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Review Article

Covid-19 Infection and its Adverse Effects on Multiorgan

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Abstract

Covid-19 pandemic, the consequence of severe acute respiratory syndrome (SARS-CoV-2), is one of the main causes of worldwide mortality. The manifestations of SARS-CoV-2 are extensively variable and array from asymptomatic infection to multiorgan failure. The primary mechanism for SARS-CoV-2 infection is the binding of the virus to the membrane bound form of ACE2, which is mostly expressed in the lungs, heart, and kidneys. The presence of comorbidities made patients at a higher risk of developing severe form of Covid-19. Several studies have suggested that SARS-CoV-2 infection have adverse effects on multiorgan. Strategies for proper diagnosis and management of multiorgan effect of Covid-19 have not been established due to the emergence of new variants. However, until more studies are carried out, treatment approaches have to be made on personalized basis depending on the specific organ damage to reduce the overall mortality rate.

Keywords: Covid-19; Myocarditis; Acute kidney injury (AKI); Delirium; Mucormycosis

1. Introduction

Covid-19 has been emerged as a global pandemic ca-

used by SARS-CoV-2. Though respiratory involvement, ranging from mild upper respiratory symptoms to acute respiratory distress syndrome (ARDS) is the hallmark of SARS-CoV-2 infection [1], it also imparts multiorgan involvement. The precise pathophysiology of SARS-CoV-2 infection is still subtle due to the emergence of new variants. Nevertheless, a reliable remark is the presence of a proinflammatory surge, the so-called cytokine storm, which is assumed to be central to the pathogenesis of the acute lung injury-acute respiratory distress syndrome spectrum that amplifies the immune response of alveolar tissue [2]. The speed of disease progression is extensively influenced by the presence of comorbidities and of extrapulmonary organ injuries. Although considerable emphasis has been on the pulmonary complications, it is important to be aware of the other complications and its effect on multiorgan which can be a substantial contributor to the mortality related to Covid-19 infection. The present review emphasizes the updated literature on Covid-19 infection and its effect on multiorgan, which includes myocarditis, acute kidney damage, delirium, gastrointestinal symptoms (see Sec. 2), and post recovery complication mucormycosis (see Sec. 3).

2. Multiorgan Manifestations

2.1 Myocarditis

Covid-19 has an extensive range of cardiovascular complications, which include acute-onset heart failure, arrhythmias, acute coronary syndrome, myocarditis, and cardiac arrest [3, 4]. The foremost case of Covid-19 complicated with fulminant myocarditis was reported by Jia et al [5]. Myocarditis shows a variety of clinical presentations, such as fatigue, chest pain, palpitations to life-threatening presentations like cardiogenic shock or sudden cardiac death associated with ventricular arrhythmias [6]. The exact mechanism of cardiac injury in Covid-19 patients remains poorly understood. However, there are several possible hypotheses on the pathogenesis of Covid-19 and myocarditis such as (i) direct damage to cardiomyocytes by circulating virus through binding to ACE2 receptors [7] (ii) severe cytokine release syndrome by dysregulated response by types 1 and 2 helper T cells which lead to severe systematic inflammatory response resulting in cardiomyocytes hypoxia and apoptosis (iii) overactivation of the autoimmune system with possible interferon mediated hyperactivation of innate and adaptive immune systems.

Cardiac injury has shown uneven rates of mortality reaching up to 51% in Covid-19 patients [3]. There are few reports showing pathological evidence that Covid-19 directly invades the heart [8]. Viral particles with the morphology and size of coronaviruses were detected in interstitial macrophages, but there was no evidence of SARS-CoV-2 genomic material in the myocardium [9]. Pathological postmortem biopsies of Covid-19 patients showed only a few interstitial mononuclear inflammatory infiltrates, but no significant damage in the heart tissue [4]. Numerous observational studies have reported cardiac injury among hospitalized Covid-19 patients [3, 10, 11]. Selman et al (2020) described the first case of Covid-19 related fatal fulminant myocarditis in an infant. The presence of the viral genome in myocardial tissue together with local inflammation is remarkable. Negative inflammatory indicators suggest the existence of direct damage by the virus [12]. A retrospective study described a new paediatric condition connecting myocarditis, infection with SARS-CoV- 2 and multisystem inflammatory

syndrome mimicking an incomplete Kawasaki disease [13]. A 10-year-old male positive for Covid-19 infection was suspected for Kawasaki disease, and later found to have myocarditis [14].

