Iranian Journal of Virology 2021;15 (1): 68-78

Review Article

The Outcome of COVID-19 Infection on Patients with Underlying Diseases

Yari A[1], Bamdad T[*1], Soleimanjahi H[1], Habibian A[1], Seyed Khorrami SM[1]

1. Department of Virology, Faculty of Medical Sciences, Tarbiat Modares University, Tehran, Iran

Abstract

One of the major concerns in the world is the Coronavirus Disease 2019 (COVID-19), an infectious disease caused by Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2). Although the knowledge is limited about the risk factors for the disease, morbidity and mortality may increase in the patients with some underlying conditions such as cardiovascular disease, hypertension, diabetes, cancer, etc. These diseases can weaken the immune system and affect the body's ability to respond to infectious agents. Therefore, these patients are more at the risk for COVID-19 and also the underlying condition may worsen the severity of COVID-19 infection. On the other hand, SARS-CoV-2 via multiple pathophysiological mechanisms can lead to the progression of the underlying diseases and resulting in a poor outcome. The coronavirus binds to angiotensin-converting enzyme 2 (ACE2) which is expressed on the cells of many organs and it can directly affect tissues. Apoptosis of the cells may occur in patients with acute respiratory disease syndrome (ARDS) due to hypoxia in COVID-19. Moreover, SARS-CoV-2 leads to an imbalanced the immune inflammatory response in some patients which may cause indirectly organ injury. In this review we described the prevalence of COVID-19 in various underlying diseases and the impact of the SARS-CoV-2 in the outcome of these diseases. However, further studies are needed to investigate the prevalence of this new virus in patients with underlying diseases and its effects on the progression of illness.

Keywords: Underlying disease; SARS-CoV-2; COVID-19; Coronavirus; Chronic disease

Background

Underlying disease is a long term or chronic illness that increases the risk of complications of infectious diseases and usually leads to weakening immune system. Therefore, by reducing the patient's response to fight off the infection, the impact of infectious agents can be worse and resulting in a poor outcome. These patients are likely to need more critical care even some of them have to be hospitalized in ICU (1). Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) which belongs to the family of *Coronaviridae* is now a major public health emergency in the world and cause of Coronavirus Disease 2019 (COVID-19). Patients with COVID-19 have a range of symptoms from mild to severe illness (2). Although the information about the risk factors for COVID-19 is limited, some of the underlying conditions may put patients at higher risk to morbidity and mortality and also each condition has its own vulnerabilities.

This review describes the impact or status of COVID-19 in various underlying diseases and pathophysiological mechanisms resulting from SARS-CoV-2 which can lead to more severe disease outcomes in patients with COVID-19.

[*] **Corresponding author:**
Taravat Bamdad.
Email: Bamdad_t@modares.ac.ir

Hypertension and COVID-19

Hypertension is a serious medical challenge because of its high frequency and concomitant risks of cardiovascular and kidney disease. According to the world health organization (WHO) 1.13 billion people worldwide have hypertension. It is a major cause of death in the world with more than 1 in 4 men and 1 in 5 women having this condition. The burden of hypertension is felt disproportionately in developing countries, where two-thirds of cases are found, largely due to increased risk factors in those populations in recent decades. It is estimated the number of adults with hypertension increase by 60% (1·56 billion) of the total in the world in 2025 (3).

Given the current unstoppable problem of SARS-CoV-2 along with the high prevalence of hypertension, it is expectable the combination of these conditions will bring many socio-economic and health burdens to human society. It is widely reported that hypertension increases the risk of severe COVID-19 development (4).

Lippi observed that hypertension causes an approximately 2.5-fold higher risk of developing severe disease or death due to SARS-CoV-2 (5). Hypertension along with old age increases the risk of severe disease. One study in china found 39.7% of 406 deceased patients with COVID-19 had known hypertension and 81% of these patients were older than 60 years of age (6). The death rate is higher in people with high blood pressure as it was reported that in Italy the mean age of deceased patients with COVID-19 was 79 years and that 69.1% had hypertension (7).

Among all underlying diseases hypertension has the greatest impact on the severity of disease and the rate of death. In a report 48% of patients had comorbidity which hypertension being the most common (30%), followed by diabetes (19%) and coronary heart disease (8%) and also showed increasing in-hospital death associated with older age (8).

Another report from Wuhan on most comorbidity in patients with COVID-19, the most common comorbidity were hypertension (27%) followed by diabetes (19%), and cardiovascular disease (6%) (9). Since the frequency of hypertension in older people is high it is not surprising that COVID-19 is more sever in the elderly and experience more complications of the disease.

As mentioned elsewhere, pro-inflammatory cytokine storm could be associated with COVID-19 severity. Accordingly, patients with COVID-19 requiring ICU admission had an increase in IL-2, IL-6, and IL-7, granulocyte colony-stimulating factor (G-CSF), chemokine ligand 2 (CCL2), and tumor necrosis factor- α (TNF-α) (10).

Interestingly, elevated expres-sion of various cytokines such as IL-6, IL-1b, and IL-23 has been associated with development of hypertension in clinical observations and one of the cytokines regulating inflam-matory responses in hypertension is IL-6 which related to COVID-19 worse outcomes (11).

SARS-CoV-2 binds to angiotensin-converting enzyme 2 (ACE2) which is expressed on the cells of some organs such as lung, gastrointestinal epithelium, cardiovascular endothelium, nervous system and the kidneys in order to cells entry (12) (Figure 1).

