COVID-19 and Co-Infections: An Overview of Ace2 Mediated Viral Entry of Sars-Cov-2 and Multiorgan Failure in Covid-19

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Abstract

COVID-19 is highly fatal disease having a high mortality rate and is declared as pandemic situation by World Health Organization. It shows a clear indication that every individual is at risk of this pandemic especially older individuals and immunocompromised persons. Its casual agent is SARS-Cov-2 and the main target site of this virus is the ACE2 receptor of lungs. But as compared to lungs ACE2 receptor is highly expressed in other organs i.e. kidney, liver, brain, GI tract, cutaneous, adipose tissues and cardiovascular system these organs are susceptible to COVID-19 infections because of having ACE2 receptor. Many of the co-infections associated with COVID-19 are reported i.e. Neurological manifestation of COVID-19, Cutaneous manifestation of COVID-19, Endothelial cell infection and endotheliitis, adipose tissues infections, Cerebral Hemorrhage, liver injury, cardiovascular complications, kidney infection, trigger immune system response and subsequent organ failure. In this review we highlights ACE2 mediated viral entry of the SARS-Cov-2 and subsequent multi organs failure in COVID-19.

Keywords: COVID-19; Co-infections; ACE2 receptor; SARS-Cov-2; Multi organs

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Introduction

In December 2019 a pandemic of acute respiratory distress syndromes occurred in Wuhan, China, the early evidence suggests this may be due to exposure to local sea foods in China [1] The pathogen was isolated from Chinese patients and designated as severe acute respiratory syndrome corona virus 2 (SARS-COV-2) .WHO announces this as global pandemic on March 11; 2020. COVID-19 mainly affects lungs by producing respiratory predominant symptoms like fever, cough, flu and dyspnea [2]. The virus primarily attacks the angiotensin converting enzyme-2 receptor (Ace2) of the lung. However recent reports suggested that COVID-19 infection is not confined only to lungs. As ACE2 receptor is the binding site of (SARS-COV-2) and there are abundance of this receptor on different body organs such as in alveolar epithelial type II cells of lung tissues, as well as extrapulmonary tissues such as the heart, endothelium, kidneys, and intestines [3, 4, 5, 6]. In addition to respiratory disease there are a lot of complications associated with COVID-19. The pandemic

has an adverse effect on the central nervous system. Reported data have shown neurological manifestations of COVID-19. Much of the research on corona virus has shown it has capability of causing brain infections in humans and other animals [7, 8]. The heart infection is highly prevalent in COVID-19 leading to cardiovascular complications [9,10]. Although lungs are its primary target but there are many related data supporting the cutaneous manifestation of COVID-19 [11, 12,]. Patients suffering from COVID-19 and admitted to intensive care unit have high incidence of venous and thrombotic complications [13]. Acute ischemic stroke is another complication of COVID-19 [14]. Enhanced ACE2 receptor expression in kidney supports nephritic cells damage in kidney due to COVID-19 [15]. This review is an effort to highlights some of the co-infections associated with COVID-19 and multi organs failure.

Background

2.1. Epidemiology

On April 11, 2020 1,610,909 confirmed cases were reported, with 99,690 (6.19% of confirmed cases) of mortality. All the ages are susceptible to this pandemic but the risk is higher in older age and immunocompromised or with co-morbidities. On the other hand mortality is related with age and more often with targeted organ failure [16, 17, 18, 19, 20, 21].

2.2. Virology

Corona virus are enveloped, positive stranded RNA virus, genome size ranges between 26kb to 32 kb, resembles a solar corona, have four sub families i.e. alpha, beta, gamma and delta Coronaviruses and was first described by Tyrell and Bynoe in 1996 [22, 23, 24, 25, 26]

2.3. Transmission

The most accepted model at first was animal to human transmission from Wuhan sea food market. Genome studies have suggested that animal is the natural reservoir of corona virus like pigs. But after sometimes person to person transmission model was the most acceptable mode of transmission i.e. by aerosol, air droplets, fecal oral transmission has also clarified [27, 28, 29, 30, 31, 32, 33, 34, 35].

3. ACE2 involvement in manifestation of co-infection in COVID-19 patients

As viral infections need entry into the cell for replications, the ACE2 receptor act as co receptor for SAR-COV-1 and SAR-COV-2 for entering to lungs and brain cell. ACE2 receptors are expressed in nearly all tissues and cells of the body i.e. in the ileum and kidney followed by adipose tissue, heart, brain stem, lung, vasculature, stomach, liver, and nasal and oral mucosa [41, 42, 43]. Current studies suggest the presence of viral load of SAR-COV-2 in brain may be attributed to internalization by ACE2 and transport by cranial nerves. And it may result in neuronal cell death. Loss of ACE2 receptor from pulmonary tissues may lead to respiratory distress. As we know that ACE2 receptor is found in nearly all tissues so the disruption or loss of this receptor may lead to dysfunction of all the organs [44, 45, 46, 47, 48].

