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Analising The Organ-Injury And Lastest Treatments For New Variants Of Sars-Cov-2 In Ederly And Immunocompromised Patients With Severe Comorbility. A Review On June 2024

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I. Introduction

The global pandemia of Omicron and the lastest Variants again puts all the scientific community in big problems.

Risk factors for COVID-19 include obesity, older age, underlying medical conditions such as diabetes, inadequate vaccination, and/or being immunocompromised**.[1]**

Ederly living with immunocompromizing conditions including but not limited to active treatment for solid tumor and hematologic malignancies, solid organ transplant recipients, or people living with human immunodeficiency virus, even with appropriate vaccination, are at a greater risk for adverse outcomes from COVID-19 including hospitalization, time in the intensive care unit (ICU), and mechanical ventilation and Severe Side Effects**.[2-3]**

It is of utmost importance to look at the possible risk of Organn-Injury in Ederly and Immunoompromized patients with COVID-19 and after the sieropositivity. It is crucial to comprehend the impact of co-existing medical conditions on the susceptibility to SARS-CoV-2 infection, leading to elevated mortality rates in elderly individuals.

It is an emergent need to take precautionary measures to avoid morbidity and mortality.

Recognizing these intricate factors is crucial for effectively tailoring public health strategies to protect these vulnerable populations**.[4]**

The present leterature review demonstrates the impact of COVID-19 on comorbidities and describe the lastest farmacacological options.

The data presented in the review will be crucial in guiding management strategies and decision-making processes aimed at addressing the challenges posed by the COVID-19 pandemic among elderly individuals with underlying health conditions.

II. Recents Updates For Combating The Impact Of COVID-19 On Comorbidities

Individuals with compromised immune systems, such as those who have undergone solid organ transplants, individuals with metastatic cancers, hematologic malignancies, advanced or untreated HIV infection, primary and secondary immunodeficiencies, recipients of cancer chemotherapy, and patients with autoimmune diseases receiving immunosuppressive biologics and medications, fall into this particular category. This diverse cohort is more susceptible to hospitalization, severe illness, mortality, and increased vulnerability to opportunistic infections when infected with COVID-19. Prolonged presence of SARS-CoV-2 and continuous viral replication heighten the risk of potential emergence of vaccine-resistant or antiviral-resistant variants, there by extending the duration of the pandemic and leading to persistent symptoms. Immunocompromised individuals face a higher likelihood of experiencing severe outcomes from COVID-19.
Vaccination remains the most crucial protective measure for this vulnerable population.

In spite of potential reduced response to vaccines, adherence to the recommended doses can still offer a degree of protection and potentially lessen the severity of the disease. According to local guidelines and recent findings, individuals with compromised immune systems should be assessed for additional doses as a precaution against diminished vaccine efficacy**.[5]** If immunocompromised individuals are exposed to COVID-19, they may require specific isolation or quarantine measures based on their individual risk factors. The

management of COVID-19 necessitates a tailored approach. Remdesivir is an antiviral treatment that may be considered for severe cases of COVID-19. The decision to use antiviral medications should be made in consultation with experts from various disciplines and based on clinical judgment. In cases of severe COVID-19, corticosteroids like dexamethasone may be administered under close medical supervision to patients with significant inflammatory responses. The use of drug therapy for specific severe cases of COVID-19 in immunocompromised patients may be considered on a case-by-case basis, particularly in the early stages of the pandemic. Recommendations for antiviral or immunomodulator therapy for adults with different severities of COVID-19 are outlined.

III. Sars-Cov-2 And Cardiovascular Complications.

An investigation into the susceptibility of individuals with cardiovascular disease to SARS-CoV-2 is of utmost importance. Previous clinical trials have established a connection between MERS and SARS infections and cardiovascular conditions. A study involving 637 MERS-CoV patients revealed that 30% of cases were at a heightened risk of cardiovascular diseases, while 50% exhibited a high prevalence of conditions such as high blood pressure and diabetes. It is widely acknowledged that SARS-CoV-2 interacts with ACE-2 receptors, predominantly found in the kidneys, lungs, heart, and gastrointestinal tract. Research has indicated that the virus gains entry into cardiac myocytes and alveolar epithelial cells through an interaction with ACE-2 receptors. **[6]**

Moreover, ACE-2 significantly influences the neurohumoral regulation of the cardiovascular system. The interaction of SARS-CoV-2 with cardiac and alveolar ACE-2 alters ACE-2 signaling, leading to immediate damage to the heart and lungs. The conversion of angiotensin-II (Ang II) to angiotensin (I-VII) through the renin-angiotensin-aldosterone system (RAAS) is facilitated by ACE-2, which protects the heart. Angiotensin (I-VII) counteracts the effects of Ang II, which is known for its vasoconstrictive and proinflammatory properties that harm capillary endothelial cells. The virus's entry increases the risk of heart damage by upregulating Ang II and downregulating ACE-2. Consequently, elevated ACE-2 receptors may offer cardioprotection while simultaneously enhancing viral replication. Individuals with Cardiovascular Disease experience a concerning rise in comorbidities. The infection disrupts various biochemical pathways crucial to the cardiovascular system, including the ACE-2 pathway, fibrinogen pathways, cardiac muscle integrity, and redox homeostasis. It also leads to the rupture of plaques in stents, exacerbating myocardial damage and dysfunction **.[Figure 1]**

The primary heart conditions linked to SARS-CoV-2 infection are heart damage in elderly, immunocompromised, hypertensive, diabetic, and cardiovascular persistently damaged patients**.[Table 2–3]**

Table 2. Clinical data study for the impact of SARS-CoV-2 on comorbidities.