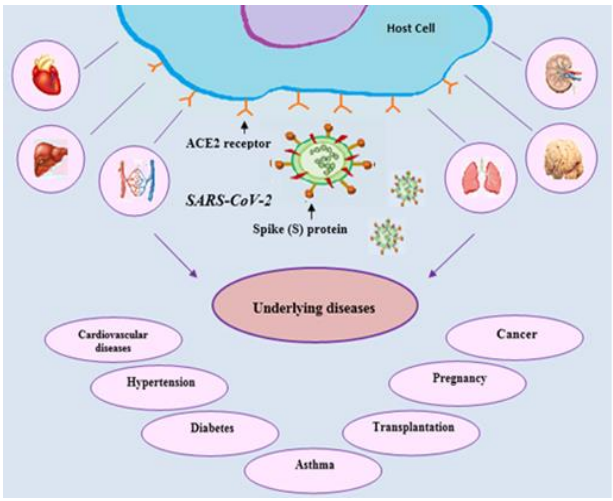

Fig. 1. The virus entry to the cells and its effects on the various underlying diseases. Spike proteins are present on the virus particle and bind to angiotensin-converting enzyme 2 (ACE2), a host cell receptor, on the cells of some organs such as lung, gastrointestinal epithelium, cardiovascular endothelium, nervous system and the kidneys that leads to entering the SARS-CoV-2 into the cells. The virus can directly affect these tissues and can adverse outcome of COVID-19 in patients with underlying disease.

Angiotensin II converts to angiotensin 1–7 by ACE2. Thus, this enzyme reduces the inflammatory effects of angiotensin II.

Increase in angiotensin II was associated with hypertension and lung failure. It has been shown that ACE inhibitors (ACEIs) can increase ACE2 by reducing the formation of angiotensin II and also angiotensin II receptor blockers (ARBs). Therefore these medications have significant immunomodulatory effects by decreasing the cytokines by which organ inflammation is reduced in patients with COVID-19. In addition, these drugs are commonly used for hypertensive patients and cardiac diseases (13). ACE2 is an active peptide of the renin-angiotensin system (RAS). RAS plays an effective role in regulating hypertension. SARS-CoV-2 binds to ACE2 and leads to RAS imbalance and follows the pathogenesis of hypertension and inflammatory lung disease. An effective therapeutic system in hypertension is targeting of RAS. Meng et al. evaluated the effect of RAS inhibitors in COVID-19 patients with hypertension who received ACEI or ARB therapy.

They suggested that using ACEIs or ARBs have a beneficial effect on the improvement of clinical outcomes of patients. Furthermore RAS inhibitors decreased the viral load indirectly by regulating immune function and inhibiting inflammatory responses (14). It is proposed soluble ACE2 could bind circulating SARS-CoV-2 viral particles; therefore, use of ACE2 as a therapeutic approach in COVID-19 will be able to reduce viral load and organ injury (15).

However, considering the ACE2 as a receptor for SARS-CoV-2 has been argued that inhibitors which lead to an increase in the ACE2 might affect negatively the outcome of COVID-19 patients. Overlay none of these possibilities have been confirmed in patients yet and need more studies.

Cardiovascular diseases and COVID-19

Previous studies have suggested that the Middle East respiratory syndrome (MERS) and severe acute respiratory syndrome (SARS) related coronavirus infections have similar pathogenicity and can cause myocarditis and signs of heart failure. Moreover, patients who suffer from heart disease have a heightened risk of morbidity and mortality of these acute viral infections (16, 17). According to Oudit's study, SARS-CoV-1 viral RNA was detected in heart autopsy of 35% of infected patients with SARS, the patients died earlier and suggested the infection of heart due to SARS-CoV-1 which caused a worse course of the disease (18). Yang reports that 67% (35/52) of critically patients with COVID-19 had ARDS and 23% (12/52) of them developed cardiac injury (20). Although the mechanism of cardiac failure by SARS-CoV-2 is not fully described, clinical manifestation of COVID-19 in comparison with pathogenesis of SARS-CoV-1 as well as high structural and the genomic similarity between SARS-CoV-1 and SARS-CoV-2, suggest that like SARS-CoV-1, the new coronavirus can cause cardiovascular disease via multiple mechanisms (1).

The first mechanism of heart function involvement in COVID-19 is mediated via ACE2 witch the virus can directly affect myocardial tissue. The second mechanism, the induced hypoxia in patients with acute respiratory disease syndrome (ARDS) due to SARS-CoV-2 may lead to oxidative stress which significantly destroys the phospholipid layer of the cell membrane and cause apoptosis of cardiomyocytes (19).

Another proposed mechanism; is that SARS-CoV-2 stimulates T helper cells and may cause indirectly cardio-vascular disorders due to an imbalanced the immune- inflammatory response which in some patients leads to disseminated intra-vascular coagulation (DIC) and organ injury. The prevalence of Covid-19 in cardiovascular patients are significant. Li et al reported the proportion of patients with cardiacerebro-vascular disease in all cases was 16.4% by analyzing of six studies including 1527 patients with COVID-19. It was showed at least 8% of total patients suffered an acute cardiac injury and the incidence was about 13 folds higher in ICU/severe patients than the non-ICU/severe counterparts. In addition, it was suggested that heart injury may be caused

by the virus directly (1). In Chen's report, a 61-year old man diagnosed with severe pneumonia and ARDS with no previous chronic underlying disease. He developed heart injury, severe respiratory failure, sepsis and eventually on the 11th day of admission he experienced a sudden cardiac arrest and died (21).