A meta-summary of SARS-CoV-2 induced myocarditis cases included 31 studies on 51 patients among them 12 cases were confirmed myocarditis while 39 had possible myocarditis. The average age was 55 years and 69% of them were males. Fever, shortness of breath, cough and chest pain were the common presenting symptoms. Electrocardiogram report showed non-specific ST segment and T-wave changes and ventricular tachycardia. Most of the patients had elevated cardiac and inflammatory biomarkers levels. Left ventricular dysfunction and hypokinesis were common among the patients. In 10 patients cardiac magnetic resonance (CMR) established the diagnosis with features of cardiac oedema and cardiac injury. Few patients required mechanical ventilation and extracorporeal membrane oxygenation, 30% of the patients recovered but 27% died [15]. Marc et al (2021) summed up the results of 277 cardiac autopsy reports from 22 studies, that demonstrated the modest frequencies of Covid-19 related cardiac histopathologies. Non-myocarditis inflammatory infiltrate and single cell ischemia are the often-reported cardiac findings occurring in 12.6% and 13.7% of the cases respectively. In 4.7% of the patients acute myocardial infarctions were reported, while in 7.2% of the cases myocarditis was reported [16].

There is current discussion on whether cardiac complications of Covid-19 result from myocardial viral infection or are secondary to systemic inflamemation and thrombosis. Adam et al (2021) has observed that cardiomyocytes are infected in patients with Covid-19 myocarditis and established an engineered heart tissue model of Covid-19 myocardial pathology. The authors also described the mechanisms of viral pathogenesis, and demonstrated that cardiomyocyte SARS-CoV-2 infection results in contractile deficits, cytokine production, sarcomere disassembly, and cell death [17]. These results suggest direct infection of cardiomyocytes in the pathogenesis of Covid-19 myocardial pathology and delivers a model system. More pathological studies and autopsy series will be helpful to explain the competence of Covid-19 in direct infection of myocardium and causing myocarditis.

A cohort study conducted post Covid-19 infection in 1597 US competitive athletes, showed 37 athletes (2.3%) with clinical and subclinical myocarditis [18]. A case series showed low prevalence of myocarditis (1.4%) among the student athletes recovering from Covid-19, based on the MRI findings [19]. Systemic responses to the vaccine, which were typically mild and transient were reported among the younger population and more often after the second dose [20, 21]. Abu et al (2021) from Israel reported six cases of myocarditis post BNT162b2 vaccination. Myocarditis was reported in five patients after the second dose of vaccination and in one patient after the first dose of the vaccine. All of them were males with an average age of 23 years. Myocarditis was diagnosed in all patients through routine clinical and laboratory investigations which included troponin and C- reactive protein levels for common etiologies of myocarditis. Myocarditis diagnosis was established after cardiac MRI. There was no indication of Covid-19 infection. None of the patients had any clinical sign or laboratory finding compatible with autoimmune

disease nor had a history of an exposure to new drugs or toxins prior to onset of their symptoms. The clinical course was mild in all the six patients [22]. Further studies on endomyocardial biopsy and autopsy are required for a well understanding of the pathogenesis of clinically suspected myocarditis in the course of SARS-CoV-2 infection.

