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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 December 2024

Weimer LE[1,*], Cattari G[2], Fanales Belasio E[3], Cuccuru E[2] and Vidili Gianpaolo[2]

[1]*National Center for Global Health, Istituto Superiore di Sanità, Rome, Italy*
[2]*Day Hospital, Department of Medicine, University Hospital, AOU Sassari, Sardegna, Italy*
[3]*Department of Infectious Diseases, DMI, Istituto Superiore di Sanità, Rome, Italy*

[*]**Corresponding author:** Liliana Elena Weimer, National Center for Global Health, Istituto Superiore di Sanità, Rome, Italy; E-mail: liliana.weimer@iss.it

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Abstract

The global pandemia of Omicron and the latest 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. Elderly 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.

It is of utmost importance to look at the possible risk of Organn-Injury in Elderly and Immunoompromized patients with COVID-19 and after the sieropositivity. It is essential to understand how co-morbid conditions increase the chance of SARS-CoV-2 infection subsequently increase mortality among elderly patients. It is an emergent need to take precautionary measures to avoid morbidity and mortality. The present literature review demonstrates the impact of COVID-19 on comorbidities and describe the latest farmacacological options .Information provided in the review will play an important role in the management and decision-making efforts to tackle such complications to reduce the further burden of the COVID-19 pandemic in the older population with pre-existing comorbidities.

Keywords: Orgn-Injury; Comorbility; New treatment; SARS-Cov-2; Ederly and Immunocompromised

Introduction

The global pandemia of Omicron and the latest 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].

Elderly 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 Elderly and Immunoompromized patients with COVID-19 and after the sieropositivity. It is essential to understand how co-morbid conditions increase the chance of SARS-CoV-2 infection subsequently increase mortality among elderly patients. 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 literature review demonstrates the

impact of COVID-19 on comorbidities and describe the latest farmacacological options. Information provided in the review will play an important role in the management and decision-making efforts to tackle such complications to reduce the further burden of the COVID-19 pandemic in the older population with pre-existing comorbidities.

Recents Updates for Combating the Impact of COVID-19 on Comorbidities

Patients with immunosuppressed conditions, people with solid-organ trans-plants, metastatic cancers, hematologic malignancies, advanced or untreated HIV (human immunodeficiency virus) infection, primary immunodeficiency's and secondary immunodeficiency, those receiving cancer chemotherapy, and patients with autoimmune diseases receiving immunosuppressive biologics and medications. This heterogonous group of persons had a higher risk of COVID-19-related hospitalization, severe COVID-19, or death and tend to have higher risk for opportunistic infections. In addition, prolonged SARS-CoV-2 infection and persistent viral replication not only cause long duration of symptoms but also risk of emergence of antiviral-resistant or vaccine-escaped variants, prolonging the pandemic.

Immunocompromised individuals are at higher risk of severe COVID-19 outcomes. Vaccination remains a critical preventive mea-sure for this vulnerable population. Although some may have a reduced response to vaccines, receiving the recommended doses can still provide some level of protection and potentially mitigate severe disease.

Given the potential for diminished vaccine response, immunocompromised individuals should be considered for booster doses based on local guidelines and emerging data. In cases of exposure to COVID-19, immunocompromised individuals may require specific isolation or quarantine measures, depending on their risk profile. The management of COVID-19 necessitates an individualized approach.

In severe COVID-19 cases, antiviral therapies such as remdesivir may be considered. The decision to use antiviral drugs should be based on clinical judgment and consultation with specialists from multidisciplinary areas [5]. In severe COVID-19 cases with significant inflammatory responses, corticoste-roids like dexamethasone may be used under close medical supervision. The use drug therapy in specific severe cases of COVID-19 among immunocompromised patients may be considered on a case-by-case basis early in the pandemic.

Therapeutic recommendations for antiviral or immunomodulator therapy of adults with varying severities of COVID-19 are summarized in (Table 1).

Sars-Cov-2 and Cardiovascular Complications

The major concern is to conclude whether people with Cardiovascular are at a greater risk for SARS-CoV-2. Clinical Trials have established the association between cardiovascular disorders with MERS and SARS infection. Analysis of 637 MERS-CoV revealed that 50 % of cases have a high prevalence of diabetes and high blood pressure, and 30% of cases have a high risk of Cardiovascular Diseases. The interaction of SARS-CoV-2 with ACE-2 receptors (largely expressed in the heart, in the lungs, Gastrointestinal System, kidneys) is well documented. It is found that with the help of ACE-2 receptor interaction, virus reaches cardiac myocytes and epithelial cells lining the alveolar tissue.

Moreover, ACE-2 has a crucial role in the neurohumoral regulation of the Cardiovascular System. The engagement of SARS-CoV-2 with cardiac and alveolar ACE-2 resulted in alteration of ACE-2 signaling that leads to acute injury to the lungs and heart. ACE-2 shields the heart from the innervation of RAAS, which is involved in the conversion of Angiotensin-II (Ang II) to Angiotensin (I-VII). Ang II is a powerful vasoconstriction with proinflammatory activity that induces capillary endothelial damage, while Angiotensin (I–VII) has opposite action. The entry of the virus down-regulates the ACE-2 and elevates levels of Ang II, which enhanced the risk of cardiac injury [6].