In another report, elevated troponin I was detected among 120 patients with COVID-19 (n=12, 10%) level, indicating cardiovascular injury, and 27.5% (n=33) of patients developed cardiomyopathy (22). Deng et al showed most enrolled 112 patients with a confirmed diagnosis of COVID-19 had normal levels of cardiac troponin I at admission time. Troponin I was raised in 37.5% (42/112) of patients and a threefold increase was observed in 28.6% (32/112) patients during hospitalization. It has been suggested that elevation in troponin levels could identify that patients are at higher risk for acute myocarditis due to secondary consequences of SARS-CoV-2.

Therefore raised troponin levels can be considered as the warning sign of adverse outcomes for the patients who presented atypical symptoms such as chest pain and minimal respiratory involve-ment (23). Shi et al support these concepts that cardiac injury is a common condition among hospitalized patients with COVID-19 and it is associated with a higher risk of death. In the study of 416 hospitalized patients with COVID-19 in Wuhan, China, 19.7% (82/416) patients had myocardial injury manifestation. These patients were older (median age 74 years), had higher leukocyte counts, the higher levels of C-reactive protein (CRP) and troponin I and the higher mortality rate (51.2% vs. 4.5%) compared to those without cardiac injury (24).

Huang et al. in a cohort study of 41 COVID-19 patients reported that higher amounts of IL-1B, IFNγ, IP10, and MCP1 in plasma might lead to activated T helper-1 (Th1) cell responses. Moreover, ICU patients had higher concentrations of inflammatory cytokines than those non- ICU patients suggesting that the cytokine storm was associated with disease severity (25). Since cytokine storm is the major pathophysiological mechanism in fulminant myocarditis (FM) and given the increased plasma inflammatory cytokine level such as IL-6 is notable in SARS-CoV-2 infected patients with cardiac injury, the death of some patients with COVID-19 was due to FM. However, more studies should be performed to investigate SARS-CoV-2 associated FM (22).

Clinical evidences suggested that underlying cardiovascular diseases which are more prevalent in older adults, affects the development and prognosis of COVID-19. On the other patients with novel coronavirus might develop an acute cardiac injury. Thus viral infection in aggravation of heart damage should be considered in the course of disease treatment. The physicians should pay attention not only to the symptoms of respiratory dysfunction but also the symptoms of cardiac and more studies are needed to identify treatments to reduce cardiac injury.

Diabetes and COVID-19

Diabetes mellitus is a chronic metabolic disease which characterized by elevated levels of blood glucose and is one of the leading causes of death throughout the world. The number of people with diabetes worldwide is about 422 millions, particularly in low-and middle-income countries and 1.6 million deaths are related to diabetes annually (according to WHO). Several investigations demonstrated that diabetes is associated with increased susceptibility infections including Mycobacterium tuberculosis, Staphylococcus aureus, the 2009 pandemic influenza A (H1N1) SARS-CoV-1 and MERS-CoV especially in older people (26-29). In patients with diabetes there was found a similar increased risk for SARS and MERS (30).

Zhang et al. reported most of the 140 infected COVID-19 patients were middle and old aged and 64.3% (90/140) patients had comorbidities and 12.1% (17/140) of them had diabetes mellitus (31). A meta-analysis data showed one of the most prevalent comorbidities is diabetes (9.7%) and another analysis through 2108 patients with COVID-19 reported a diabetes prevalence of 10.3% (32). In Onder's report among 355 patients with COVID-19 who died in Italy, 126 patients (35.5%) had diabetes and

proposed the presence of comorbidities may be the risk factors for severe patients compared to non-severe patients (33).

The examination of the animal model showed that ~35% of the capillaries and ~30% of alveoli in the hamster's lungs in diabetes became narrowed and collapsed alveolar epithelium. This study has supported morphological changes of the lungs which related to diabetes (34). On the other hand, in vitro studies have showed that influenza virus replication was significantly increased after treatment of pulmonary epithelial cells with high glucose concentrations. These data indicated that hyperglycemia may enhance viral replication in vivo (35). Diabetes is a chronic inflammatory disease that can cause an ineffective immune response.

Hyperglycemia promotes the increased synthesis of pro-inflammatory cytokines and oxidative stress leads to more infections or adverse outcomes in patients with diabetes (36).

It has been showed plasma levels of furin are elevated in patients with diabetes mellitus (30). Furin is a cellular protease that participates in facilitating cell-cell fusion and viral entry into lung cells by cleaving the spike protein at the S1/S2 site. Hoffmann and colleagues show that SARS-CoV-2 has acquired a highly cleavable multi basic motif in the S1/S2 domain unlike other identified coronaviruses that harbor a monobasic cleavage site. By considering that viruses with a multi basic cleavage site which are activated by protease enzymes including furin are able to spread systemically and cause massive disease, it is not unexpected that the presence of highly cleavable sites in SARS-CoV-2 infection of humans makes it more pathogenic at the presence of furin (37).

Other studies also found that patients with diabetes have a significantly absolute lower count of lymphocytes while the absolute count of neutrophils and levels of some inflammation cytokines are much higher compared to those without diabetes. D-dimer (fibrin degradation fragment) increases significantly during the inflammatory storm. Moreover, it is activated thrombin due to hypoxia which leads to disseminated intravascular coagulation. Guo and collogues reported coagulation index and D-dimer were significantly higher in diabetic patients compared to those without diabetes. It has been showed that COVID-19 dysregulates the glucose metabolism (38). As a result, it affects the severity of diabetes and consequently poor prognosis (26).