2.2 Acute kidney injury (AKI)

In critically ill Covid-19 patients, acute kidney injury (AKI), an unexpected decrease in kidney function has appeared as a serious impairment. The SARS-CoV-2 virus enter tubular cells through the angiotensin-converting enzyme 2 (ACE2) receptor. Angiotensin converting enzyme 2 (ACE2) is present in podocytes, mesangial cells, parietal epithelium of the bowman's capsule, proximal cells and the collecting duct of the kidney [23]. SARS-CoV-2 can straight infect podocytes and tubular epithelial cells [23, 24]. The initial reports across the world showed that the incidence rate of AKI as <5% surpassing to 25% [25-28]. The occurrence of AKI in SARS patients with normal kidney function is reported to be 6.7%, which might be due to acute tubular necrosis (ATN) and occasional rhabdomyolysis [29]. A meta-analysis showed increased mortality rate in Covid-19 patients with AKI and incidence of AKI was also higher in severe cases [30]. Post-mortem histology of kidneys has confirmed thrombi and erythrocyte aggregates obstructing peritubular capillaries and impacting intrarenal microcirculation. Renal histology reports confirmed pigmented tubular casts containing high levels of creatine phosphokinase [31]. Collapsing glomerulopathy, a hostile variant of focal segmental glomerulosclerosis through high rates of podocyte injury and depletion was reported in renal biopsies of patients with SARS-CoV-2 infection related AKI [32]. Proteinuria and haematuria are the conditions reported in patients with SARS-CoV-2 infection related AKI [33]. ERA-EDTA Registry results show a high mortality due to Covid-19 in dialysis patients and kidney transplant recipients across Europe [34].

However, whether AKI leads to increased mortality in patients with Covid-19 remains unknown [35, 36]. Severe renal impairment has been reported in half of the Covid-19 patients in the Middle East. Diabetes and hypertension were the most common existing comorbidities among them [37]. Ali et al (2020) from Iran reported Acute kidney injury in pregnant women following SARS-CoV-2 infection [38]. Isil et al (2021) found abnormal renal imaging in a patient with only mild form of Covid-19 [39]. Two paediatric cases showed acute necrotizing glomerulonephritis associated with Covid-19 infection [40]. Acute kidney injury (AKI) has become an area of concern in Covid-19 patients and has increased the risk of mortality [33, 27]. The case reports and autopsy series of covid-19, demonstrate specific causes of AKI such as volume depletion, multiorgan failure, viral infection resulting in kidney tubular injury, thrombotic vascular processes, glomerulonephritis, or rhabdomyolysis [31, 32, 41]. Pre-existing comorbidities along with genetic makeup may play a role in resulting condition. According to Pan et al (2020) the expression of the ACE2 receptor in renal podocytes and proximal tubule cells was more definite in occidental subjects than in Asians, signifying the ethnic difference [42]. Severe Covid-19 infection may damage the kidney and cause acute tubular necrosis (ATN), leading to proteinuria, haematuria, and elevated serum creatinine. The deposition of immune complexes of viral antigen or virus-induced specific immunological effector mechanisms

specific to T-cell lymphocytes or antibodies can induce inflammatory processes and leads to further kidney damage.

2.3 Delirium as a presenting sign of Covid-19

Covid-19 infection has several neurological manifesttations, for a detailed review the reader is referred to Sultana and Ananthapur (2020) [43]. In the present section, the focus is on delirium as a presenting sign of Covid-19. Delirium is defined as an acute confused state, characterized by compromised cognition, psychomotor disorders, inattention, and a fluctuating course [44]. Delirium is arbitrated by several mechanisms which include oxidative stress, inflammation, neuronal aging, cellular signalling and messaging dysregulation [45], which lead to neurotransmitter imbalances of acetylcholine, melatonin, dopamine, glutamine, GABA, serotonin, and histamine [46]. Covid-19 infection has systemic effects throughout the body, including the brain [47-49]. The WHO recognized altered consciousness and confusion as core symptoms of Covid-19 [50]. The foremost question still remains unanswered is whether delirium in Covid-19 characterizes a primary manifesttation, signalling invasion of the brain by the virus, or it simply establishes a secondary encephalopathy caused by inflammation or further systemic effects of the virus. Altered consciousness exists as a neurologic manifestation of Covid-19, extending from drowsiness to confusion, delirium, lethargy and coma, in nearly 15% of hospitalized Covid-19 patients [51]. Delirium might depend on the direct effects of SARS-CoV-2 infection, likely viral invasion to the central nervous system (CNS), secondary encephalopathy due to systemic inflamemation, or other precipitating factors, such as prolonged duration of hospital stay, urinary retention, constipation, pain, and various metabolic abnormallities that occur during severe infection [52, 53]. Neurotransmitter imbalance, pro-inflammatory cytokines, tissue hypoxia, and sleep deprivation play important role in the pathomechanism of delirium.