Patients (No.)		Age (years)	Comorbidities %				References
All	**Male**	Empty Cell	**HT**	**DM**	**RD**	**CVD**	Empty Cell
41	30	49.0	15.0	20.0	2.0	15.0	(Yang et al., 2020)
137	61	57.0	9.5	10.2	1.5	7.3	(K. Liu et al., 2020)
12	8	53.7	25.0	16.7	8.3	33.3	(Y. Liu et al., 2020)
138	75	56.0	31.2	10.1	2.9	14.5	(Bai et al., 2020)
140	71	57.0	30.0	12.1	1.4	5.0	(J. jin Zhang et al., 2020)
9	5	35.2	0	11.1	0	0	(MQ et al., 2020)
1099	640	47.0	14.9	7.4	1.4	2.5	(Guan et al., 2020)

Source: Jonaid Ahmad Malik, Sakeel Ahmed , Mrunal Shinde , Mohammad Hajaj Said Almermesh , Saleh Alghamdi , Arshad Hussain , Sirajudheen Anwar . The Impact of COVID-19 On Comorbidities: A Review Of Recent Updates For Combating It. Saudi Journal of Biological Sciences.Volume 29, Issue 5, May 2022, Pages 3586-3599

Table 3. SARS-CoV-2 and Comorbidities.

S. No.	Disease	SARS-CoV-2 targets/Mechanism	Symptoms/Syndrome	References
1	Hypertension	Overexpression of ACE-2 receptor	Blood pressure increased	(L et al., 2020).
2	Cardiovascular Diseases	Impaired immune system (patients experience inflammation in the cardiac muscles), Elevated troponin level, Interaction of the SARS-CoV-2 with ACE-2 in cardiac myocyte	Myocardial infarction, heart attack, dysrhythmia	(Sprockel et al., 2021)

S. No.	Disease	SARS-CoV-2 targets/Mechanism	Symptoms/Syndrome	References
3	Neurological Complications	Inflammatory response and hypercoagulation, enhanced D-dimers, prolongation of prothrombin time and DIC	Acute Cerebrovascular Disease Encephalopathy GBS HLH	(Tang and Hu, 2021, Uginet et al., 2021)
4	Liver diseases	ACE-2 and TMPRSS2 expression in liver cells	Elevated serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST)	(Marjot et al., 2021)
5	Renal diseases	Imbalance of the Renin-Angiotensin System (RAS), Increased levels of dipeptidyl peptidase-4 and ACE-2	Acute kidney injury (AKI) (sudden loss of kidney function)	(Bitencourt et al., 2020)
6	Endothelial dysfunction	Immune-inflammatory responses, expression and function of its receptor angiotensin-converting enzyme 2 (ACE2) in the vasculature	Inflammation-induced heart failure	(Sisti et al., 2021)
7	HIV	Impaired immune response and ACE-2 receptor in the lungs	Jaundice A low CD4 count	(Ssentongo et al., 2021)
8	Obesity	The abnormal cytokines secretions and adipokines	Chronic obesity with effect on bronchi and lung parenchyma	(Simonnet et al., 2020)
9	Stroke	Hypercoagulability, endothelial injury, vasculitis	Shaking with chills	(Qureshi et al., 2021, Spence et al., 2020)
10	Diabetes	ACE-2 expression, cytokines storm	Pneumonia like symptoms Blood counts of IL-6, C.R.P., and ferritin	(Maddaloni and Buzzetti, 2020)
11	Gangrene	COVID-19 associated hypercoagulability	Localized death, decomposition, and putrefaction of toe or foot fingers	(E et al., 2020)
12	Pulmonary diseases Asthma	local/systemic inflammation, compromised host response, overexpression of ACE-2 receptor in lungs cells	Shortness of breath, cough, pneumonia (2.5-fold more risk), Severe hypoxemia	(Dong et al., 2020; Qiu et al., 2020)
13	Cancer	Immune dysregulation and chronic inflammation, increase in cytokine levels including IL-6	Adult respiratory distress syndrome	(Jyotsana and King, 2020; Wang et al., 2020b)

