



RISK FACTORS AND CO-MORBIDITIES ASSOCIATED WITH COVID-19

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ABSTRACT

The rapid outbreak of Corona-virus disease 2019 (Covid-19), has recently become a public health emergency of international concern. Corona-virus arose from severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection¹. SARS-CoV-2 first attacked the Wuhan city of China in December 2019, since then there has been no arrest to the spread of the virus. It has spread in 215 countries all over the world to date. Coronavirus is an enveloped, non-segmented, single-stranded RNA virus². At present, six human coronaviruses have been identified. And the SARS-CoV-2, which isolated from the lower respiratory tract of pneumonia patients with unknown causes in Wuhan, is recognized as the seventh human coronavirus³. The most common symptoms of COVID-19 are fever, dry cough, difficulty in breathing, and tiredness. Other symptoms that are less common and may affect some patients include aches and pains, nasal congestion, headache, conjunctivitis, sore throat, diarrhoea, loss of taste or smell, or a rash on skin or discoloration of fingers or toes⁴. Findings suggest that patients with co-morbidities have more significant disease severity compared with those without any co-morbidity. Further, a higher number of co-morbidities correlate with greater disease severity of Covid-19. Therefore, patients with co-existing co-morbidities are more likely to have poorer baseline well-being, and both the category and number of co-morbidities should be taken into account when predicting the prognosis in patients with COVID-19^{5,6}.

KEYWORDS

Corona Virus, COVID-19, SARS, MERS, Hypertension, Diabetes, Coronary Heart Disease.

1. INTRODUCTION

A cluster of pneumonia attacks was observed in Wuhan city of China in December 2019. The pathogen was designated as SARS-CoV-2 by the International Committee on Taxonomy of Viruses. This pneumonia was named as Coronavirus Disease-2019 (COVID-19) by World Health Organization (WHO)⁷. Nowadays, there are more than thirteen million confirmed cases and over 5.5 lakh deaths occurred in 215 countries/territories according to the report of WHO until 14th July 2020⁸. The rapidly increasing number of patients, especially critical or mortal patients, brought a significant challenge to public health.

There are many coronaviruses, ranging from the common cold to much more serious viruses such as Severe Acute Respiratory Syndrome (SARS) and Middle East Respiratory Syndrome (MERS). They are viruses that have been transmitted from animals to people. Like any other respiratory disease, the transmission of COVID-19 is through air-droplets that are dispersed when an infected person talks, sneezes, or coughs. The virus can survive from a few hours up to a few days, depending on the environmental conditions. It can be spread through close contact with an infected person or by contact with air droplets in the environment and then touching the mouth or nose^{9,10}. Symptoms usually start within 3-7 days of exposure to the virus, but in some cases, it may take up to 14 days for symptoms to appear. Common signs are typical flu-like symptoms: a fever, cough, breathing difficulties, tiredness, and muscle aches. At present, there is no vaccine against COVID-19, and clinical studies are going on to find a cure for this disease.

1.1 Pathogenesis

SARS-CoV-2 attacks the alveolar epithelial cells via angiotensin-converting enzyme 2 (ACE2). ACE2 is the ACE of isozyme, mainly distributed in cardiovascular, kidneys, testes, lung and colon, and other organizations¹¹. The main role of ACE2 is to incise Ang II to generate An ACE2 receptor on the surface of alveolar epithelial cells. The expression of ACE2 in alveolar epithelial cells is down-regulated by mechanisms such as internalization, shedding and viral replication¹⁵. Then the increased concentration of Ang II leads to inflammatory response, and g 1-7, which mediates the protective effects of vasodilation, anti-inflammatory and anti-proliferation. Ang 1-7 antagonize Ang II-induced vascular smooth muscle contraction, cell proliferation, fibrosis promotion, and vascular inflammation.^{12,13,14}

When SARS-CoV-2 binds to exudation of neutrophils, maintaining oxygenation¹⁶. At the same time, the viral infection will cause the imbalance of T helper macrophages, and fibrinous, resulting in loss of pulmonary ventilation function and difficulty in -1 and T helper-2 responses, and induce an inflammatory storm by increasing the levels of inflammatory factors such as interleukin-4, interleukin-10, and

interleukin-6¹⁷. Inflammatory storm in critical patients releases cytokines, causing systemic immune injury, which may be an important cause of multiple organ failure and even death.¹⁸

1.2 Risk Factors 19

Findings suggest that, similar to other severe acute respiratory outbreaks, co-morbidities such as COPD, diabetes, hypertension, and malignancy predisposed to adverse clinical outcomes in patients with Covid-19. Two or more co-morbidities are more commonly seen in severe cases than in non-severe cases. It has been well accepted that some co-morbidities frequently co-exist. For instance, diabetes and COPD often co-exist with hypertension or coronary heart diseases. Therefore, patients with co-existing co-morbidities are more likely to have poorer baseline well-being.