Therefore, elevated ACE-2 receptors will enhance the virus content but have a cardiprotective potential. There is an alarming escalation in comorbidities among Cardiovascular Disease patients. The infection intervenes with biochemical pathways relevant to the Cardiovascular System like ACE-2 pathway, cardiac muscle integrity, fibrinogen pathways, redox homeostasis, induces breakage of plaques present in the stent, and finally, aggravates myocardial damage and dysfunction (Figure 1). Heart injury in patients elderly, immunocompromized, with hypertension, diabetes and cardiovascular persistent damage are the basic heart illnesses associated with SARS-CoV-2 infection (Tables 2 -3).

Sars-Cov-2 and Cardiovascular Disease

Underlying cardiovascular diseases may be more mutual in the geriatric subjects, persons with weakened immunological systems, high ACE-2 concentrations Individuals with Cardiovascular had a greater death rate with SARS-CoV-2 infection. SARS-CoV-2 contamination can exacerbate Myocardia Infarction and necrosis, aggravating myocardial infarction. The exact mechanism contributing to heart injury in COVID-19 individuals is unknown but assumed to be the involvement of ACE-2. In a mouse model, lung infection produced ACE-2 dependent cardiac complications in subjects with SARS-CoV-2 infection. In Toronto, post mortem analysis of SARS-CoV-2 patient's revealed SARS coronavirus RNA's existence in heart samples. Other studies demonstrated that SARS-CoV-2

associated cardiac complications are distinguished by a cytokine crisis caused by misbalance in helper T-cell subtype responses and intracellular calcium overload due to hypoxia, which leads to cardiomyocyte death [7].

Sars-Cov-2 and Myocarditis

Troponin levels (cut-off of 28 pg/mL) representing one of the earliest cardiac damage linked to SARS-CoV-2. A study with 41 COVID-19 subjects in Wuhan concluded that 12 % of subjects had an elevated troponin level. In later trials, cardiac injury associated with an elevated troponin concentration was seen in several hospitalized COVID-19 subjects, and 22–31% were admitted to the ICU. Myocarditis also has been linked to elevated virus load with mononuclear invasion in the autopsy samples of COVID-19 patients, which accounts for 7% of COVID-19-related fatalities.

Sars-Cov-2 and Hypertension

Drugs like ACE-2 inhibitors and Angiotensin receptors blockers were administered to patients with cardiovascular disorders, including congestive heart failure and hypertension. The administered drugs lead to overexpression of ACE-2, thus resulting in an increased risk of devastating COVID-19. The Word Cardiovascular Society proposed that subjects administered with ACE-2 elevating drugs for hypertension, diabetes, or cardiac diseases have a higher risk of SARS-CoV-2 infection and, therefore, should be monitored [8]. It is unclear whether elevated Blood Pressure in an uncontrolled manner is a risk factor for acquiring COVID-19 or whether controlled blood pressure among patients with hypertension. Lippy et al. demonstrated a 2.5-fold more risk of lethality in COVID-19 with high Blood Pressure, predominantly in geriatric patients. During the infection, the ACE-2 receptor mediates the entry of the virus into the lung, and patients with high blood pressure have more devastating results than other clinical conditions.

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

Cardiac injury is manifested in multiple ways in Sars-Cov-2 patients. Contamination, inflammation and febrile conditions turn the vascular system more vulnerable to clot formation and interferes with the body's ability to dissolve a clot. Despite arteries being devoid of fatty acids calcified flow-limiting blockages, chances of cardiac injury similar to the injury induced by a heart attack (Myocardial Infarction type 2). The pathology occurs when there is a lack of oxygen supply to the cardiac myocytes, one of the predominant clinical conditions associated with SARS-CoV-2 infection. During fever and inflammation, the oxygen demands of various organs get increased. Suppose the infection is localized in the lung, the stress level increases, affecting the gaseous exchange, resulting in a drastic reduction in the supply of O_2 to the cardiac muscles. Since the virus targets the heart, COVID-19 positive patients experience inflammation in the cardiac muscles, along with those individuals who had been formerly healthy with no heart problems. This very characteristic of the inflammatory pathway leads to damage to the cardiac muscle, dysrhythmia, and heart failure. High systemically mediated inflammation increases both atherosclerotic plaques breakdown and Acute Myocardial Infarction. In a study, viral infections were associated with an elevated risk of Acute Myocardial Infarction between the first seven days of diagnosis of the illness, with 6.1 being the incidence ratio for influenza and other viruses having a 2.8 ratio. COVID-19 individuals are at higher risk for AMI due to significant inflammatory responses and hypercoagulability. The therapy of Acute Myocardial Infarction in COVID-19 subjects remains questionable. While fibrinolysis may be contemplated in individuals with a STEMI with COVID-19. According to the ACC, fibrinolysis should be avoided in those with “low-risk STEMI.” Several facilities conduct PCI more frequently, and it remains the therapy of preference for lower STEMI with no right ventricular inclusion or lateral Acute Myorcardial Infarction, mostly with no hemodynamic instability. If PCI is done, personnel must adopt suitable PPE, and the catheterization laboratories must be fully disinfected. Individuals with NSTEMI who are hemodynamically vulnerable must be addressed in the same way STEMI individuals [9].