A possible pathway which SARS-CoV-2 can cause diabetes in COVID-19 is pancreatic islets damage which has a negative effect on the prognosis of COVID-19. Data from many studies proposed some viruses are diabetogenic such as varicella-zoster virus. Yang et al found SARS-CoV-1 is able to damage the pancreas due to ACE2 expression in this organ and cause diabetes mellitus. The patients with SARS-CoV-1 had higher fast blood glucose levels. As such viral infections increase patients' blood sugar levels, they cause an adverse effect on the recovery of the condition (39). Liu showed about 1-2% of the non-severe patients with SARS-CoV-2 and about 17% of the severe patients had the pancreatic injury. In addition, the inflammatory responses in severe COVID-19 patients may also cause mild damage of pancreas (40).

One of the examined drugs in treatment for COVID-19 is Chloroquine (CQ), a low-cost antimalarial drug. CQ modulates the immune system, has an anti- inflammatory effect and blocks viral infection. A clinical trial in China including 100 patients showed that CQ shortens the disease course and improves clinical symptoms without severe side effects. Hydroxychloroquine (Chloroquine derivative) has been approved in India since 2014 to treat type 2 diabetes as the third or fourth line drug in order to reduce blood glucose by changing of insulin metabolism and increasing insulin accumulation (41). Some diabetic patients unclearly recover from autoimmune attacks for a period of time, a few weeks to a year, by regaining partial transient β-cell activity. So if the CQ is prescribed to these patients with COVID-19 it might occur hypoglycemia which leads to an increase of mortality in subjects hospitalized with pneumonia. Therefore, the caution should be taken in using of CQ in the treatment of type 1 diabetic patients with COVID-19 and need more clinical attention (42). Although, according to many researches,

the higher risk for complications and mortality of COVID-19 is related to individuals with diabetes mellitus but the susceptibility to SARS-CoV-2 infection may not be higher in these individuals.

Asthma and COVID-19

Centers for disease control and prevention (CDC) expressed that patients with moderate to severe asthma are at risk for more sever COVID-19. Additionally, a report showed a higher rate of hospitalized patients with COVID-19 in range of 18-49 years patients with a history of asthma (43). To date, there is no evidence that asthma and respiratory allergies increase the rate of COVID-19 infection. Jackson et al. suggested that the expression of ACE2 in lung cells was lowest in patients with asthma and respiratory allergies. Therefore, this result could be a reason to observe the unexpected reduction in susceptibility to COVID-19 infection.

However, more studies are necessary focused on respiratory allergy and asthma for understanding the impact of asthma on COVID-19 severity (44).

Cancer and COVID-19

Cancer is the second leading cause of death in the world and approximately 1 in 6 deaths is due to cancer, globally. Cancer patients are more susceptible to infections and the studies show these patients might experience worse prognosis of COVID-19 .

Dai et al collected the information of patients who affected by the SARS-CoV-2 from 14 hospitals in Hubei Province, China. It is observed in COVID-19 patients with cancer (105) the rates of having at least one critical symptom; ICU admission and death was higher in comparison with patients without cancer (536 age-matched). Severity of disease in COVID-19 patients was associated with the type of cancer. Patients with lung cancer (20.95%), gastrointestinal cancer (12.38%), breast cancer (10.48%), thyroid cancer (10.48%) and hematological cancer (8.57%) had the highest frequency of severe events. On the other, patients with hematological cancer had a high death rate (33.33%) and after that lung cancer (18.18%). However, patients with metastatic cancer had even higher risks of death. Moreover, incidence of SARS-CoV-2 infections in patients with cancer was 10-fold higher than patients without cancer. The main reason for high mortality in patients with hematological cancer is the presence of dysfunctional plasma cells, lymphocytes or white blood cells in general in this malignancy (45). The study of Zhang showed a total of 53.6% of COVID-19-infected cancer patients who developed severe events and the mortality rate was 28.6%. Furthermore cancer patients were susceptible to severe pneumonia because of their immunosuppressive condition and antitumor therapy. Therefore, it was recommended to avoid treatments which led to immunosuppression or reduction in treatment dosage (46). Accumulating evidence similarly supported that cancer patients with COVID-19 have higher case fatality (7.6%) than the general population (47). Miyashita et al reported that among 334 cancer patients infected by COVID-19 there was not significantly higher mortality rate for all patients with cancer, but in cancer patients younger than 50 years found a significantly higher rate. A systematic review reported by Desai et al, found out 2% prevalence of cancer patients with COVID-19. Overall, due to morbidity and mortality rates in cancer patients with COVID-19, cancer care should be organized during the COVID-19 pandemic.

Kidney disease and COVID-19

Chronic kidney disease (CKD) is a disorder affecting the function and structure of the kidney over months or years. it has been reported CKD is associated with an increased severity and mortality of COVID-19 infection (48). Furthermore, in a meta-analysis has shown the prevalence of underlying CKD among patients with a sever COVID-19 was more frequent compared to other patients (3.3% vs 0.4) (49). The outcomes of another study showed that the prevalence of CKD in

COVID-19 was 1% (50). Williamson et al, in a Cohort study reported the rate of COVID-19 deaths in patients with reduced kidney function was 1.33% (51). As mentioned above, similar to SARS-CoV-1 infection SARS-CoV-2 binds to ACE2 receptor. The studies showed that ACE2 receptor is relatively overexpressed in the renal endothelial cells of patients with CKD (52). On the other hand, the findings by electron microscopy showed the presence of viral inclusion bodies in a peritubular space and viral particles within endothelial cells of the glomerular capillary loops of a patient with COVID-19 (53). Taken together, apoptosis and pyroptosis Induced by SARS-CoV-2 might have an effect on endothelial cells injury and could explain the observed kidney systemic impaired function in patients with COVID-19. These findings show the patients with CKD are vulnerable to the SARS-CoV-2 infection and provide the need to pay more attention to the monitoring of patients with preexisting kidney dysfunction which is associated with adverse outcomes in COVID-19.

