ligand 2, chemokine ligand 3, and chemokine (C-C motif) ligand 5)] and cytokines (such as reactive oxygen species, GM-CSF, IL-1β, IL-6, IL-8). Unlike SARS, Th2-related cytokines are additionally increased in COVID-19. However, severe cases have higher levels of inflammatory cytokines such as IL-6 or IL-2 than in mild cases. In general, severe cases leading to death or multi-organ damage are due to the induction of cytokine storm by the virus (9). Histological examinations have demonstrated the accumulation of inflammatory cells around small vessels and thrombotic microangiopathy in the lung tissue, and steatosis, dilatation of sinusoids, necrosis, and infiltration of the lymphocytes in the liver of victims. Autopsy has revealed areas of fibrosis and hypertrophy in cardiac tissue. Therefore, consideration should be paid to the immune system pathologies, microangiopathic and thrombotic events in the treatment (14).

According to the latest reports by CDC (the Center for Disease Control and Prevention), older age and having some medical conditions such as smoking, obesity (body mass index, BMI ≥30 kg/m^2), chronic obstructive pulmonary disease (COPD), heart disease, cancer, solid organ transplant, type 2 diabetes mellitus, chronic renal failure, and sickle cell anemia in younger adults are known disease severity risk factor. While liver disease, immunocompromised other than organ transplantation, hypertension, pregnancy, BMI >25 kg/m^2, moderate to severe asthma, neurological disease, cystic fibrosis, thalassemia, type one diabetes mellitus, and pulmonary fibrosis might be risk factors (16). Accordingly, immunodeficiency state is a risk factor for COVID-19, since these individuals may remain contagious for a longer time versus other individuals (16). In a study by Li et al on 548 patients in Wuhan, 269 patients had severe disease and 46 patients needed respiratory support. Patients with ARDS had higher levels of cytokines produced by Th1 (including interleukin 6 [IL-6] and tumor necrosis factor-alpha [TNF-α]). In their study severe cases showed rapid disease progression and multiple organ failure syndrome. Severity risk factors included old age, high D-dimer level, and lactate dehydrogenase at the time of admission. Risk factors for increased mortality in severe cases were male gender, high levels of lactate dehydrogenase, hyperglycemia, leukocytosis, older age, and cardiac injury. Hypertension was also cited in this study as an independent risk factor for disease severity. There was no difference in the patient's previous medications between the severe and non-severe groups (17). Another study conducted in Mexico on 89 756 patients found that the hospitalization rate was seven times higher in people over 65 years than in people less than 45 years old. The most common comorbidities were endocrine and cardiovascular diseases. Diabetes, obesity, COPD, hypertension, cardiovascular disease, and having more than one comorbidity were risk factors for complications and increased need for

hospitalization. However, smoking was not a risk factor for increasing the need for hospitalization (18), however other studies have shown that smokers are more likely to have disease complications than non-smokers when hospitalized (19,(20).

Gut microbiota is thought to have a role in regulating the function of the acquired and innate immune systems, and the host's defense against infections. Elderly, diabetics, cardiovascular patients, and those with immunodeficiency are less able to deal with the disease. It has been observed that these groups have a disorder in the gut microbiota called dysbiosis (21). Recent studies showed the significance of chronic kidney disease (CKD) as a potential risk factor for SARS-Cov2 mortality (22). The recent investigation by Williamson et al, showed that individuals with critical forms of chronic renal failure have a potential risk of SARS-Cov2 mortality. Moreover, they found the risk of CKD is even elevated than patients with chronic heart disease, obesity, pulmonary disease, and hypertension. The detail of the study showed CKD patients were divided into 3 including cases with an estimated glomerular filtration rate (eGFR) of 30–60 mL/min/1.73 m^2, and individuals with an eGFR of <30 mL/min/1.73 m^2 and finally patients on regular dialysis. The study showed a significant association of kidney dysfunction level and the risk of SARS-Cov2 mortality (23). The highest mortality rate is among the elderly (24). In one study, the death rate between groups who did not need respiratory support was 26.6% in over 65 and 1.98% in younger people (25). With aging and underlying nutritional deficiencies, the immune system weakens, which occurs in both acquired and innate immune systems. Increased number of memory T cells, decreased naïve T cells, dysfunction of T cell, and thymus regression is also expected. Additionally, there are disorders in the production of cytokines and lymphocyte proliferation, which result in increased inflammation and increased mortality. The incidence of chronic diseases increases with age (15). In a study by Nimkar et al, acute renal impairment, ARDS and old age were accompanied by a higher mortality rate. Renal involvement results from several mechanisms such as cytokine storm, and cardiorenal syndrome, which would be the result of decreased volume, cardiomyopathy, and increased vascular permeability. Acute kidney damage is independently associated with increased mortality, and more common in the African American race, patients with CKD, elderly, and hyperlipidemia (26).

Adequate levels of vitamin D in the blood have been shown to be effective in defending against respiratory infections. Some studies have suggested that a low level of vitamin D is accompanied by increased disease severity, but not yet proven (27).