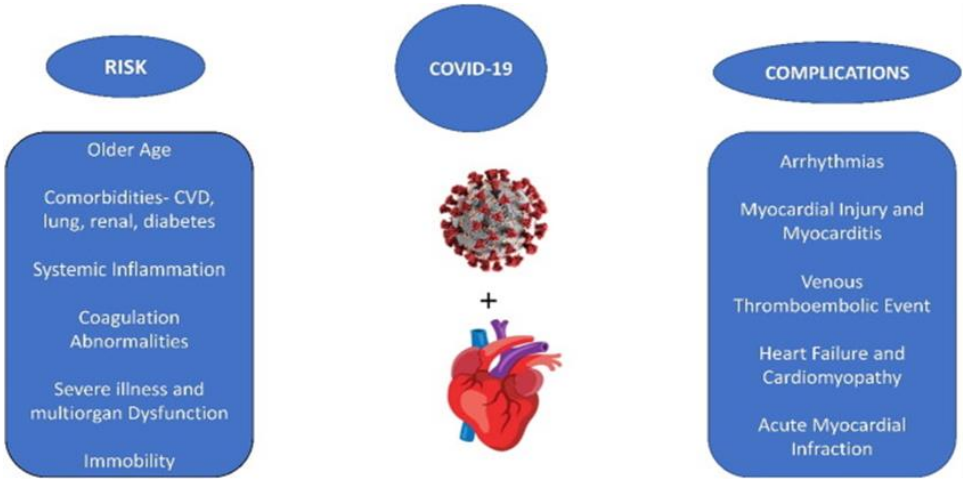


Fig. 1. Risk and the complications of COVID-19 associated with cardiovascular disease.
Source: Jonaid Ahmad Malik, Sakeel Ahmed , Mrunal Shinde , Mohammad Hajaj Said Almermesh , Saleh Alghamdi , Arshad Hussain , Sirajudheen Anwar . The Impact of COVID-19 On Comorbidities: A Review Of Recent Updates For Combating It. Saudi Journal of Biological Sciences.Volume 29, Issue 5, May 2022, Pages 3586-3599

Sars-Cov-2 and Cardiovascular Disease

Cardiovascular diseases are more prevalent in elderly individuals, those with compromised immune systems, and those with high ACE-2 levels. Patients with pre-existing cardiovascular conditions had a higher mortality rate when infected with SARS-CoV-2. The presence of SARS-CoV-2 can worsen myocardial infarction and necrosis, exacerbating heart damage. The specific mechanism behind heart injury in COVID-19 patients is not fully understood, but it is believed to involve ACE-2. Studies using a mouse model have shown that lung infection with SARS-CoV-2 can lead to ACE-2 dependent cardiac complications. In Toronto, autopsies of SARS-CoV-2 patients revealed the presence of SARS coronavirus RNA in heart tissue. Other research has indicated that SARS-CoV-2 related cardiac issues are characterized by a cytokine storm resulting from an imbalance in helper T-cell responses and intracellular calcium overload due to hypoxia, ultimately leading to cardiomyocyte death**. [7]**

Sars-Cov-2 and Myocarditis

Troponin levels, with a cut-off of 28 pg/mL, have been identified as an early indicator of cardiac damage associated with SARS-CoV-2. A study conducted in Wuhan with 41 COVID-19 patients found that 12% of the subjects had elevated troponin levels. Subsequent trials revealed that cardiac injury, as indicated by elevated troponin concentrations, was observed in a number of hospitalized COVID-19 patients, with 22-31% of them requiring admission to the ICU. Furthermore, myocarditis has been linked to an increased viral load and mononuclear invasion in autopsy samples of COVID-19 patients, accounting for 7% of COVID-19-related deaths.

Sars-Cov-2 and *Hypertension*

Drugs such as ACE-2 inhibitors and Angiotensin receptor blockers have been prescribed to individuals suffering from Cardiovascular disorders, such as congestive heart failure and hypertension. The administration of these medications can lead to an increase in ACE-2 expression, consequently raising the susceptibility to severe COVID-19. The Cardiovascular Society has suggested that individuals receiving ACE-2 elevating drugs for conditions like hypertension, diabetes, or cardiac diseases may face a higher risk of SARS-CoV-2 infection and should therefore be closely monitored. It remains uncertain whether uncontrolled high blood pressure poses a greater risk for contracting COVID-19 compared to controlled blood pressure in hypertensive patients. Lippy et al. have shown a 2.5-fold increase in lethality from COVID-19 in individuals with high blood pressure, particularly among the elderly. The ACE-2 receptor plays a crucial role in facilitating the entry of the virus into the lungs during infection, with individuals having high blood pressure experiencing more severe outcomes compared to those with other clinical conditions.

Sars-Cov-2 and Acute Myocardial Infarction and chronic Myocardial Infarction

Cardiac damage presents itself in various forms among Sars-Cov-2 patients. The presence of contamination, inflammation, and fever makes the vascular system more susceptible to clot formation and hinders the body's ability to dissolve a clot. Despite the absence of fatty acid calcified flow-limiting blockages in the arteries, the likelihood of cardiac injury is comparable to that of a heart attack (Myocardial Infarction type 2). This pathology arises when there is an inadequate supply of oxygen to the cardiac myocytes, a prevalent clinical condition linked to SARS-CoV-2 infection. During periods of fever and inflammation, the oxygen requirements of different organs increase. If the infection is concentrated in the lungs, stress levels rise, impacting gaseous exchange and leading to a significant decrease in oxygen supply to the cardiac muscles. As the virus specifically targets the heart, individuals who are COVID-19 positive experience inflammation in the cardiac muscles, including those who were previously healthy with no heart issues. This particular feature of the inflammatory pathway results in damage to the cardiac muscle, dysrhythmia, and heart failure. Elevated systemically mediated inflammation heightens the breakdown of atherosclerotic plaques and the occurrence of Acute Myocardial Infarction. Research has shown that viral infections are linked to an increased risk of Acute Myocardial Infarction within the first seven days of illness diagnosis, with an incidence ratio of 6.1 for influenza and 2.8 for other viruses. COVID-19 patients face a higher risk of AMI due to significant inflammatory responses and hypercoagulability. The treatment of Acute Myocardial Infarction in COVID-19 patients remains uncertain.