Sars-Cov-2 and Cardiomyopathy

In acute Congestive failure (CF), COVID-19 contamination is the predominantly manifested. Acute Heart Failure evident in 23 % of COVID-19 subjects at the time of diagnosis, with cardiomyopathy appearing in 33% of the individual. A study reported that Heart Failure was detected in 24 % of subjects and associated with an increased fatality rate. Almost half of the patients with Heart Failure had no prior history of Hypertension or Cardiovascular Disease. It is unknown whether this Heart Failure results from nascent cardiomyopathy or deterioration of formerly undiscovered Heart Failure. Right Heart Failure can also happen, especially in a population with acute respiratory distress syndrome and acute lung injury.

Sars-Cov-2 and Neurological Diseases

The structural features of the human corona virus and the mechanism of inducing infection make it a potential host for CNS. The exact mechanism of the human corona virus entering the CNS remains unclear. The distribution of ACE-2 receptors in the neuronal tissue is insufficient to describe viral neurotropism.

Another possible mechanism could be axonal transport, which leads to neuronal damage.

The aerosol droplets facilitate the human corona virus to enter the nasal mucosa of the infected host; thereby, the virus gains access to the CNS. Once in the CNS, the membrane-bound ACE-2 receptor, ubiquitously present in cerebral capillary endothelium, glial cells, and neurons, assures SARS-CoVs to fuse with cell surface via spike proteins. Strong adhesion subsequently leads to further axonal transport resulting in the spread of infection to the piriform cortex and other regions associated with olfaction. Within days after the viral entry, it diffuses into the CNS and is observed in the neuronal region of infected mice or healthy subjects after the acute manifestation of the infection [10].

Many neurologic complications, including confusion, stroke, and neuromuscular disorders, also manifest during acute COVID-19. Furthermore, disorders such as impaired concentration, headache, sensory disturbances, depression, and even psychosis may persist for months after SARS-CoV-2 infection, as part of a constellation of symptoms now called Long COVID. Even young people with mild disease can develop acute COVID-19 and Long COVID neuropsychiatric syndrome.

Table 1: *Therapeutic recommendations for immunomodulator or Antiviral Drugs for Elderly and Immunocompromized persons with severities of COVID-19.*

Disease severity	Patient disposition	Recommendations
Nonhospitalized adults with mild to moderate COVID-19 who do not require supplemental oxygen	All patients	All patients should be offered symptom management. The Panel recommends against the use of dexamethasone or other systemic corticosteroids in the absence of another indication
	Patients who are at high risk of progressing to severe COVID-19	Preferred therapies. Listed in order of preference: ritonavir-boosted nirmatrelvir (Paxlovid) remdesivir Alternative therapy. For use when the preferred therapies are not available, feasible to use, or clinically appropriate: molnupiravir
Hospitalized adults with COVID-19 but do not require oxygen supplementation	All patients	The Panel recommends against the use of dexamethasone or other systemic corticosteroids for the treatment of COVID-19
	Patients who are at high risk of progressing to severe COVID-19	Remdesivir
Hospitalized adults with COVID-19 and requiring conventional oxygen	Patients who require minimal conventional oxygen	Remdesivir
	Most patients	Use dexamethasone plus remdesivir. If remdesivir cannot be obtained, use dexamethasone

Disease severity	Patient disposition	Recommendations
	Patients who are receiving dexamethasone and who have rapidly increasing oxygen needs and systemic inflammation	Add oral baricitinib or intravenous tocilizumab to 1 of the options above
Hospitalized and requires HFNC oxygen or NIV	All patients	Dexamethasone should be administered to all patients. If the patient has not already received a second immunomodulator, promptly add 1 of the following (listed in order of preference): oral baricitinib intravenous tocilizumab Add remdesivir to 1 of the options above in certain patients
Hospitalized and requires MV or ECMO	All patients	Dexamethasone should be administered to all patients. If the patient has not already received a second immunomodulator, promptly add 1 of the following (listed in alphabetical order): oral baricitinib intravenous tocilizumab

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)

Patients (No.)		Age (years)	Comorbidities %				References
All	Male	Empty Cell	HT	DM	RD	CVD	Empty Cell
1099	640	47.0	14.9	7.4	1.4	2.5	(Guan et al., 2020)

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)
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)

S. No.	Disease	SARS-CoV-2 targets/Mechanism	Symptoms/Syndrome	References
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)