Neurological Disorders and COVID-19

Cerebrovascular diseases are other comorbidities among the patients with COVID-19 that associated with severe respiratory complications (20). Some patients with COVID-19 without typical symptoms have presented only neurological manifestations in the early stages of the illness including headache, malaise, dizziness and skeletal muscle injury. Mao reported among of 214 patients with COVID-19, 78 (36.4%) of them had neurologic manifestations. The results showed that the brain tissue autopsy of patients with COVID-19 was edematous and some neurons degenerated that support SARS-CoV-2 may enter the central nervous system (54). Moreover, cerebral hemorrhage was observed in some cases of patients with COVID-19. Although the association between SARS-CoV-2 and cerebral hemorrhage is unclear, based on some evidence it is suggested the virus probably induce cerebral hemorrhage in COVID-19 patients. First, ACE2 signaling plays a role in lowering blood pressure and on the other, the expression level of ACE2 decreases in patients with hypertension thus following SARS-CoV-2 infection the function of ACE2 proteins are more reduced and it is likely caused cerebral hemorrhage in these patients. Second, it is suggested SARS-CoV-2 infection can cause coagulopathy and increase prothrombin time which leads arterial infarctions. The other, it was detected SARS-CoV-2 RNA in the CSF (cerebrospinal fluid) that may lead to neurological harm and damage directly (55).

In a study reported neurologic symptoms including encephalopathy, necrotizing encephalopathy and confusion has also been observed in 58 of 64 patients with COVID-19.

There is urgent need for more studies about neurodegenerative disorders in infected patients especially who suffer neurological conditions such as stroke, multiple sclerosis, etc. (56). Centers for Disease Control and Prevention have been prepared guidelines and recommendations for the care and management of COVID-19 in patients with underlying diseases. Some of them are documented in the Table 1 (57).

Transplantation and COVID-19

However viruses often cause more severe disease in people with transplant recipients, there is no information about whether SARS-CoV-2 infection will be more serious in clinical outcomes of transplant recipients compared to immune competence. Although the risk of COVID-19 transmission in transplantation is unclear, SARS-CoV-2 has a transmissible potency by organ donation. Data from SARS-CoV-1 epidemic showed the presence of the virus in organs such as liver, kidney, and intestines. Additionally, it has been reported that SARS-CoV-2 was isolated from blood of COVID-19 patients. Thus, all organs can acquit the virus through blood system (58).

Guillena emphasized in a case report that organ transplant recipient who infected with COVID-19 often present atypical clinical manifesttations (59).

Table 1. Some recommendations for patients with underlying disease about care of COVID-19	
General care of patients	Inform the symptoms of COVID-19. Train hand washing, hygiene, and minimizing exposure to sick contacts. Receive vaccinations against influenza and pneumococcal disease. Stay home and away from crowded places as much as possible. Elective surgeries are rescheduled if possible. On May 1, 2020, FDA issued the use of remdesivir to treat adults and children hospitalized with severe COVID-19.
Serious heart conditions and pulmonary hypertension	Continue ACE-I or ARB according to the doctor's prescription Patients with hypertension control and check their blood pressure
Diabetes	Test the blood sugar every four hours Have at least a two-week supply of the diabetes pills and insulin.
Cancer	Stopping chemotherapy may be an option for patients in deep remission Home infusion of chemotherapy drugs should feasible for the patient and medical team Prophylactic growth factors and antibiotics may make patients less vulnerable to potential COVID-19 complications Delaying of stem cell transplantation Long term immune suppression may be put patients at increased risk of COVID-19 Patients receiving radiation for symptom control or at low risk of harm could delay schedule for radiation treatment
Transplantation	Prolonged use of corticosteroids and other medications can weakens immune system which immunocompromised patients have less ability to fight the virus. Therefore, the continuation of the drug should be according to the doctor's advice
Asthma	Keep the asthma under control Avoid the allergens that trigger asthma Minimize use of disinfectants that can cause the asthma attack

COVID-19: Coronavirus Disease 2019, ACE-I: Angiotensin converting enzyme inhibitors, ARB: Angiotensin-II receptor blockers.

The immunosuppressive agents can increase the risk of viral infection. These drugs target the proliferation and differentiation of T cells. According to the research, T lymphocyte reduction in severe COVID-19 patients is common which leads to worse the disease outcome. Moreover immunosuppression in posttransplant patients may exacerbate the severity of COVID-19 infection. Thus in such high-risk populations, a clinical suspicion is crucial and it should be considered screening for SARS-CoV2 (60).

