



## **A Systemic Review of Pathological Findings in COVID-19 and Its Mechanism of Disease**

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### **Authors' contributions**

*This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.*

### **Article Information**

DOI: 10.9734/JPRI/2021/v33i60A34523

### **Open Peer Review History:**

This journal follows the Advanced Open Peer Review policy. Identity of the Reviewers, Editor(s) and additional Reviewers, peer review comments, different versions of the manuscript, comments of the editors, etc are available here: <https://www.sdiarticle5.com/review-history/79596>

**Review Article**

**Received 14 November 2021**

**Accepted 19 December 2021**

**Published 20 December 2021**

### **ABSTRACT**

The Severe Acute Respiratory Syndrome (SARS) coronavirus 2 (SARS-CoV2) has spread worldwide at a rapidly alarming pace and has resulted in the coronavirus disease 2019 (COVID-19) pandemic. The virus has more intensive and prolonged standing effects in the host body post-infection than the other related groups of viruses. The disease has caused an unforeseen need for the availability of intensive support because of the resulting critical respiratory distress and consequent multi-organ failure. What starts as an elegant fever with cough and headache, with body pain, runny nose, sore throat, quickly develops into loss of perception of taste and smell, with nausea, diarrhea, troubled breathing, chills; and finally results into grievous damage to the vital organs of the body, such as heart, lungs, liver, kidneys, blood vessels, and even brain, necessitating the need of urgent and competent availability of critical care infrastructure. It is now the disease with the highest number of affected individuals recorded in the modern era. And, not only does the infection of Covid inflict highly significant morbidity and mortality rates amongst the population, but there have also been multiple and significant strains to the overburdened health care system and also, massively on the economy.

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Here in this article, our focus will primarily be upon the systemic pathology in the various organ systems and how the coronavirus has been affected. We shall discuss the Respiratory System, the Cardio-Vascular System, the Renal System, Central Nervous System, and the pathophysiology involved herewith after covid infection.

**Keywords:** COVID-19; systemic findings; pathological findings; mechanism of disease; co-morbidity; organ damage.

## 1. ETIOLOGY

Coronaviruses are a group of enveloped, positively charged, single-stranded RNA-bearing viruses which primarily cause respiratory, heart, or bowel ailments in humans and animals. They are of 4 subtypes, namely-  $\alpha$ , B,  $\delta$ ,  $\gamma$

Wherein for humans are mainly infected with  $\alpha$ -coronaviruses and  $\beta$ -coronaviruses, while  $\delta$ CoV and  $\gamma$ CoV principally infect birds. The interpretive importance of these microorganisms lies in their ability to cause massive pandemics with devastating consequences. In the past two decades, there have been reports of three massively overwhelming outbreaks of viral pneumonia and coronavirus-associated co-morbidities that have spread to different demographic groups worldwide with varying degrees of intensity and duration. In 2002, the severe acute respiratory syndrome (SARS) virus was found to have originated in China with having resulting in heavy casualties worldwide with a fatality rate of 11%. Then, after a decade, in 2012, the Middle East respiratory syndrome virus (MERS) was observed in Saudi Arabia, affecting more than 3,000 people with a staggering 34% death rate. And then, almost over a decade, the Severe Acute Respiratory Syndrome Coronavirus 2 (SARSCoV2) reappeared in China in late 2019 and was named Coronavirus Disease 2019 (COVID19). Since then, COVID19 has spread rapidly worldwide, causing immense disruption to lifestyle, population, economy, and overall global health, leading to the classification of a pandemic by the World Health Organization in March 2020.

## 2. FREQUENCY OF CLINICAL SYMPTOMS OF COVID-19

Listed below are the most typical clinical manifestations in Covid-19 induced disease.

Understanding the same allows early detection, self-diagnosis, and consequent management of the disease.