4. Neurological manifestation of COVID-19

Moriguchi et al., 2020 reported a 59 years old male patients having no familial history of seizures but a complaint of atrial fibrillation and treated sleep apnea who was admitted in emergency department on March 26,2020 with fever, dry cough and headache. His first RT-PCR result was negative for SAR-COV-2, but later he was tested positive for SAR-COV-2 by RT-PCR assay from tracheal secretion and chest CT- SCAN.

Figure 1. Shows the ACE-2 receptor mediated entry of SARS-Cov-2 into the cell [62]

From APRIL 10 he started short seizures. When the patients awoke from seizure a 49 minutes EEG was performed and the results of the peak confirm the epileptic seizures. He felt first seizure for six minutes, second seizure for 5 minutes. His brain MRI was normal, laboratory test was also normal, on APRIL 14 the patient has only one brief episode of seizure but his EEG was normal then. The result suggests seizures associated with COVID-19 with no history of meningitis or encephalitis [36]

4.1. Mechanism of seizures induction by COVID-19

The movement of human corona viruses toward brain is supported by the presence of ACE2 receptor in brain cell. SAR-COV-2 inhibit the ACE2 receptor which slows the baroreflex which in turn slow down the blood flow toward brain and thus increases seizures threshold [37, 38, 39,]

5. Endothelial cell infection and endotheliitis in COVID-19

As ACE2 receptors are also expressed in endothelial cell. However vascular damage in COVID-19 by endothelial cell entry of SAR-COV-2 is unknown. But SARS-COV-2 can directly infect blood vessels [50, 51, 52, 53]

6. COVID-19 and adipose tissues

According to previous studies it is well known that adipose tissues are more prone to Influenza virus and HIV. The transmission and mortality rate of influenza virus is more related to obesity [54, 55, 56, 57]. As ACE2 expression in adipose tissues is much and higher than lung, kidney and other organs and has higher RNA level than lungs. There may be some possibilities of SARS-COV-2 infection in adipose tissues but till now it is not reported [58].

7. Liver and COVID-19

Previous studies have reported liver abnormalities in patients infected by SARS-coV-2 and COVID-19 medications side effects on liver have been illustrated previously [59]. In addition after performing liver biopsy of COVID-19 patients fatty liver and liver injuries were reported [60].

8. Cerebral Hemorrhage a complication of COVID-19 patients

In a study a COVID-19 patients was reported whose first symptom was cerebral hemorrhage. When craniotomy was performed the patient has high fever and the case was challenging to treat. After

Figure 2. Pathology of endothelial cell dysfunction in COVID-19 and viral inclusion in kidney cells and also viral particles in endothelial cells adapted from [49]

Figure 3.

Shows the CT scan image of lung and brain of COVID-19 patient who have the complication of cerebral hemorrhage[61]

Table 1

Total COVID-19 infected patients having cardiovascular complications	138
Percent patients presented with shock	8.7%
Percent patients with acute cardiac injury	7.2%
No of patients received extracorporeal membrane oxygenation	4 out of 138
New onset heart failure or cardiomyopathy in patients with COVID-19	25%
Postulated mechanism for cardiovascular system failure in COVID-19	direct myocardial injury, indirect injury through cytokine release, a prothrombotic state causing microvascular thrombosis, and exacerbation of underlying cardiovascular disease e.g. plaque rupture in susceptible patients

Table 1. shows percent COVID-19 infected patients with cardiovascular complication and propose mechanism for cardiovascular system failure in COVID-19 patients [63, 64, 65, 66, 67].

CSF testing the intracranial infections was reported and it shows a clear evidence for the involvement of COVID-19 in cerebral hemorrhage and cerebral blood vessels damage [61]

9. Cardiovascular complications in COVID-19

According to previous studies and results of previous outbreaks such as SARS-Cov-1 and MERS cardiovascular complications are associated with COVID-19 [63]. The actual mechanism through which COVID-19 induces cardiovascular infections is not understood yet but there are some proposed mechanism i.e. by inducing direct myocardial injury or through indirect injury by cytokine storms [63, 64, 65]

Table 2.

Total patients under study for Cutaneous manifestation of COVID-19	72
Patients showing morbilliform	36.1% (26/72) patients
Patients with papulovesicular rash	(34.7%, 25/72)
urticaria	(9.7%, 7/72)
painful acral red purple papules	(15.3%, 11/72)
livedoreticularis lesions	(2.8%, 2/72)
petechiae	(1.4%, 1/72)

Table 2 shows different cutaneous lesions in patients infected with COVID-19 [73]

Table 3.