Pregnancy and COVID-19

Physiological and immunological changes in pregnant women are related to higher maternal and fetal morbidity and mortality which resulted in viral pneumonia (61). Clinical findings suggest that SARS during perinatal period may be asymptomatic to causing harmful side effects including spontaneous miscarriage, disseminated intravascular coagulopathy, preterm delivery, intrauterine growth retard, and abrupt abortion for both mother and neonate (62). Generally, the studies showed clinical presentation in pregnant women with COVID-19 was similar to non-pregnant women and had minor problems than those with SARS (63). In a systematic review including nineteen studies, the most common adverse pregnancy outcome in 41 hospitalized pregnant women infected with COVID-19 was preterm birth and none of their newborns showed clinical manifestations of vertical transmission (64).

Although the results of nucleic acid detection of cord blood and placenta in a woman with COVID-19 infection in the study's Wang was negative, but it must be considered false negatives may occur in detection of viral load and suggested that the pregnant women in the early stage of disease may have been asymptomatic and it is possible that fetus was infected in utero before the mother had clinical manifestation. Therefore, the possibility of mother-to-child transmission of SARS-CoV-2 is not ruled out (65). Another study reviewed 13 articles about the possibility of vertical transmission of the virus. According to the results, SARS-CoV-2 can cause complications such as fetal distress and preterm delivery while newborns were tested for SARS-CoV-2, the results were negative (63). Overall, given to the evidence could not confirm vertical

transmission of COVID-19 infection in pregnancy and it should be followed up suspected pregnant women during pregnancy and post-delivery.

Conclusion

According to currently information regarding SARS-CoV-2, some underlying conditions may increase the severity of COVID-19 infection. Unfortunately, the management of this new virus in patients with underlying diseases is more complicated than expected. More efforts should be carried out to control the viral pandemic. In addition, further studies are needed about the prevalence of COVID-19 in underlying disease and other comorbidities in order to overcome the disease and reduce severity of it. Therefore, full attention should be paid for treatment of these patients and healthcare centers must provide guidelines to care and disease prevention.

Acknowledgment

We gratefully thank to the help and collaboration of the research deputy of Tarbiat Modares University for the support and contribution to conduct this study.

Conflict of interest

The authors declare that they have no conflict of interest.

Funding

No dedicated funding has been used for this paper

References

1. Dhainaut JF CY, Janes J, Nelson DR Underlying disorders and their impact on the host response to infection. Clin Infect Dis. 2005;41 Suppl 7:S481-S489.
2. Li B, Yang, J., Zhao, F. et al. Prevalence and impact of cardiovascular metabolic diseases on COVID-19 in China. Clin Res Cardiol. 2020;109, 531–538.
3. Mills KT, Bundy JD, Kelly TN, Reed JE, Kearney PM, Reynolds K, et al. Global Disparities of Hypertension Prevalence and Control: A Systematic Analysis of Population-Based Studies From 90 Countries. Circulation. 2016;134(6):441-50.
4. Kearney PM, Whelton M, Reynolds K, Muntner P, Whelton PK, He J. Global burden of hypertension: analysis of worldwide data. Lancet. 2005;365(9455): 217-23.
5. Lippi G, Wong J, Henry B. Hypertension and its severity or mortality in Coronavirus Disease 2019 (COVID-19): a pooled analysis. Pol Arch Intern Med. 2020;130(4):304-309.
6. Kreutz R, Algharably EAE-H, Azizi M, Dobrowolski P, Guzik T, Januszewicz A, et al. Hypertension, the renin-angiotensin system, and the risk of lower respiratory tract infections and lung injury: implications for COVID-19. Cardiovasc Res. 2020:cvaa097.
7. Luigi Palmieri XA, Pierfrancesco Barbariol, Antonino Bella, Stefania Bellino, Eva Benell. Characteristics of SARS-CoV-2 patients dying in Italy wwwepicentroissit. April 23th , 2020.
8. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet. 2020 ;395 (10229): 1054-62.
9. Wu C, Chen X, Cai Y, Xia Ja, Zhou X, Xu S, et al. Risk Factors Associated With Acute Respiratory Distress Syndrome and Death in Patients With Coronavirus Disease 2019 Pneumonia in Wuhan, China. JAMA Intern Med. 2020;180(7):934-943.
10. Ruan Q, Yang K, Wang W, Jiang L, Song J. Clinical predictors of mortality due to COVID-19 based on an analysis of data of 150 patients from Wuhan, China. Intensive care med. 2020;46(5):846-8.
11. Carnevale D, Wenzel P. Mechanical stretch on endothelial cells interconnects innate and adaptive immune response in hypertension. Cardiovasc Res. 2018;114(11):1432-4.
12. Thum T. SARS-CoV-2 receptor ACE2 expression in the human heart: cause of a post-pandemic wave of heart failure? Eur Heart J . 2020;41(19):1807-9.
13. Fang L, Karakiulakis G, Roth M. Are patients with hypertension and diabetes mellitus at increased risk for COVID-19 infection? Lancet Respir Med. 2020;8(4): e21.
14. Meng J, Xiao G, Zhang J, He X, Ou M, Bi J, et al. Renin-angiotensin system inhibitors improve the clinical outcomes of COVID-19 patients with hypertension. Emerg Microbes Infect. 2020;9(1):757-60.
15. Schiffrin EL, Flack JM, Ito S, Muntner P, Webb RC. Hypertension and COVID-19. Am J Hypertens. 2020; 33(5):373-4.
16. Alhogbani T. Acute myocarditis associated with novel Middle East respiratory syndrome coronavirus. Ann Saudi Med. 2016;36(1):78-80.
17. Yu CM, Wong RSM, Wu EB, Kong SL, Wong J, Yip GWK, et al. Cardiovascular complications of severe acute respiratory syndrome. Postgrad Med J. 2006;82 (964):140-4.