Fibrinolysis may be considered for patients with a STEMI and COVID-19. The American College of Cardiology advises against fibrinolysis in cases of "low-risk STEMI." Many medical centers prefer performing PCI more frequently, making it the preferred treatment for lower-risk STEMI cases without right ventricular involvement or lateral Acute Myocardial Infarction, especially in the absence of hemodynamic instability. When PCI is performed, healthcare workers should wear appropriate personal protective equipment, and catheterization labs should be thoroughly disinfected. Patients with NSTEMI who are hemodynamically unstable should be managed similarly to those with STEMI.While fibrinolysis may be considered for

individuals with STEMI and COVID-19, the ACC advises against fibrinolysis in those with "low-risk STEMI." Many institutions opt for PCI more frequently, which remains the preferred treatment for lower STEMI cases without right ventricular involvement. **[9]**

Sars-Cov-2 and Cardiomyopathy

Acute Congestive failure (CF) is primarily observed in cases of COVID-19 infection. At the time of diagnosis, 23% of COVID-19 patients exhibit symptoms of Acute Heart Failure, while 33% show signs of cardiomyopathy. A study has indicated that 24% of patients with COVID-19 have been diagnosed with Heart Failure, which is associated with a higher mortality rate. Interestingly, nearly half of the patients with Heart Failure did not have a history of Hypertension or Cardiovascular Disease. It remains unclear whether this Heart Failure is a result of newly developed cardiomyopathy or the worsening of previously undetected Heart Failure. Additionally, Right Heart Failure may also occur, particularly in individuals with acute respiratory distress syndrome and acute lung injury.

Sars-Cov-2 and Neurological Diseases

The human coronavirus possesses structural features and infection mechanisms that suggest it may have the potential to infect the central nervous system (CNS). The specific process by which the human coronavirus enters the CNS is not yet fully understood. While the distribution of ACE-2 receptors in neuronal tissue is not enough to explain viral neurotropism, axonal transport may play a role in causing neuronal damage. Aerosol droplets play a crucial role in allowing the human coronavirus to enter the nasal mucosa of the infected individual, providing a pathway for the virus to reach the CNS. Once inside the CNS, the membrane-bound ACE-2 receptor, found in various cells such as cerebral capillary endothelium, glial cells, and neurons, enables SARS-CoVs to merge with the cell surface through spike proteins. This strong adhesion then facilitates axonal transport, leading to the spread of infection to regions like the piriform cortex that are linked to olfaction. Within a few days of viral entry, the virus diffuses into the CNS and can be detected in the neuronal regions of infected mice or healthy individuals following the acute phase of the infection**.[10]**

Various neurological issues, such as cognitive impairment, cerebrovascular accidents, and neuromuscular conditions, can arise during the acute phase of COVID-19. Additionally, symptoms like difficulty focusing, headaches, sensory abnormalities, mood disorders, and in severe cases, psychosis, may endure for an extended period following SARS-CoV-2 infection, forming what is now known as Long COVID. It is important to note that even individuals with mild cases of the disease can experience both acute COVID-19 and Long COVID neuropsychiatric complications.

Sars-Cov-2 and Clinical Manifestations

Neurological symptoms in individuals who test positive for COVID-19 have become more apparent, particularly in cases where there were pre-existing neurological conditions linked to severe SARS-CoV-2 infections. A study conducted on hospitalized patients with SARS-CoV-2 revealed that 8% of them had pre-existing neurological disorders, with a focus on pre-existing strokes. Additionally, there was a notable increase in the risk of Acute Respiratory Distress Syndrome among patients without neurological complications. Another study involving 179 individuals diagnosed with SARS-CoV-2 pneumonia found that prior cardiovascular issues significantly increased the likelihood of mortality. Among the hospitalized patients, 6–36% exhibited neurological symptoms. Furthermore, 20% of patients experienced hypoxic-ischemic encephalopathy. Extensive research efforts have been dedicated to exploring the neurotropic nature of Covid-19 in order to understand the broad range of brainstem-mediated symptoms affecting both the pulmonary and cardiovascular systems**.[11]**

The Covid-19 virus is characterized by specific features such as an envelope, non-segmented, single-stranded, positive-sense RNA. The virus causes neurological damage through various pathways, including direct injury to specific receptors like ACE-2, secondary hypoxic injury, cytokine storm, and retrograde travel to nerve fibers. In contrast to lung epithelial cells, ACE-2 receptors are also present on the endothelium of the Blood Brain Barrier, allowing the virus to access the central nervous system and harm the vascular system. The interaction between SARS-CoV-2 and lung epithelial cells triggers a systemic inflammatory response syndrome, leading to increased levels of IL-2, IL-6, IL-15, and TNF-α. Activation of glial cells results in the production of a proinflammatory state in the central nervous system, with IL-6 levels being particularly associated with the severity of Covid-19 illness. The damage to alveoli and systemic effects of the virus cause severe hypoxia, leading to vasodilation in cerebral blood vessels, which can result in decompensated cerebral edema and ischemia. Eventually, the virus can travel in a retrograde manner through the bulb and olfactory nerves, creating a pathway connecting nasal cavity epithelial cells to the central nervous system, potentially explaining the common symptom of anosmia.

Impact of COVID-19 on acute cerebrovascular disease with neurological indications: strocke, ictus, tromboembolism.