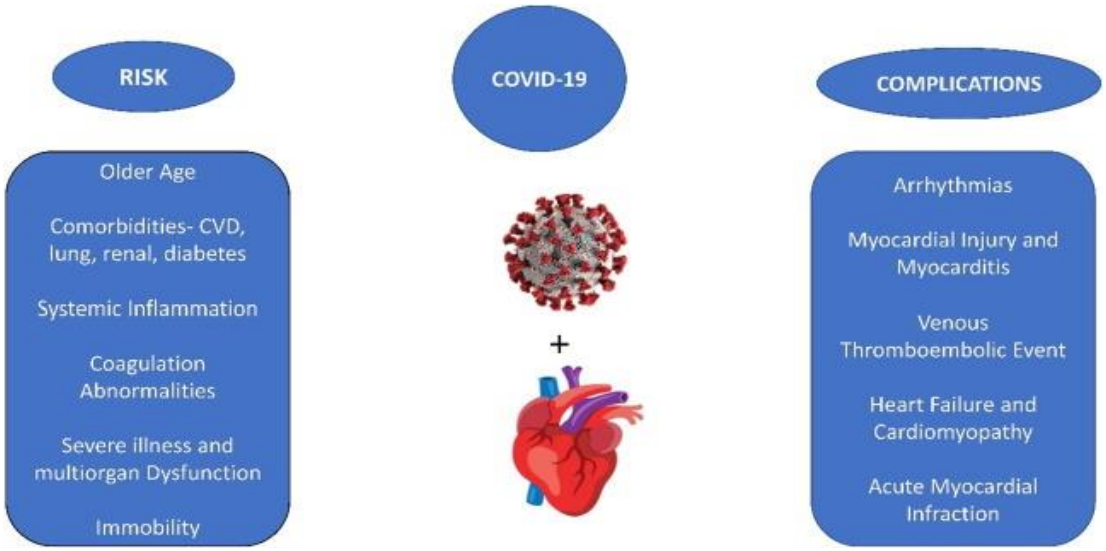

Figure 1: *Risk and the complications of COVID-19 associated with cardiovascular disease.*

Sars-Cov-2 Clinical Manifestations

Neurological manifestations in COVID-19 positive individuals have become more evident with the prior existence of neurological problems associated with more intense SARS-CoV-2 infections. In a study, Sars-Cov-2 hospitalized patients, 8% had pre-existing neurological disorders, especially pre-existing strokes. Moreover, there was a considerable increase in Acute Respiratory Distress Syndrome risk devoid of neurological complications. In another study where 179 subjects were diagnosed with SARS-CoV-2 pneumonia, prior cardiovascular complications significantly enhanced mortality. Within the hospitalized group of patients, 6-36% of subjects had neurological manifestations.

Moreover, 20% of patients were inflicted with hypoxic-ischemic encephalopathy. Rigorous efforts made to investigate neurotropism of Covid-19 to address extensive brainstem-mediated manifestations in both pulmonary and cardiovascular systems [11]. The identifying features of Covid-19 virus include an envelope, non-segmented, single-stranded, positive-sense

RNA. The multifaceted pathways through which the virus inflicts neurological damage directly injure particular receptors, like ACE-2, 2° hypoxic injury, cytokines storm and anti-retrograde traveling to the nerve fibers.

Unlike lung epithelia, ACE-2 receptors are also expressed on the Blood Brain Barrier endothelium that links the viral access to the CNS and damages the vascular system. The coalition of the SARS-CoV-2 with the lungs epithelia produces a universal Systemic inflammatory response syndrome that enhances the levels of IL-2, IL-6, IL-15, TNF- α; activation of glial cells leads to extensive production of proinflammatory state in CNS. Specifically, IL-6 levels correlate with the enhanced intensity of the COVID-19 illness.

This alveolar injury and systemic implications cause severe hypoxia, leading to vasodilation in cerebral vessels, resulting in decompensated cerebral edema and ischemia. Eventually, the viruses proceed backward through the bulb and olfactory nerves, generating a pathway joining the epithelial cells in the nasal cavity and CNS which may also elucidate the common symptom of anosmia.

Impact of COVID-19 on acute cerebrovascular disease with neurological indications: strocke, ictus, tromboembolism. One of the most prevalent and significant neurological manifestations observed in COVID-19 patients includes acute cerebrovascular disease. SARS-CoV-2 produce a universal inflammatory response and hyper coagulation, resulting from enhanced D-dimers, prolonging prothrombin time and disseminated intravascular coagulation.

In an Italian cohort, the rate of ischemic stroke was 2.5% in hospitalized COVID-19 patients, despite prophylaxis thromboembolism admission. In comparison, the Chinese cohort reported a 5% higher rate of ischemic stroke. Comparably, in Dutch, the prevalence of ischemic stroke was found to be 3.7% in ICUs admitted patients despite the prophylaxis of thromboembolism. Notably, in younger patients, ischemic stroke with large vessel occlusions was reported. Moreover, COVID-19 patients are prone to severe hypoxia in the cerebral region and infarcts, especially in patients with a prior cerebrovascular disorder. Inflammation and hyper coagulation can significantly enhance the chances of ischemic stroke, the greater risk associated with older patients.

The protection of front-line workers during the evaluation of COVID-19 patients with stroke-like symptoms is of utmost importance. However, continuous medical care is required for patients diagnosed with ischemic stroke based on their institution laying special attention to intravenous thrombolytic medicaments and endovascular thrombectomy in the appropriate clinical scenarios without altering intervention criteria [12].