18. Oudit G, Kassiri Z, Jiang C, Liu P, Poutanen S, Penninger J, et al. SARS-coronavirus modulation of myocardial ACE2 expression and inflammation in patients with SARS. Eur J Clin Invest. 2009;39(7):618-25.
19. Tan W AJ. The cardiovascular burden of coronavirus disease 2019 (COVID-19) with a focus on congenital heart disease. Int J Cardiol. 2020 2020; 309:70-77.
20. Xiaobo Yang YY, Jiqian Xu, Huaqing Shu, Jia'an Xia, Hong Liu, Yongran Wu, Lu Zhang, Zhui Yu, Minghao Fang, Ting Yu, Yaxin Wang, Shangwen Pan, Xiaojing Zou, Shiying Yuan, You Shang. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. Lancet Respir Med. 2020;8: 475–81.
21. Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet. 2020;395 (10223): 507-513
22. Chen C, Zhou Y, Wang DW. SARS-CoV-2: a potential novel etiology of fulminant myocarditis. Herz. 2020; 45(3):230-2.
23. Deng Q, Hu B, Zhang Y, Wang H, Zhou X, Hu W, et al. Suspected myocardial injury in patients with COVID-19: Evidence from front-line clinical observation in Wuhan, China. Int J cardiol. 2020;311:116-21.
24. Shi S, Qin M, Shen B, Cai Y, Liu T, Yang F, et al. Association of Cardiac Injury With Mortality in Hospitalized Patients With COVID-19 in Wuhan, China. JAMA Cardiol. 2020;5(7):802-810.
25. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. 2020 ;395(10223) :497-506.
26. Yang JK, Feng Y, Yuan MY, Yuan SY, Fu HJ, Wu BY, et al. Plasma glucose levels and diabetes are independent predictors for mortality and morbidity in patients with SARS. Diabet Med: 2006 (6):623-8.
27. Weina Guo ML, Yalan Dong, Haifeng Zhou, Zili Zhang, Chunxia Tian, Renjie Qin, Haijun Wang, Yin Shen, Keye Du, Lei Zhao, Heng Fan, Shanshan Luo, Desheng Hu. Diabetes is a risk factor for the progression and prognosis of COVID -19. Diabetes Metab Res Rev. 2020 (e3331).
28. Schoen K, Horvat N, Guerreiro NFC, de Castro I, de Giassi KS. Spectrum of clinical and radiographic findings in patients with diagnosis of H1N1 and correlation with clinical severity. BMC Infect Dis. 2019;19(1):964.
29. Banik GR, Alqahtani AS, Booy R, Rashid H. Risk factors for severity and mortality in patients with MERS-CoV: Analysis of publicly available data from Saudi Arabia. Virol Sin. 2016;31(1):81-4.
30. Muniyappa R, Gubbi S. COVID-19 pandemic, coronaviruses, and diabetes mellitus. Am J Physiol Endocrinol Metab. 2020;318(5):E736-e41
31. Zhang JJ, Dong X, Cao YY, Yuan YD, Yang YB, Yan YQ, et al. Clinical characteristics of 140 patients infected with SARS-CoV-2 in Wuhan, China. Allergy. 2020;75(7):1730-1741.
32. Fadini GP, Morieri ML, Longato E, Avogaro A. Prevalence and impact of diabetes among people infected with SARS-CoV-2. J Endocrinol Invest. 2020; 43(6):867-9.
33. Ashkan Baradaran MHE, Aslan Baradaran, Amir R. Kachooei. Prevalence of Comorbidities in COVID-19 Patients: A Systematic Review and Meta-Analysis. Arch Bone Jt Surg. 2020;8 (Supplement 1): 247-255.
34. Popov D, Simionescu M. Alterations of lung structure in experimental diabetes, and diabetes associated with hyperlipidaemia in hamsters. Eur Respir J. 1997 Aug;10(8):1850-8.
35. Kohio HP, Adamson AL. Glycolytic control of vacuolar-type ATPase activity: a mechanism to regulate influenza viral infection. Virology. 2013;444(1-2):301-9.
36. Hussain A, Bhowmik B, do Vale Moreira NC. COVID-19 and diabetes: Knowledge in progress. Diabetes Res Clin Pract. 2020;162: 108142.
37. Hoffmann M, Kleine-Weber H, Pöhlmann S. A Multibasic Cleavage Site in the Spike Protein of SARS-CoV-2 Is Essential for Infection of Human Lung Cells. Mol Cell. 2020;78(4):779-84.e5.
38. Smith S, Boppana A, Traupman JA, Unson E, Maddock DA, Chao KY, et al. Impaired glucose metabolism in patients with diabetes, prediabetes and obesity is associated with severe Covid-19. medRxiv. 2020.
39. Yang J-K, Lin S-S, Ji X-J, Guo L-M. Binding of SARS coronavirus to its receptor damages islets and causes acute diabetes. Acta Diabetol. 2009;47:193-9.
40. Liu F, Long X, Zou W, Fang M, Wu W, Li W, et al. Highly ACE2 expression in pancreas may cause pancreas damage after SARS-CoV-2 infection. medrxiv. 2020.
41. Singh AK, Singh A, Shaikh A, Singh R, Misra A. Chloroquine and hydroxychloroquine in the treatment of COVID-19 with or without diabetes: A systematic search and a narrative review with a special reference to India and other developing countries. Diabetes Metab Syndr. 2020;14(3):241-6.
42. Baretić M. Case report of chloroquine therapy and hypoglycaemia in type 1 diabetes: What should we have in mind during the COVID-19 pandemic? Diabetes Metab Syndr. 2020;14(4):355-6.
43. (CDC) CfDCaP. Morbidity and mortality weekly report-coronavirus disease 2019 in Children. www.cdc. 2020.
44. Jackson DJ, Busse WW, Bacharier LB, Kattan M, O'Connor GT, Wood RA, et al. Association of respiratory allergy, asthma, and expression of the SARS-CoV-2 receptor ACE2. J Allergy Clin Immunol 2020 ;146(1):203-206.e3
45. Dai M, Liu D, Liu M, Zhou F, Li G, Chen Z, et al. Patients with cancer appear more vulnerable to SARS-COV-2: a multi-center study during the COVID-19 outbreak. Cancer Discov. 2020;10(6):783-791.