One of the most common and important neurological symptoms seen in individuals with COVID-19 is acute cerebrovascular disease. The SARS-CoV-2 virus triggers a widespread inflammatory response and excessive blood clotting, leading to elevated D-dimers, prolonged prothrombin time, and Disseminated Intravascular Coagulation. In an Italian study group, the incidence of ischemic stroke among COVID-19 patients admitted to hospitals was 2.5%, despite receiving preventive treatment for blood clot formation. In contrast, a Chinese study group reported a higher rate of 5% for ischemic stroke. Similarly, in the Netherlands, the prevalence of ischemic stroke was found to be 3.7% among patients admitted to intensive care units, despite receiving preventive treatment for blood clot formation. It is worth noting that younger patients were also reported to experience ischemic stroke with blockages in large blood vessels. Furthermore, individuals with COVID-19 are at risk of experiencing severe oxygen deprivation in the brain, leading to infarctions, particularly in those with a history of cerebrovascular disease. Inflammation and excessive blood clotting significantly increase the likelihood of ischemic stroke, with older patients facing a higher risk.

Safeguarding the well-being of healthcare workers on the front lines while assessing individuals with stroke-like symptoms in the context of COVID-19 is crucial. Nevertheless, it is imperative to provide ongoing medical attention to patients identified with ischemic stroke, with a focus on the administration of intravenous thrombolytic drugs and endovascular thrombectomy in suitable clinical situations, all while adhering to established intervention guidelines.[12]

Sars-Cov-2 and Parkinson Disease and Associated Symptoms

Early accounts indicate a deterioration in parkinsonian symptoms during infection and a bleak prognosis. SARS-CoV-2 infection has led to an escalation in both motor and non-motor symptoms of Parkinson's Disease, encompassing stiffness, tremors, gait difficulties, mood disturbances, cognitive impairment, and fatigue. Individuals with Parkinson's Disease who have contracted the virus have reported a worsening of their symptoms, which may be linked to systemic inflammation, changes in dopaminergic signaling, or alterations in drug metabolism. While direct infection of the central nervous system by SARS-CoV-2 is unlikely to exacerbate symptoms, COVID-19 has been associated with changes in neuroimaging and the presence of SARS-CoV-2 RNA in cerebrospinal fluid. The aggravation of Parkinson's Disease symptoms during COVID-19 may be partly attributed to the inflammatory response of the disease. The widespread occurrence of COVID-19-related exacerbation of symptoms in Parkinson's Disease patients emphasizes the importance of considering COVID-19 as a potential cause for the rapid escalation of Parkinson's Disease-related symptoms. In patients with Parkinson's Disease, a higher proportion of women have been affected by COVID-19 compared to men. However, women were not disproportionately represented in other studies of Parkinson's Disease patients with COVID-19. Previous research has indicated that COVID-19 tends to cause more severe illness in men than in women **[13]**, although women may still be at a higher risk. Furthermore, it has been observed that many symptoms related to Parkinson's Disease worsened in patients who contracted COVID-19. For instance, 18% of individuals with SARS-COV-2 reported new motor symptoms, while 55% experienced worsening of at least one pre-existing motor symptom. Additionally, non-motor symptoms were found to either emerge or deteriorate across various domains, including mood (20% new, 51% worsening), cognitive function (7.8% new, 41% worsening), sleep (12% new, 59% worsening), and autonomic dysfunction (12% new, 59% worsening).

Impact of COVID−19 on encephalitis and encephalopathy

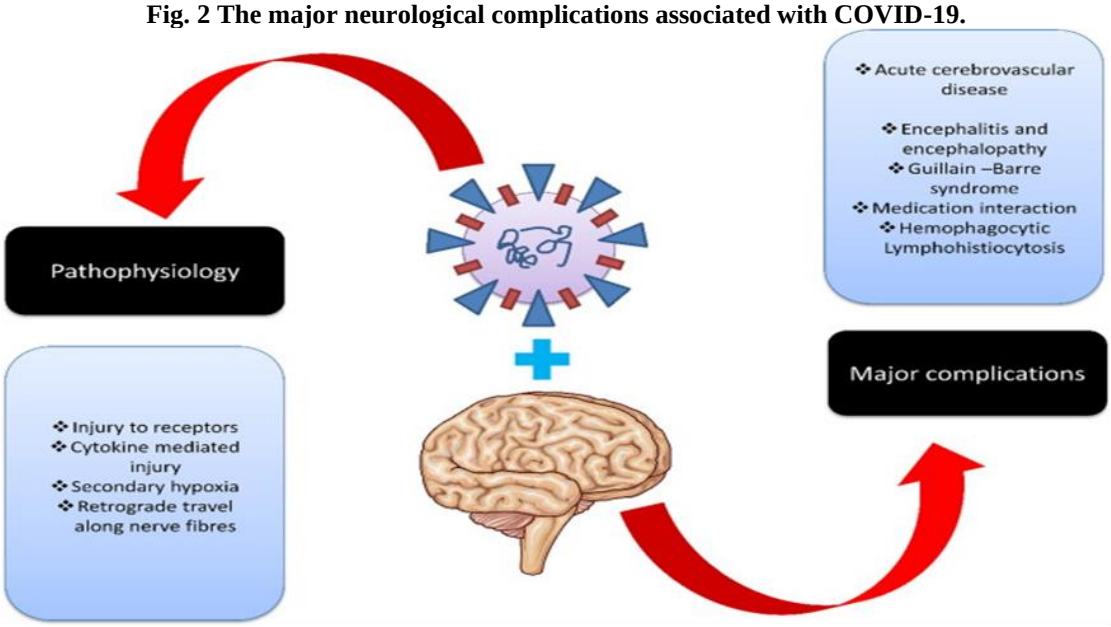
Rare cases of encephalitis related to SARS-CoV-2 have been reported. Encephalitis is characterized by symptoms such as convulsions, nausea, unconsciousness, and the onset of febrile conditions. The exact pathophysiology of this condition is not fully understood, but it is believed to result from secondary edema leading to inflammation-induced injury rather than direct viral infection. Acute Necrotizing Encephalopathy is a rare brain disorder that occurs due to a cytokine crisis and damage to the Blood Brain Barrier, with a distinct absence of demyelination. Imaging studies such as a Non-contrast head CT scan typically reveal symmetric, widespread lesions, while MRI with T2-weighted FLAIR shows hyperintense signal and internal hemorrhage. The thalamus, brainstem, cerebellum, and cerebral white matter are among the most commonly affected regions. Although Acute Necrotizing Encephalopathy is more commonly associated with influenza or zika infections, cases have also been observed in patients with SARS-CoV-2**.[15]**