In a meta-analysis by Kumar et al, patients with diabetes were not more susceptible to COVID-19 than non-diabetics (12), but mortality and disease severity were higher in this group (12,28), and the need for hospitalization in the intensive care unit and ADRS were more common following infection (12). According to the study by Guo et al, diabetes would be an independent disease severity risk factor. These patients more frequently exhibited tissue damage, hypercoagulable states, and severe immune response (29).

The exact cause is not known. However, according to the recent studies, improper immune response and therefore increasing cytokines such as IL-7, IL-2 and TNF-alpha in diabetic patients causes more severe lung involvement(12). Patients with metabolic syndrome and diabetes have ten times more mortality risk (30).

Obesity is associated with increased susceptibility to disease and a chronic inflammatory condition. Increased fat consumption due to increased migration of T cells to adipose tissue exacerbates the local inflammatory response. Adipose tissue can produce cytokines (adipokines) which augment insulin resistance in type 2 diabetes mellitus and can act on macrophages and stimulate the production of inflammatory mediators such as IL-1, IL-6, and TNF-alpha. The presence of regulatory T cells in adipose tissue in these people and the increased Th 17-disturbed immunity are in connection with cytokines such as macrophage inflammatory protein-1 alpha, tumor necrosis factor-alpha and interleukin 6. In addition, Th17 cells are associated with autoimmune diseases such as rheumatoid arthritis and psoriasis. In very obese people, disease severity and the risk of ARDS is incremented (15). Obesity also over-activates the mTOR pathway, the master regulator of the metabolism. Overactivation of the mTOR pathway results in overproduction of translation initiation factors, the materials which are shared by coronavirus the translation machinery. It has been suggested that the hyperactivation of the mTOR pathway in obesity/overnutrition could provide an ideal platform for coronavirus replication, whose translation depends on the host's translation apparatus. Still, more researches are required to reveal all mechanisms by which obesity can increase COVID-19 susceptibility (31).

Pregnant women have an increased mortality risk and more complications from infectious diseases. Physiological changes in the cardiovascular, immune, and respiratory systems increase the susceptibility to severe infectious diseases. These physiological changes are associated with decreased ability to clear lung secretions and diminished total lung capacity. Due to the rapid course and the presence of these physiological changes, pregnant women with COVID-19 can be at a higher risk for the development of respiratory disorders and hypoxia. The predominance of Th2 cells over Th1 cells also leads to increased susceptibility to viral diseases. According to the mentioned reasons, pregnant women are susceptible to graver diseases during epidemics (10).

Another risk factor for COVID-19 infection is cancer (16). During a study on 3232 COVID-19 hospitalized infected patients (January and March 2020) in Wuhan,

Meng et al found, gender, age and presence of cancer were independent risk factors for SARS-Cov2 mortality Meng et al, also found that cancer patients with complications had a significantly higher risk of poor outcomes. Using propensity score matching, 109 cancer cases were matched to non-cancer individuals which showed the cancer individuals even had an elevated risk of mortality than the controlled non-cancer individuals (32). A more recent systematic review and meta-analysis revealed in more details the risk and prognosis of SARS-Cov2 infection in individuals with cancers (22 studies; 1018 cancer patients). ElGohary et al detected that the frequency of malignancy among individuals with SARS-Cov2 was 2.1% in the overall cohort. Besides, patients with malignancy had considerably lower platelet concentrations and more raised D-dimer levels, higher CRP (C-reactive protein) levels, and disturbed prothrombin time. They concluded that patients with malignancy are at an increased risk of SARS-Cov2 complications (33). It is possible that the delay in diagnosis and treatment could be one underlying factor. Likewise, recent reports detected that CRP, IL-6 (34,35) and D-dimer serum concentrations correlate with a graver SARS-Cov2 (36). Moreover, sequential assessment of serum procalcitonin may predict the progress of COVID-19 (37). In asthma, there is increased allergic reactions and susceptibility to viral infections. The production of interferons, which play a key role in protection against viruses, is impaired in asthmatic patients. On the other hand, diminution in interferon reduces ACE2 receptor expression. As the virus uses this receptor entering the target cell, the virus invasion seems to be less in patients with asthma (38). Asthma is currently mentioned as a risk factor, which can be due to triggering asthma attack by viral infections, thereby it is necessary to be controlled during the current pandemic (39).

Sickle cell anemia, a blood disorder and one of the most common genetic diseases (40), exposes the patient to an increased risk of respiratory infections and causes complications such as acute chest syndrome (41). These patients have systemic vasculopathy, splenic dysfunction, and a high risk of thrombosis and are considered a high-risk group. All of these can contribute to a graver COVID-19 (40).

Conclusion

Due to the COVID-19 pandemic and its severe complications, it is critical to identify the high-risk groups. Since this disease has a rapid transmission, following the instructions announced by the WHO, prevention is vital, especially in people with risk factors Elderly people with underlying diseases, obese people, and pregnant women are at increased risk for disease complications and mortality. Complying with the instructions in order to protect these susceptible population from infection is one of the most important steps that we need to take to combat the disease.

Authors' contribution

Primary draft by RC. First edit by MH. Extensive edit by AB and ZM. All authors read and signed the final manuscript.

Conflicts of interest

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Ethical considerations

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