46. Zhang L, Zhu F, Xie L, Wang C, Wang J, Chen R, et al. Clinical characteristics of COVID-19-infected cancer patients: A retrospective case study in three hospitals within Wuhan, China. Ann Oncol. 2020;31(7):894-901.
47. Report of the WHO-China Joint Mission on Coronavirus Disease 2019 (COVID-19) wwwWhoInt/ docs/default-source/corona. 2020.
48. Emami A, Javanmardi F, Pirbonyeh N, Akbari A. Prevalence of underlying diseases in hospitalized patients with COVID-19: a systematic review and meta-analysis. Arch Acad Emerg Med. 2020;8(1)
49. Sardu C, Gambardella J, Morelli MB, Wang X, Marfella R, Santulli G. Hypertension, thrombosis, kidney failure, and diabetes: Is COVID-19 an endothelial disease? A comprehensive evaluation of clinical and basic evidence. J C Med. 2020;9(5):1417.
50. Oyelade T, Alqahtani J, Canciani G. Prognosis of COVID-19 in patients with liver and kidney diseases: an early systematic review and meta-analysis. Trop Med Infect Dis. 2020;5(2):80.
51. Williamson EJ, Walker AJ, Bhaskaran K, Bacon S, Bates C, Morton CE, et al. Factors associated with COVID-19-related death using OpenSAFELY. Nature. 2020;584(7821):430-6.
52. Pan X-w, Da Xu HZ, Zhou W, Wang L-h, Cui X-g. Identification of a potential mechanism of acute kidney injury during the COVID-19 outbreak: a study based on single-cell transcriptome analysis. Intensive care med. 2020:1.
53. Varga Z, Flammer AJ, Steiger P, Haberecker M, Andermatt R, Zinkernagel AS, et al. Endothelial cell infection and endotheliitis in COVID-19. The Lancet. 2020;395(10234):1417-8.
54. Mao L, Jin H, Wang M, Hu Y, Chen S, He Q, et al. Neurologic manifestations of hospitalized patients with coronavirus disease 2019 in Wuhan, China. JAMA Neurol. 2020;77(6):683-90.
55. Jordan R, Adab P, Cheng KK. Covid-19: risk factors for severe disease and death. BMJ. 2020;368:m1198.
56. De Felice FG, Tovar-Moll F, Moll J, Munoz DP, Ferreira ST. Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) and the Central Nervous System. Trends Neurosci. 2020;43(6):355-7.
57. Centers for Disease Control and Prevention. 2020.
58. Ilaria Gandolfini MD, Enrico Fiaccadori, Gianluigi Zaza, Lucio Manenti, Anna Degli Antoni, Licia Peruzzi, Leonardo V. Riella, Paolo Cravedi, Umberto Maggiore. COVID-19 in kidney transplant recipients. Am J Transplant. 2020;00:1–3.
59. Guillen E, Pineiro GJ, Revuelta I, Rodriguez D, Bodro M, Moreno A, et al. Case report of COVID-19 in a kidney transplant recipient: Does immunosuppression alter the clinical presentation? Am J Transplant 2020; 20(7):1875-1878.
60. Huang J, Lin H, Wu Y, Fang Y, Kumar R, Chen G, et al. COVID-19 in posttransplant patients-report of 2 cases. Am J Transplant. 2020;20(7):1879-1881.
61. Zambrano L, Fuentes Barahona I, Bejarano-Torres D, Bustillo C, Gonzales G, Vallecillo-Chinchilla G, et al. A pregnant woman with COVID-19 in Central America. Trop Med Infect Dis. 2020:101639.
62. Wong SF, Chow KM, Leung TN, Ng WF, Ng TK, Shek CC, et al. Pregnancy and perinatal outcomes of women with severe acute respiratory syndrome. Am J Obstet Gynecol. 2004;191(1):292-7.
63. Panahi L, Amiri M, Pouy S. Risks of Novel Coronavirus Disease (COVID-19) in Pregnancy; a Narrative Review. Arch Acad Emerg Med. 2020;8(1): e34-e.
64. Di Mascio D, Khalil A, Saccone G, Rizzo G, Buca D, Liberati M, et al. Outcome of Coronavirus spectrum infections (SARS, MERS, COVID-19) during pregnancy: a systematic review and meta-analysis. Am J Obstet Gynecol MFM. 2020;2(2):100107.
65. Wang S, Guo L, Chen L, Liu W, Cao Y, Zhang J, et al. A case report of neonatal COVID-19 infection in China. Clin Infect Dis 2020:ciaa225.

.