COVID-19 and Guillain-Barre' Syndrome

Guillain-Barré Syndrome presents as a symmetrical, progressive flaccid paralysis, often triggered by bacterial or viral infections affecting the respiratory or gastrointestinal systems. This progressive neurological disorder has been linked to SARS-CoV-2 infection, with five cases reported in Italy and two in Wuhan, China.

Patients experienced initial upper respiratory symptoms 1 to 14 days before the onset of weakness, with three cases progressing to respiratory failure. All patients tested positive for SARS-CoV-2 through nasal swab PCR and lung imaging, although cerebrospinal fluid samples were negative. Treatment with IVIG was administered to all patients, with those experiencing respiratory complications showing poorer outcomes. Interestingly, 50% of patients had normal brain and spine MRI results, highlighting the need for more comprehensive testing and consultations, such as nerve conduction studies, especially in cases where there is a significant clinical concern despite the absence of radiological abnormalities**.[16]**

Fig. 2 The major neurological complications associated with COVID-19.



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Impact of Sars-Cov-2 on Diabetes Mellitus

Diabetes Mellitus is characterized by an abnormal and excessive cytokine response, as evidenced by elevated levels of IL-6, CRP, and ferritin in Sars-Cov-2 patients. This suggests that individuals with diabetes are at increased risk for severe outcomes, including shock, ARDS, and rapid Sars-Cov-2 infection when exposed to inhaled corticosteroids. Additionally, COVID-19 patients with diabetes exhibited higher D-dimer levels. The hypercoagulation cascade in COVID-19 can lead to catastrophic thromboembolism and potential fatality in the presence of pre-existing pro-thrombotic hypercoagulable state exacerbated by Diabetes Mellitus. Diabetes Mellitus is associated with decreased levels of ACE-2, resulting in reduced AT-II and, to a lesser extent, AT-I, particularly AT I-7 and AT 1–9 individually. The respiratory ACE-2/AT 1-7 system has been shown to possess anti-inflammatory and antioxidant properties, and ACE-2 has also been shown to protect against lethal AIA H5N1 infections. Therefore, the increased prevalence of severe lung injury and ARDS associated with COVID-19 in individuals with Diabetes Mellitus may be attributed to reduced ACE-2 expression. ARBs/ACEi are commonly used as antihypertensive and renoprotective medications in individuals with diabetes. Increased production of ACE-2 is associated with the use of ARBs/ACEi as an adaptive response to elevated AT-II levels. However, SARS-CoV-2 requires ACE-2 as a receptor for entry into host cell pneumocytes.

ACE-2 overexpression facilitates the entry and replication of the coronavirus. As the viruses utilize the enzyme to infiltrate the host tissue, ACE-2 is downregulated, leading to a compromised lung defense against infection **[17].**

Recent research indicates that SARS-CoV-2 non-structural proteins specifically interact with the b1-chain of hemoglobin, resulting in the dissociation of iron from porphyrin and subsequently reducing hemoglobin's capacity to transport oxygen.

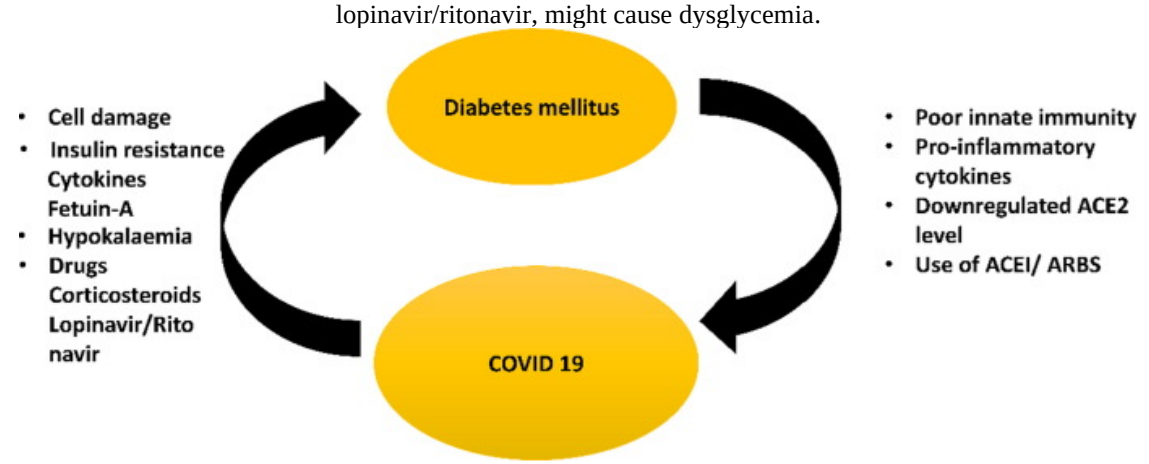
SARS-CoV-2 and pathophysiology of diabetes Mellitus