Till now the available data shows that following are the risk factors associated with COVID-19

1) Elderly people¹⁹- As the body's immunity declines with age, elderly patients are more likely to develop a critical illness or even die. Aged over 65 years, patients might face a higher risk of developing into the critical or mortal condition, and the co-morbidities such as hypertension, diabetes, cardiovascular disease, or respiratory diseases could also significantly affect the prognosis of the COVID-19.

2) Male gender^{20,21}- Studies have found that women are less susceptible to viral infection than men, possibly because of the protection of X chromosome and sex hormones, which play an essential role in innate and adaptive immunity. At the same time, men tend to be associated with bad lifestyle habits such as smoking and underlying diseases. A study revealed that men have more amount of ACE2 in the body as compared to women, and as ACE2 binds with SARS-COV2, this may explain the tendency of males to get more infected with the Corona-virus as compared to females. Generally, testosterone has an immunosuppressive effect, while estrogen has an immunoenhancing impact on the immune system. Oestrogen has been shown to regulate immune response by impairing adverse selection of high-affinity auto-reactive B cells, modulating B cell function, and leading to Th2 response. As a result, the majority of critical or mortal patients are male.

3) Diabetes- When people with diabetes develop a viral infection, it can be harder to treat due to fluctuations in blood glucose levels and, possibly, the presence of diabetes complications. There appear to be two reasons for this. Firstly, the immune system is compromised, making it harder to fight the virus and likely leading to a more extended recovery period. Secondly, the virus may thrive in an environment of elevated blood glucose²². There is a bidirectional relationship

between Covid-19 and diabetes. Diabetes is associated with an increased risk of severe Covid-19. In contrast, new-onset diabetes and severe metabolic complications of pre-existing diabetes, including diabetic ketoacidosis and hyperosmolarity for which exceptionally high doses of insulin are warranted, have been observed in patients with Covid-19. The reason behind the new onset of diabetes or the onset of diabetic complications in diabetics patients might be following-

A) SARS-CoV-2, the virus that causes Covid-19, binds to ACE2 receptors, which are expressed in key metabolic organs and tissues, including pancreatic beta cells, adipose tissue, the small intestine, and the kidneys. Thus, it is plausible that SARS-CoV-2 may cause pleiotropic alterations of glucose metabolism that could complicate the pathophysiology of pre-existing diabetes or lead to new mechanisms of disease.

B) The other reason can be explained that as a defence mechanism to any viral or bacterial infection, the body tries to raise the temperature to kill off certain viruses sensitive to temperature changes like the flu. Once the pyrogens trigger the hypothalamus to raise body temperature, the process of gluconeogenesis starts in the body to release the stored energy and to produce heat. This process of gluconeogenesis might be responsible for the raised blood sugar level in both normal as well as diabetic patients during infection.

C) Certain reports are suggestive that use of medicines with sodium-glucose co-transporter-2 (SGLT2) inhibitors such as dapagliflozin or remogliflozin should be avoided in severely symptomatic and hospitalised diabetic patients as it can lead to dehydration and diabetic ketoacidosis.

These manifestations of diabetes pose challenges in clinical management and suggest a complex pathophysiology of Covid-19-related diabetes.

4) Hypertension²⁶ - Patients with raised blood pressure have a two-fold increased risk of dying from the coronavirus COVID-19 compared to patients without high blood pressure. Angiotensin-converting enzyme 2 (ACE2) is required for viral entry of SARS-CoV-2. ACE2 is widely expressed in the human body, with expression found in the gastrointestinal tract, heart, and kidney, and alveolar cells in the lungs. Angiotensin-converting enzyme inhibitors (ACEIs) and Angiotensin receptor blockers (ARBs) are the two types of renin-angiotensin-aldosterone system (RAAS) inhibitors widely used for treating hypertension, and heart and renal failure. Evidence suggests that there is a counter-regulatory relationship between ACE2 and its homolog, Angiotensin Converting Enzyme (ACE), as they take part in opposite axes in the Renin-Angiotensin-System (RAS). For example, drugs that inhibit ACE activity induces ACE2 expression²⁷. Therefore, high levels of ACE could indicate low levels of ACE2 and vice versa²⁷. The use of ACEIs will not just increase the amount of ACE2 in the body but also causes dry cough because of the raised level of bradykinin in the body. Thus, once countered with Corona-virus, such patients will have a higher chance of severe onset of COVID-19 pathology and symptomatology. That's why treatment with ACEIs or ARBs might augment the patient's susceptibility to viral host cell entry and propagation.