Sars-Cov-2 and Parkinson Disease and Associated Symptoms

Early reports describe worsening of parkinsonian symptoms during infection and poor prognosis. SARS-CoV-2 infection increased both motor and non-motor symptoms of Parkinson Disease, including stiffness, tremor, trouble walking, mood problems, cognition, and exhaustion. Viral infected Parkinson Disease patients report worsening Parkinson Disease symptoms, contribute to systemic inflammation, altered dopaminergic signaling, or changes in drug pharmacokinetics. Direct infection of the CNS by SARS-CoV-2 is unlikely to worsen symptoms. Although COVID-19 has been linked to alterations in neuroimaging and SARS-CoV-2 RNA has been found in the cerebral fluid. Exacerbation of Parkinson Diseases symptoms during COVID-19 could be partially attributed to the disease's inflammatory response. The widespread occurrence of COVID-19-related symptoms exacerbation in Parkinson Disease patients underscores the need to consider COVID-19 as a possible explanation for rapidly increasing Parkinson Disease-related symptoms.

A higher percentage of women with Parkinson Disease affceted by COVID-19 than men. Women were not overrepresented in other case studies of patients with Parkinson Disease and COVID-19. COVID-19 has been shown to cause more severe disease in men than in women [13], but women may be more vulnerable.

Many Parkinson Disease-related symptoms worsened with COVID-19 infection. 18% of SARS-COV-2 patients reported new motor symptoms, while 55% indicated worsening at least one previous motor symptom. Non-motor symptoms were reported as new or deteriorating in all domains: mood (20 % new, 51 % worsening), cognitive (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

SARS-CoV-2 related encephalitis have been rarely found. Encephalitis is characterized by convulsions, nausea, unconsciousness the onset of febrile conditions. The pathophysiology remains unknown but is believed from secondary edema to inflammation-induced injury versus direct viral infection.

Acute Necrotizing Encephalopathy is a rare brain condition resulting from cytokine crisis and Blood Brain Barrier damage, characterized by the absence of demyelination. Initially, a Non-contrast head CT scan illustrates symmetric, widespread lesions, whereas MRI with T2-weighted FLAIR shows hyperintense signal and internal hemorrhage. The most commonly affected

regions are the thalamus, brainstem, cerebellum, cerebral white matter. Acute Necrotizing Encephalopathy is more associated with influenza or zika infection, but this condition is also observed with SARS-CoV-2 [15].

COVID-19 and Guillain-Barre' Syndrome

Guillain Barre' Syndrome is a symmetrical, escalating flaccid paralysis, often caused by bacterial or viral illnesses of the pulmonary or GIT. This progressive neuropathy has been identified to be analogous with SARS-CoV-2 contamination, with five incidents found in Italy and two more incidents from Wuhan (China). All subjects felt a prelude of upper respiratory infections spanning from 1 to 14 days before the progression of symptomatic weakness; respiratory failure was reported in three patients. All subjects had a positive nose swab PCR test and lung scanning feature of SARS-CoV-2, but all CSF specimens were negative for SARS-CoV-2. Since all subjects were administered with IVIG, others that suffered pulmonary insufficiency fared poorly. Notably, brain and spine MRI failed to reveal discrepancies in 50 % of the patients, indicating the requirement of more profound tests and consultations, like studies based on the conduction of nerves, when there is a significant therapeutic concern even in the lack of radiological data [16].

Impact of Sars-Cov-2 on Diabetes Mellitus

Diabetes Mellitus is a proinflammatory condition defined by an incorrect and excessive cytokine reaction, as demonstrated in Sars-Cov-2 subjects, there are an increased blood counts of IL-6, CRP, and ferritin. This shows that persons with diabetes are vulnerable to an Inhaled corticosteroids, leading to shock, ARDS, and prompt Sars-Cov-2 infection. Furthermore, COVID-19 individuals with diabetes had greater D-dimer concentrations. The hypercoagulation cascade in COVID-19 results in catastrophic thromboembolism and probable fatality in the context of a pre-existing latent pro-thrombotic hypercoagulable state predisposed condition exacerbated by the presence of Diabetes Mellitus. Diabetes Mellitus is linked to lower levels of ACE-2, subsequently decreased AT-II and to a lesser extent AT-I, especially AT I-7 and AT 1–9 individually. The respiratory ACE-2/AT 1-7 system has been demonstrated to possess anti-inflammatory and antioxidant characteristics, and ACE-2 has also been demonstrated to protect against deadly AIA H5N1 infections. As a result, the surge in prevalence of serious injury to lungs and ARDS associated with COVID-19 could be explained by reduced ACE-2 expression in Diabetes Mellitus. ARBs/ACEi are routinely utilized as anti-hypertensive and renoprotective medicines in persons with diabetes. Enhanced production of ACE-2 is linked to the utilization of ARBs/ACEi as an adaptable reaction to the increasing concentrations of AT-II. However, SARS-CoV-2 requires ACE-2 as a receptor as an entrance into the pneumocytes of the host cell. Therefore ACE-2 overexpression would make it easier for the coronavirus to enter and multiply. When the viruses use the enzyme to access the host tissue, ACE-2 is down regulated, and it can no longer defend the lungs from infection [17]. According to a recent study, SARS-CoV-2 non-structural proteins target hemoglobin's b1-chain, causing iron to dissociate from porphyrin and decreasing hemoglobin's ability to deliver oxygen (Figure 2).