A recent review on psychiatric and neuropsychiatric appearances of Covid-19 and other coronaviruses showed high rates of delirium [54]. A systematic review and meta-analysis showed that the presence of delirium is associated with increased risk of mortality in hospitalized older adults with Covid-19 [55]. A multicentric cohort study stated that the acute brain dysfunction was extremely predominant and extended in critically ill Covid-19 patients and use of benzodiazepine, lack of family visitation was recognized as modifiable risk factors for delirium [56]. A cohort study of 322 hospitalised and 535 community-based older adults revealed probable delirium as a presenting symptom of Covid-19 in frail and older adults [57]. According to a study preexisting cognitive impairment was the main risk factor for delirium in older patients with Covid-19. Delirium was related with increased in-hospital mortality, but not with the length of stay [58]. Walid et al (2020) presented a unique case of delirium, otherwise asymptomatic for Covid-19 [59]. Delirium was common and seen frequently without other typical symptoms of Covid-19, and associated with poor hospital outcomes and mortality in older adults [60, 61]. A case report described, delirium as the only first manifestation of Covid-19 without obvious lung disease [62]. Acute onset of altered mental status and delirium with normal respiration and metabolic balance in the first 48 hours was reported in two Covid-19 infected cases [63]. The existence of delirium is an important factor in predicting worse

functional outcomes in patients with Covid-19 [64]. Although several studies from all over the world have reported delirium as the presenting sign of Covid-19, the existing diagnosis criteria do not include delirium as the first presenting symptom of Covid-19, thus leading to under diagnosis of Covid-19 infection. There is lack of concern and attention towards the implications of delirium in identification and management of Covid-19 situation. Under detection of delirium as a primary manifestation of Covid-19 may result in under diagnosis of Covid-19 infection, which further enhance the spread of infection and mortality. In long term, it might lead to cognitive and functional decline [65]. Taking the results of published literature into due consideration, it is necessary to include delirium in the list of presenting signs of Covid-19 infection for better diagnosis and management of the condition.