COVID-19 has the potential to heighten insulin resistance in individuals with Type 2 Diabetes Mellitus and Type 1 Diabetes Mellitus, particularly those who are overweight and develop insulin resistance. Even mild cases of Sars-Cov-2 can trigger proinflammatory effects, as evidenced by elevated IL-1b, IL-6, TNFα, MCP-1

& IP-10, leading to insulin resistance. Additionally, overweightness, commonly associated with T2 Diabetes Mellitus, exacerbates the cytokine response, further worsening insulin resistance. COVID-19 also increases serum concentrations of fetuin-A, an α2- Hermans-Schmid glycoprotein linked to insulin resistance. Furthermore, COVID-19 is often associated with hypokalaemia, decreased pulmonary ACE-2, angiotensin-II deprivation, and increased aldosterone secretion. Hypokalaemia, in turn, can worsen glucose regulation in T1DM and T2DM patients. It is also crucial to consider the indirect impact of COVID-19 medications on the deterioration of glycemic control. Corticosteroids, commonly administered to patients with ARDS and infection, can lead to hyperglycemia. However, brief exposure in the current clinical context may not be clinically significant; lopinavir-ritonavir may cause lipodystrophy and subsequent insulin resistance. Furthermore, due to its inhibitory effect on enzymes, ritonavir has the potential to prolong the half-life of glucocorticoids, indirectly leading to an abnormal glycemic profile. Type 1 interferon, specifically interferon-b1, has emerged as a promising therapeutic option for COVID-19, with interferon therapy being associated with the destruction of β-cells. In the context of COVID-19, Azithromycin has been used in combination with HCQ. This macrolide antibiotic may increase the risk of dysglycemia in patients with diabetes mellitus. Data from Wuhan has shown that around 10% of individuals with both COVID-19 and type 2 diabetes mellitus have experienced at least one hypoglycemic episode (3.9 mmol/L) in addition to worsening hyperglycemia. Conversely, hypoglycemia can lead to an increased incidence of cardiovascular episodes in diabetic individuals by overstimulating the sympathetic nervous system, mobilizing proinflammatory mononuclear cells, and enhancing platelet activity. Therefore, COVID-19 exacerbates the glycemic profile in patients with underlying diabetes mellitus, further compromising the innate immune response and promoting the release of proinflammatory cytokines, thereby establishing a cascade of events as illustrated in **Fig. 3.**

Fig.3. . Representation of the mutual contact amongst the novel COVID-19 and DM. DM increases the seriousness of COVID-19 disease by compromising innate immunity, causing an excessive proinflammatory Cytokine reaction, and lowering ACE-2 expression.

Besides, the usage ACEi/ARBs in patients with DM has been extensively linked to the intensity of disease severity in COVID-19. COVID-19, on the other hand, worsens sugar levels in persons with DM, possibly due to direct β-cell destruction mediated by viruses, increased resistance to insulin via fetuin-A and cytokines, and hypokalaemia. Furthermore, medications used to treat COVID-19, such as corticosteroids and lopinavir/ritonavir, might cause dysglycemia.



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Impact of COVID-19 on gangrene

Gangrene is the result of tissue decomposition and putrefaction caused by a severe microbial infection or inadequate blood supply to the organs. While gangrene is commonly found in the extremities such as the feet, toes, hands, or fingers, it can occur in any part of the body. Limited reports have linked dry and intestinal gangrene to COVID-19, indicating that individuals may develop dry gangrene in their toes and fingers due to blood coagulation issues associated with Sars-Cov-2. The elderly population with underlying health conditions are particularly vulnerable to severe effects of COVID-19. In COVID-19 patients receiving anticoagulation therapy, there have been cases where ischemic necrosis and dry gangrene of the lower extremities have developed as a result of disease progression **.[18-19-20]**

The COVID-19 disease can become more complex due to the development of Acute Respiratory Distress Syndrome, sepsis, and multi-organ dysfunction. Patients without vasculopathy may experience dry gangrene as a result of COVID-19's coagulopathy and disseminated intravascular coagulation. Studies also indicate that SARS-COV-2 infection can lead to increased blood clotting in various forms such as gangrene, stroke, pulmonary embolism, and other acute thrombotic complications, thus supporting the use of anticoagulant medications. The susceptibility of COVID-19 patients to developing thrombosis appears to be multifactorial, involving a proinflammatory state, cytokine crisis, hypoxia-induced blood clots, cytopathological effects, and inflammation of endothelial cells leading to the formation of fibrin clots within the lungs or throughout the body. The hypothesis regarding the formation of blood clots (which can progress to thrombosis and gangrene) in COVID-19 patients suggests that "An internal injury in the blood vessel endothelium, either directly caused by SARS-CoV-2 infection or by the virus-mediated inflammatory immune response, may lead to vasoconstriction and the activation of coagulation and blood clotting pathways, resulting in the formation of blood clots" **[21].** Currently, there have been very few reported cases of gangrene associated with COVID-19. This symptom is considered to be one of the rarest and requires further research to draw any specific conclusions.