SARS-CoV-2 and pathophysiology of diabetes Mellitus

COVID-19 can increase insulin resistance in Type 2 Diabwetes Mellitus and Type 1 Diabetes Mellitus (particularly individuals who remain overweight and develop insulin resistance). Even modest Sars-Cov-2 can induce proinflammatory effects, seen by elevated IL-1b, IL-6, TNFα, MCP-1 & IP-10, leading to insulin resistance. Furthermore, overweightness, which is usually related to T2 Diabetes Mellitus, increases the cytokine reaction, exacerbating resistance to insulin.

Covid-19 also raises serum concentrations of fetuin-A, an α2-Hermans-Schmid glycoprotein linked to insulin resistance. Finally, COVID-19 is frequently linked to hypokalaemia, decreased pulmonary ACE-2, angiotensin-II deprivation, and increased aldosterone secretion. Hypokalaemia, in turn, can exacerbate glucose regulators in T1DM and T2DM patients. It is also important to estimate the indirect effect of COVID-19 medicines on glycaemic control deterioration. Corticosteroids, commonly given in subjects with ARDS and infection, can cause hyperglycemia excursions. However, brief exposure in the current clinical context might not be clinically meaningful; lopinavir-ritonavir may cause lipodystrophy and consequent insulin resistance. More importantly, as ritonavir is an enzyme inhibitor, it can lengthen the t1/2 of glucocorticoids, indirectly contributing to an abnormal glycaemic profile. Interferon-b1 (type 1 interferon) has also been found as a probable therapeutic approach for COVID-19, and interferon treatment has been linked to β-cell destruction. In COVID-19, Azithromycin was also utilized in conjunction with HCQ. The macrolide antibiotic can raise the likelihood of dysglycemia in DM patients. Data from Wuhan demonstrated that roughly 10 % of individuals with COVID-19 and T2DM experienced at least one incident of hypoglycaemic (3.9 mmol/L) episode in addition to worsening hyperglycemia [18]. On the other hand, hypoglycemia provides an elevated incidence of (CV) episodes in the diabetic population by over-activating the SNS, mobilizing mononuclear cells that are proinflammatory, and raising platelet activity. Thus, COVID-19 worsens the glycaemic profile in patients with underlying DM, which further weakens the innate immune reaction and stimulates the production of proinflammatory cytokines, creating a chain of circumstances in following (Figure 3).

Impact of COVID-19 on gangrene

Gangrene is defined as decomposition, and putrefaction of body tissues due to serious microbial infection or lack of blood supply to the organs. Gangrene is usually associated with the body extremities such as feet, toes, hands, or fingers but can affect any body part. Very few reports have been published which relates dry and intestinal gangrene with COVID-19, suggesting people developing dry gangrene in toes and fingers due to Sars-Cov-2 associated blood coagulation issues.

Geriatric population with comorbidities are more severely affected by COVID-19. COVID-19 patients on therapy for anticoagulation, the subject's AVT progressed, leading to ischemic necrosis and dry gangrene of the lower extremities [18-20].