Common sites of lesion in COVID-19	Trunk, head, feet, skin
Trunk	(66.7%, 50/72)
Head and feet	19.4% (14/72)
skin	12.5% (9/72)

Table 3 shows common sites of cutaneous manifestation of COVID-19 [74]

Table 4.

Total no of COVID-19 patients admitted with kidney abnormalities	A total of 701 patients were included in a study
Glomerular filtration rate recorded in most of COVID-19 patients	< 60 ml/min per 1.73 m ² was reported in 13.1% of patients
Percentage of patients having elevated creatinine and blood urea nitrogen level	14.4% and 13.1% of the patients
Patients with proteinuria	43.9% of patients
Patients with hematuria	(26.7%)

Table 4 Kidney abnormalities associated with COVID-19[75]

10. Cutaneous manifestation of COVID-19

There are many case reports on cutaneous manifestations of COVID-19 [68, 69]. For the diagnosis of different infectious disease cutaneous manifestations are very important. As COVID-19 remains asymptomatic for 14 days cutaneous manifestations may be an indicator of infection cause by SARS-Cov-2 [70, 71, 72]

Table 5.

Percent patients infected with SARS and having chances to develop acute kidney injury	6.7% of patients with SARS developed acute kidney injury
Percent mortality of COVID-19 patients having acute kidney injury	mortality of those with AKI was 91.7%

Table 5 Comparison of acute kidney injury and mortality rate with SARS-Cov [76]

Table 6.

SARS-Cov-2 target site on GI tract	ACE2 receptor of GI tract
Common symptoms associated with GI tract complications in COVID-19 patients	Nausea, vomiting and abdominal pain

Table 6 represents target site of SARS-Cov-2 on GI tract and common symptoms of GI tract complication in COVID-19 [77, 78]

Table 7.

COVID-19 and immune system	Induces triggers immune response to produce inflammation in multi organ
Types of serum inflammatory mediators associated with cytokine storms in COVID-19	interleukin (IL)-2, IL-7, IL-10, granulocyte colony stimulating factor, interferon-inducible protein 10, monocyte chemo attractant protein 1, macrophage inflammatory protein 1a, and tumor necrosis factor a (TNF-a).
Lymphocyte hyper activation in COVID-19	CD4 ⁺ and CD8 ⁺ cell counts in peripheral blood were greatly reduced, (CD4 3.47%) and CD38 (CD8 39.4%) are highly increased which shows lymphocytes hyper activation
Response of pro-inflammatory T-cells	CCR4 ⁺ CCR6 ⁺ Th17 cells increased, and CD8 ⁺ T cells demonstrated high cytotoxicity owing to their excessive activation

Table 7 shows activation different types of inflammatory mediators and lymphocyte hyper activation in COVID-19 which results in inflammatory response against multi organs and susceptible organs failure in COVID-19 [79, 80, 81, and 82].

11. COVID-19 and kidney

In previous epidemics of SARS and MERS kidney infections was reported as one of the most drastic complications of the epidemic with high mortality rate up to 90% due to kidney involvement and acute kidney injury [73, 74]

12. COVID-19 and gastrointestinal complications

A number of patients tested positive for COVID-19 by performing RT-PCR from their stool sample shows many GI tract complications. The reason for GI tract complications is clear as ACE-2 receptor is highly expressed in gastrointestinal tract and thus GI tract serves as target site for SARS-Cov-2. [77, 78]

13. COVID-19 and immune system

Immune system is greatly influenced by any infection in the body. In COVID-19 pandemic immune system triggers cytokine storms and induces inflammatory responses and in multi organs hence result in multi organ failure. Concentration of serum inflammatory mediators like interleukin ((IL)-2, IL-7, IL-10) and interferon's are highly elevated in sera of patients infected with COVID-19 [79].

Conclusion

From the above study it is concluded that as ACE2 is involved in viral entry of SARS-Cov-2 and as this receptor is present on many organs so all these organs are susceptible to COVID-19. And these co-morbidities help in the progression of the disease leading to a high mortality rate. Acute kidney failure, liver injury, nervous system damage, cutaneous lesion, cardiovascular system failure all these are the outcomes of COVID-19. All those patients having co-morbidities and infected with COVID-19 need intensive care because they are at high risk. This paper adds in highlighting co-morbidities association with COVID-19.

Conflict of interest

The authors declare no conflicts of interest.

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The authors state that they abide by the "Requirements for Ethical Publishing in Biomedical Journals" [83].

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