Impact of COVID-19 on endothelial dysfunctioning

Endothelial cellular injury is involved in the pathogenesis of multi-organ failure in COVID-19, leading to hypertension and kidney disorders through the interaction with ACE-2 receptors on the endothelial system. Endothelial cells (ECs) play a role in protecting the cardiovascular system by releasing proteins that affect blood clotting and the immune system. Damage to these cells results in extensive damage to cardiovascular tissues, ultimately leading to sudden heart attacks in Sars-Cov-2. Furthermore, injury to the endothelial cells causes inflammation in the blood vessels, leading to plaque rupture and heart attacks, as well as subsequent cytokine storm-induced heart failure. The main factors contributing to endothelial damage include an imbalance between antioxidants and the production of ROS and RNS, left ventricle remodeling, and fibrosis caused by the release of transforming growth factor-beta (TGFβ) by differentiated monocytes.

Drug Therapy for the lastest Variants

Effectiveness of Monoclonal Antibody-based therapy Against Covid Variants (July 2024)

Monoclonal antibodies directed against the S protein of SARS-CoV-2 exert their effects based on their unique structural characteristics. The Fab fragments of these antibodies hinder the virus from attaching to ACE2 receptors, while the Fc fragment can trigger the complement system and attach to Fc receptors on cytotoxic cells, which can then eliminate virus-infected cells through ADCC. **[Table4]** Regrettably, certain monoclonal antibodies may bind to macrophage Fc receptors, leading to an exaggerated inflammatory response due to ADE of cytokine production. The RBD of SARS-CoV-2 has emerged as a primary target for monoclonal antibodies due to its pivotal role in the virus's entry into host cells. Examination of the structural interplay between RBD and anti-RBD NAbs has enabled the categorization of these antibodies based on their structural attributes and mode of action. Class 1 NAbs, such as regdanvimab (CT-P59), focus on the receptor binding motif (RBM) and obstruct the interaction with the ACE2 receptor by recognizing the RBD in the up conformation. Class 2 NAbs, like bebtelovimab (LY-CoV1404), target the ACE2 binding site of the RBD in both up and down conformations. Class 3 antibodies, such as sotrovimab (S309), aim at the conserved core domain of the RBD without disrupting interactions with the ACE2 receptor. Class 4 antibodies, exemplified by S2X259, target epitopes in both the RBM and the core domain of the RBD. Nevertheless, frequent mutations in the RBD have altered the epitopes recognized by monoclonal antibodies, leading to the emergence of viral variants resistant to these antibodies. To combat this challenge, researchers are investigating other regions of SARS-CoV-2 as potential targets for therapeutic monoclonal antibodies.

Table 4. Anti-SARS-CoV-2 RBD therapeutic monoclonal antibodies.

Therapeutic mAb	Use	mAb-resistant SARS-CoV-2 variants	Status	PDB ID
Bebtelovimab	Treatment	Omicron: (BQ.1; BQ.1.1; BA.2; BA.2.12.1 and BA.5)	Not currently authorized by the FDA	7MMO]
Regdanvimab (CT-P59) (Regkirona)	Treatment	Gamma Delta Omicron: B.1.1.529	Paused by Omicron resistance	7CM4

Therapeutic mAb	**Use**	**mAb-resistant SARS-CoV-2 variants**	**Status**	**PDB ID**
Sotrovimab (S309)	Treatment	Delta Omicron	Strong recommendation against its use	7TN0
Amubarvimab (BrII-196), Romlusevimab (BRII-198)	Treatment	Omicron	Available in China	–
Bamlanivimab (LY-CoV555) and Etesevimab (CB6)	Treatment	Beta Gamma] Omicron]	Paused by Omicron resistance	7KMH 7F7E]
	Post-exposure prophylaxis			
REGEN-COV: [**Casirivimab** (REGN10933)/**Imdevimab** (REGN10987)]	Treatment	Omicron	Paused by Omicron resistance	6XDG [
	Post-exposure prophylaxis			6XDG 7ZJL
Evusheld [**Cilgavimab** (COV2-2130/**tixagevimab** (COV2-2196 [	Pre-exposure prophylaxis	Omicron	Not authorized for emergency use in the U.S	8D8Q 8D8R

Source: Jonaid Ahmad Malik, Sakeel Ahmed , Mrunal Shinde , Mohammad Hajaj Said Almermesh , Saleh Alghamdi , Arshad Hussain , Sirajudheen Anwar . The Impact of COVID-19 On Comorbidities: A Review Of Recent Updates For Combating It. Saudi Journal of Biological Sciences.Volume 29, Issue 5, May 2022, Pages 3586-3599

IV. Conclusion

It is imperative to analyze the adaptation trajectory of SARS-CoV-2 in order to forecast potential future occurrences based on the molecular mechanisms that drive the evolutionary success of the virus. Individuals infected with SARS-CoV-2 who have a medical history of cardiovascular disease, advanced age, compromised immune systems, cancer, obesity, chronic respiratory conditions, diabetes, or neurological disorders tend to have a poorer prognosis and are at higher risk of developing Acute Respiratory Distress Syndrome or pneumonia. The emergence of advanced therapies targeting SARS-CoV-2 has paved the way for the integration of new medical technologies to combat infectious diseases. The utilization of monoclonal antibodies for preventive purposes in these high-risk populations holds promise for offering prolonged protection against both symptomatic and severe cases of COVID-19. Nevertheless, the frequent emergence of novel SARS-CoV-2 variants that evade antibody detection poses significant challenges in predicting the efficacy of monoclonal antibodies against these new strains. A concerted global public health initiative is necessary to raise awareness about reducing the impact of these underlying health conditions that contribute to fatalities in individuals with SARS-CoV-2.