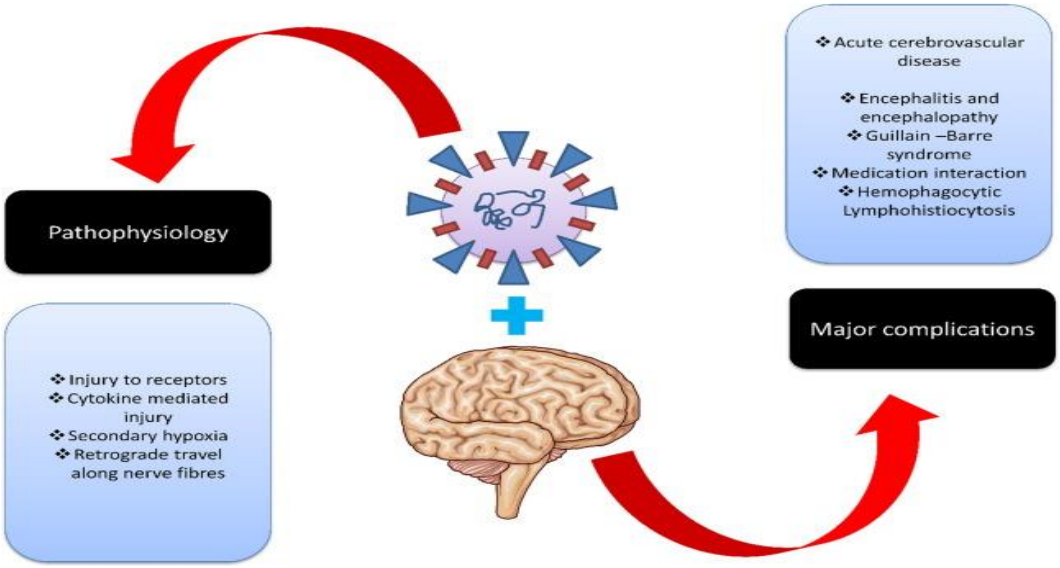

Figure 2: *Major neurological complications associated with COVID-19.*

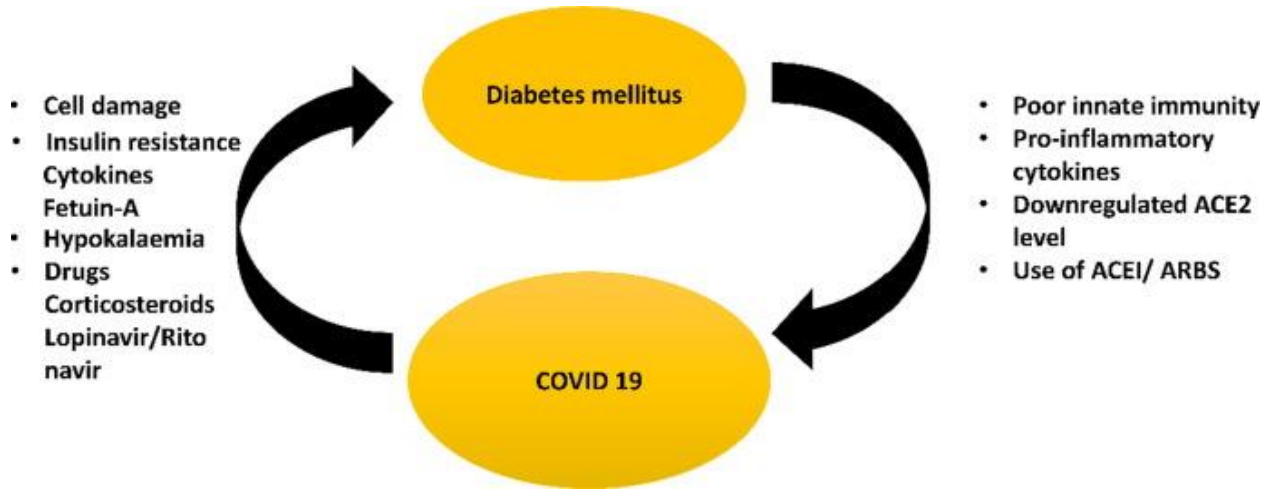

Figure 3: *Representation of the mutual contact amongst the novel COVID-19 and DM. DM increases the seriousness of COVID-19 disease by compromising innate immunity, causing an excessive proinflammatory Cytokine reaction, and lowering ACE-2 expression.*

Subjects of COVID-19, the disease could get more intricated by Acute Respiratory Distress Syndrome, sepsis, and multi-organ dysfunction. Non-vasculopathy patientS develops dried gangrene due to COVID-19′s coagulopathy and disseminated intravascular coagulation. Literature also supports that SARS-COV-2 infection leads to hypercoagulability in different forms like gangrene, stroke, pulmonary embolism, and other acute thrombotic complications, thus approving the use of anticoagulant drugs. In COVID-19 patients, the susceptibility of catching thrombosis appears to be multifactorial, including proinflammatory condition, cytokine crisis, hypoxia-induced thrombus, cytopathological effects, and endothelium cell inflammation resulting in the

development of intra alveolar or systemic fibrin clots. Hypothesis about how blood clot formation (which can further advance into thrombosis and gangrene) takes place in the COVID-19 patients' states that "Due to an internal injury in the endothelium of blood vessels either directly by SARS-CoV-2 infection or by the virus-mediated inflammatory immune response, may result in vasoconstriction and the activation of coagulation and blood clotting pathways, resulting in the formation of blood clots" [21], This hypothesis is further demonstrated in (Figure 4). As of now, very few cases have been seen where gangrene is associated with COVID-19. This symptom is considered one of the rarest and needs more research to reach any specific conclusion.