5) Respiratory diseases- When the patient has previous respiratory diseases such as chronic obstructive pulmonary disease, the patient's lung function is damaged. They have lower resistance to the virus and are prone to developing ARDS.

6) Cardiac diseases²⁷ - Patients with chronic heart disease are more likely to be infected due to their weakened heart function and low immunity. When infected with SARS-CoV-2, they are more likely to have acute cardiovascular events and develop into severe diseases. SARS-CoV-2 can cause myocardial injury by direct and/or indirect action. The direct injury is to infect cardiomyocytes by identifying the ACE2 receptor. In contrast, the indirect injury may be caused by an inflammatory storm inducing by an immune response and/or oxygen supply imbalance inducing by acute respiratory distress syndrome.

7) Pregnancy²⁸ - Pregnant women are more at risk of contracting COVID-19 due to their weakened immune system. Studies demonstrate that COVID-19 is an immune condition that is marked by reduced lymphocytes and elevated selected proinflammatory

cytokines. The similar immune expression has been shown in pregnancy by several studies. Also, the placenta has been shown to possess ACE2 receptors on the villous cytotrophoblast and the syncytiotrophoblast. Furthermore, the presence of the ACE2 receptors in the placenta may increase the risk of mother to baby transmission of the virus.

8) Renal diseases^{29,30} - Patients with pre-existing CKD will be at increased risk of AKI through pyrexia, inadequate fluid intake from anorexia, sore throat, diarrhoea, and NSAIDs used by patients for treatment of myalgias and headaches. Thus patients with kidney disease are likely to be more at risk of serious morbidity and mortality during a pandemic.

9) Malignancy³¹ - Cancer seems to have comparable associations with an increased risk of death from coronavirus disease 2019 (COVID-19) to those of other co-morbidities, such as chronic respiratory disease and hypertension. A systematic review revealed little evidence that immuno-modulatory agents, such as steroids, cytotoxic agents, tacrolimus, JAK inhibitors, and biologics, including anti-TNF antibodies, increase the risk of severe COVID-19 symptoms. Though in another study³³ from 18th March to 26th April 2020, 800 patients with a diagnosis of cancer and symptomatic COVID-19 were analysed. After adjusting for age, gender, and co-morbidities, chemotherapy in the past four weeks had no significant effect on mortality from COVID-19 disease when compared with patients with cancer who had not received recent chemotherapy. No significant impact was found on mortality for patients with immunotherapy, hormonal therapy, targeted therapy, radiotherapy use within the past 4 weeks.

CONCLUSION

When patients are combined with basic diseases such as diabetes and hypertension, etc. then the body is in a state of stress for a long time, and the immunity tends to be low. Moreover, the long-term history of diabetes and hypertension will damage the vascular structure, and it is more likely to develop into critical disease in infection. Thus, underlying diseases such as diabetes, hypertension, cardiovascular disease or respiratory disease are risk factors for disease progression.

In the present scenario of COVID-19, elderly people and pregnant females should be given extra care in terms of preventive measures such as proper sanitization, avoiding social gathering, wearing masks, proper diet & nutrition, and effective management of existing diseases. Androgen suppression therapy or orchiectomy can be taken into account in male patients aged above 65 years of age infected with the Corona-virus.

Diabetic patients are more prone to COVID-19 and to develop diabetic complications. Thus it is essential to regularly monitor and effectively control the blood glucose of such patients along with the conventional treatment that is being used to fight COVID-19. Even regular monitoring of blood glucose in the normal individual is also warranted to check the new onset of diabetes.

As we have discussed above that hypertensive patients have a two-fold risk of dying from COVID-19. The mortality is much higher in hypertensive patients who are not taking any antihypertensive drugs as compared to patients with antihypertensive drugs. So in this situation, the use of other antihypertensive drugs such as calcium channel blockers, diuretics, etc. can be taken into account to control the blood pressure instead of ACEIs or ARBs.

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