2.4 Gastrointestinal symptoms associated with Covid-19

Gastrointestinal signs are accompanied by inflame-mation and intestinal damage due to loss of intestinal barrier integrity and gut microbes which activate innate and adaptive immune cells to release prion-flammatory cytokines into the circulatory system, resulting in systemic inflammation. In a study of 206 patients with mild Covid-19 infection, 48 patients presented only digestive symptoms, disclosing that patients with gastrointestinal symptoms had a lengthier duration between symptom onset and viral clearance and faecal virus-positive compared with respiratory symptoms [66]. According to a systematic metanalysis the frequency of diarrhoea was as low as 2% and up to 50% in Covid-19 positive cases [67]. Receptors for transmembrane protease serine 2 (TMRPSS2), an enzyme expressed in the small intestinal epithelial cells are used by SARS-CoV-2 to get entry into the infected cells [67]. The SARS-CoV-2 activity might cause ACE2 alterations in the gut that intensify the susceptibility to intestinal inflammation and diarrhoea. In enterocytes, esophagus and lungs a high co-expression of ACE2 and TMPRSS2 was detected [68]. ACE2 and TMPRSS2 transcripts co-expression was maximum in the small intestine, 20% in enterocytes and 5% in the colon cells, as studied by a single-cell RNA sequencing in the gastrointestinal tract [69]. ACE2 also shows substantial influence on the intestinal microbiota composition [70]. Changes in the immune system result in variations in the intestinal flora, and coronavirus infection also persuades bacterial changes that might alter the gut-brain axis. A meta transcriptional analysis found that 36 differentially expressed genes are associated with immune pathways and cytokine signalling such as interferon gamma and severity of Covid-19 [71]. A metanalysis of 1,810 paediatric Covid-19 patients, reveals an incidence of gastrointestinal symptoms in 6% of the patients with higher occurrence of fever (55%), cough (45%), and dyspnea (19%) [72]. In a pool of 371 children comprised in 14 studies, 7.4% showed gastrointestinal symptoms such as vomiting, diarrhoea and abdominal pain [73]. Even rare manifestations of SARS-CoV-2 infection have also been reported in children, with substantial mucosal inflammation being seen in the acute phase, with terminal ileitis related with symptoms of fever and abdominal pain impersonating an unusual appendi-citis [74]. Identification of gastrointestinal symptoms relating to SARS-CoV-2 infection can aid in designing new treatments targeting gut microbiota, to combat associated symptoms in Covid-19 treatment.

3. Post Covid-19 Recovery Complication

3.1 Mucormycosis

Covid-19 pandemic has resulted in an innumerable clinical manifestations and complications. The emergence of second wave added a new post Covid-19 recovery complication to the existing clinical manifestations of Covid-19 in the form of mucormycosis, popularly known as black fungus. Mucormycosis a rare fungal infection pronounced by infarction and necrosis of host tissues that results from invasion of the vasculature by hyphae. The utmost medical presentation of mucormycosis is rhino-orbitalcerebral infection, believed to be secondary to inhalation of spores into the paranasal sinuses of the host [75]. Predisposing conditions for mucormycosis include diabetes, systemic cortico-steroid use, neutropenia, hematologic malignancies, stem cell transplant, and immunocompromised individuals [76]. Around seventy percent of rhino-orbitalcerebral mucormycosis cases are found in patients with diabetes mellitus, majority of them had also established ketoacidosis at the time of exhibition. Infection typically presents by acute sinusitis, fever, nasal congestion, purulent nasal discharge and headache. Obtundation is resulted due to the spread of infection from the ethmoid sinus to the frontal lobe. The fungi gain entry into the host through inhalation into the paranasal sinuses and might eventually spread to the sphenoid sinus, palate and cavernous sinus. Clinical features include blurry vision, inflammation around the orbit, sinusitis, facial pain or numbness, headache, proptosis, ophtha-lmoplegia, or even periorbital cellulitis [77, 78].

Mucormycosis is caused due to fungi Mucorales. Depending on the site of infection the clinical manifestations are cutaneous, pulmonary, sinusitis, gastrointestinal, or even dissemination. Rhinocerebral mucormycosis is well-known in diabetic patients [79]. Rhinocerebral mucormycosis presents black necrotic eschars due to tissue necrosis from angioinvasion and subsequent thrombosis. Early diagnosis and treatment are very important to prevent morbidity and mortality. The major investigative modalities for mucormycosis include histopathology, direct microscopy, and culture from clinical specimens [80]. The incidence rate of mucormycosis differs from 0.005 to 1.7 per million population. It is very difficult to diagnose mucormycosis. Initial diagnosis and treatment are crucial, as a delay of even 6 days is related with a doubling of 30- day mortality from 35% to 66% [81]. Mucormycosis condition is encountered in immunocompromised patients. The early clinical symptoms suspected for diagnosis include unilateral facial pain or swelling, orbital swelling, or proptosis. Though tissue necrosis is a delayed sign, it is considered as hallmark of mucormycosis, resulting from angioinvasion and vascular thrombosis.