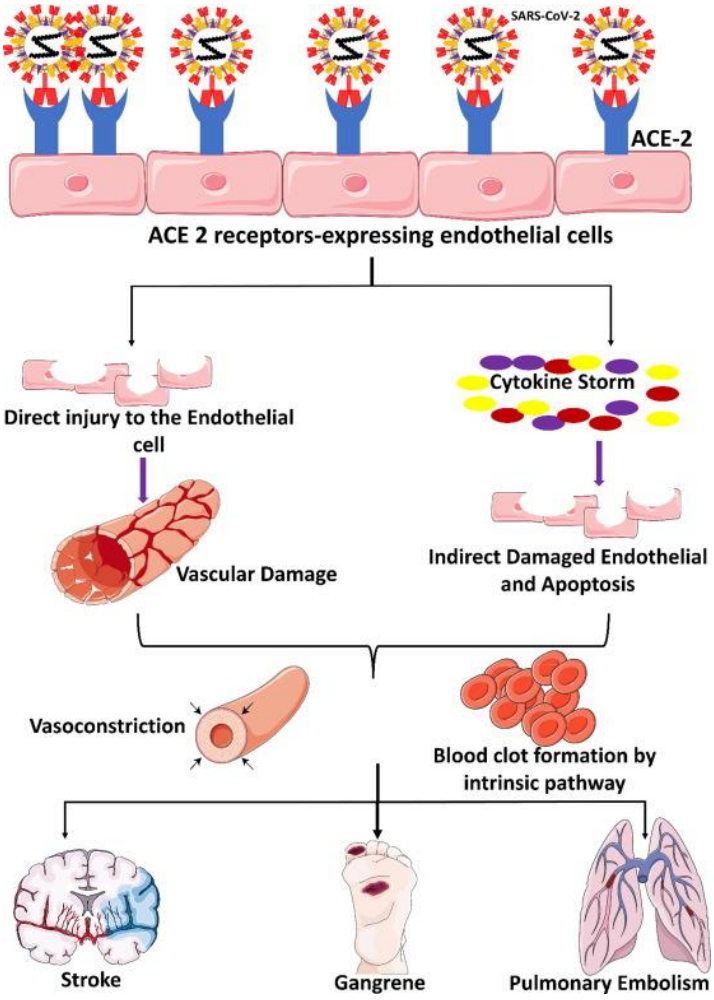

Figure 4: *Demonstration of the mechanism of SARS-CoV-2 to cause gangrene and other vascular-related complications.*

Impact of COVID-19 on endothelial dysfunctioning

Endothelial cellular damage participates in the pathology of multiple-organ collapse in COVID-19 leads to high BP and nephrological disorders mediated by the interaction with ACE-2 receptors present on the endothelial system. The protection of the CVS is mediated by endothelial cells (ECs), releasing the proteins that influence the blood clotting and immune system. Damage to the Endothelial cells results in extensive cardiovascular tissues damage, eventually causing spontaneous heart attacks in Sars-Cov-2. Moreover, injury to the endothelial cells leads to inflammation in the blood vessels, causing plaque rupture and heart attack, and subsequent cytokine storm to inflammation-induced heart failure. The major contributing factors towards endothelial damage includes disbalance between antioxidants and production of ROS and RNS, left ventricle remodeling, fibrosis by releasing transforming growth factor-beta (TGFβ) by differentiated monocytes.

Drug Therapy for the Latest Variants

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

Monoclonal antibodies against the SARS-CoV-2 S protein act through mechanisms related to their structure. First, the antigen-binding fragments (Fab) prevent the virus from binding to the ACE2 receptors, and second, the Fc fragment can activate the complement system and bind to the Immunoglobulin Fc receptors (FcRs) on cytotoxic cells that can eliminate virus-infected cells through Ab-dependent cell-mediated cytotoxicity (ADCC). Unfortunately, some mAbs can bind to macrophage FcRs and induce a hyperinflammatory response resulting from Ab-dependent enhancement (ADE) of cytokine production.

The SARS-CoV-2 RBD has become the main target of mAbs because of its crucial role in virus entry into host cells (Table 4). Analysis of the structural relationship between RBD and anti-RBD NAbs has led to the classification of these antibodies according to structural features and mechanism of action. Class 1 NAbs, e.g., CT-P59 (regdanvimab), target the receptor binding motif (RBM). They recognize the RBD in the up conformation, thus blocking the interaction with the ACE2 receptor. Class 2 NAbs, e.g. LY-CoV1404 (bebtelovimab), target the ACE2 binding site of the RBD in both up and down conformations. Class 3 antibodies, e.g., S309 (sotrovimab), target the conserved core domain of the RBD without altering interactions with the ACE2 receptor. Class 4 antibodies, e.g., S2X259, target epitopes in both the RBM and the core domain of the RBD. Unfortunately, frequent mutations in the RBD have modified the epitopes recognized by mAbs, resulting in the emergence of viral variants resistant to mAbs. To address this issue, researchers are exploring other SRS-CoV-2 regions as potential targets for therapeutic mAbs.

Conclusion

Studying the adaptation trajectory of SARS-CoV-2, it is crucial to anticipate possible future events rooted in the molecular mechanisms that underpin the evolutionary success of SARS-

CoV-2 is essential. People with Sars-Cov-2 who have a past medical history of cardiovascular disorder, elderly, immunocompromized, patients with cancer, obesity, chronic lung disease, diabetes, or neurological disease had the worst prognosis and are more likely to develop Acute Respiratory Stress Syndrome or pneumonia.

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
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

The potential role of advanced therapies against SARS-CoV-2 has introduced it as a new platform to encourage the adaptation of emerging medical technologies for infectious diseases. The use of monoclonal antibodies for prophylaxis in these cohorts has the potential to provide long-term protection from both symptomatic and severe COVID-19 for these vulnerable groups. However, the frequent observation of novel SARS-CoV-2 variants that escape antibody recognition has raised significant challenges in predicting monoclonal antibody protection against new variants. Global public health effort is required to increase awareness about minimizing the burden of these comorbidities that cause fatalities in Sars-Cov-2.

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