Amanda Werthman-Ehrenreich reported the first case of mucormycosis with orbital compartment syndrome in a patient with Covid-19 infection [82]. Akshay et al [83] reported the first case of mucormycosis in a heart transplant recipient prior to Covid-19. The patient was diabetic, and on immunosuppressive and corticosteroid medication and later passed away [83]. Andre et al reported pulmonary aspergillosis and mucormycosis in a Covid-19 patient [84]. Ricardo et al from Chile reported 16 cases of Covid-19 associated invasive mold infection (CAIMI) among 146 nonimmuno compromised patients with severe Covid-19 [85]. Nariman et al reported Covid-19 associated pulmonary mucormycosis in a 44-year-old hyperglycaemic hispanic female [86]. Amirreza et al

reported one case of rhino-orbitocerebral mucormycosis and another case of rhino-orbital mucormycosis among the two cases of Covid-19 under corticosteroid [87]. The first report of gastrointestinal mucormycosis in Brasil was resported by Epifanio et l in an 86 years old male patient [88]. Acute invasive rhino-orbital mucormycosis in a patient with covid -19 associated acute respiratory distress syndrome was reported from California, USA [89]. A case of rhinocerebral mucormycosis coexisting with Covid-19 pneumonia in a 41-year-old man with a history of type 1 diabetes mellitus (T1DM) was presented by Kirill et al [90]. A 53-year-old male patient with secondary acute myeloid leukemia (AML) infected with Covid-19 was diagnosed with mucormycosis postmortem [91]. A fatal Case of Rhizopus azygosporus pneumonia after Covid-19 infection was reported in a 56-year-old man treated with methylprednisolone and tocilizumab [92]. Fatal rhino-orbital mucormycosis was described in a 24-year-old female diabetic patient with Covid-19 [93].

Aastha et al from Mumbai, India reported Sino-orbital mucormycosis in a Covid-19 patient [94]. Deepak et al from Chandigarh, India described a case of probable pulmonary mucormycosis in a 55-year-old man with diabetes, end-stage kidney disease, and Covid-19 [95]. Marina et al from Karnataka, India reported a case of paranasal mucormycosis in Covid-19 patient [96]. Rhino-orbital mucormycosis associated With Covid-19 was diagnosed in a 60-year-old male, diabetic patient from Lilavati Hospital and Research Centre, Mumbai, India [97]. Sharma et al from Jaipur, India studied the likely association between invasive fungal sinusitis (mucormycosis) and coronavirus disease and found twenty-three patients with mucormycosis. The ethmoids (100 %) were the most common sinuses affected. Intra-orbital extension was observed in 43.47 % of cases, while intracranial extension was seen only in 8.69 %. 21 cases out of 23 were diabetic, out of them 12 were having uncontrolled diabetes. All of them were on steroid treatment [98]. Uncontrolled diabetes, overuse of steroids and immunosuppressive nature of virus are the contributing factors for the spread of mucormycosis. In patients suspected for mucormycosis, quick diagnosis and treatment should be started especially in patients with poorly controlled diabetes mellitus due to angio invasive nature and rapid disease progression that contribute to the severity of the infection. Treatment of mucormycosis should include multidisciplinary approach which includes prompt diagnosis and treatment with antifungals and surgical interventions. After the diagnosis is confirmed, empiric antifungal treatment should be started. Prompt surgical opinion should also be sought.

4. Conclusion

Understanding Covid-19 infection and its effect on multiorgan is still obscure. A presumptive diagnosis should be made on the presenting signs and symptoms of SARS-CoV-2 infection. There is a paucity of controlled randomized studies to clearly understand the effect of Covid-19 infection on multiorgan. Further studies are needed for the better understanding of Covid-19 infection and its effect on multiorgan. It is important for the emergency clinicians to be aware of the multiorgan complic-ations arising out of Covid-19 infection while treating the patients and management of the condition to reduce the mortality rate.

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Conflicts of Interest

None to declare.

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