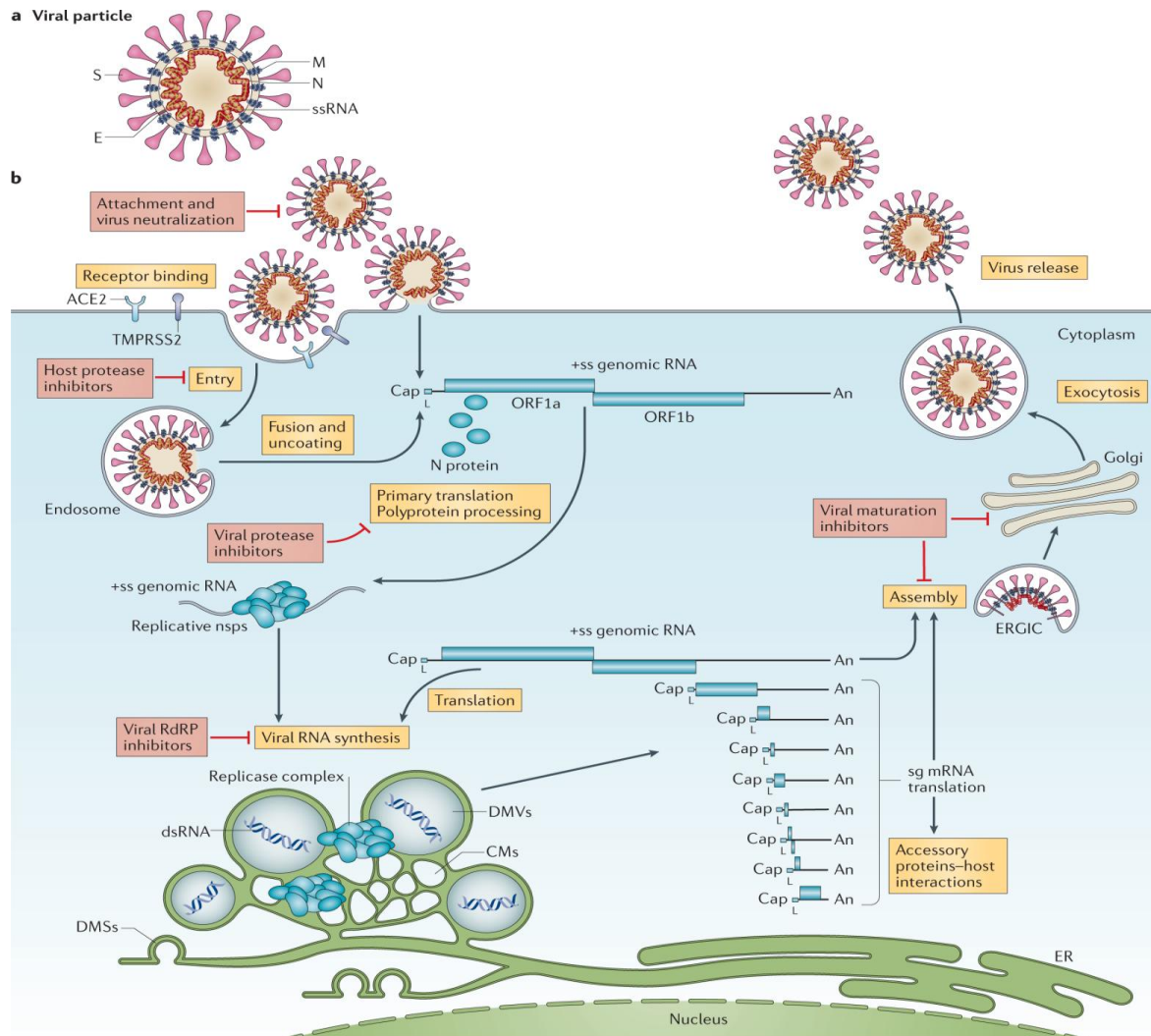
### A. Respiratory System

SARS-CoV-2 gains entry into live human cells by binding to the Angiotensin-Converting Enzyme (ACE2) receptor, which is found in the airway's epithelium and lung parenchyma. Undeviating injurious stimuli cause pulmonary symptoms to the tissues of the lung and the following defective and overactive response by the host body [1].

Rapid viral multiplication and a robust cytokine response harm the epithelial cells and the endothelial cells of the lung, consequently ending up in hypoxia [2]. The level of cytokine production (Tumour Necrosis Factor (or) TNF, Interleukins IL-6, and IL-1) is closely connected to the graveness of the situation [1]. Many medications projecting the stimuli to the cytokines and the resulting stimulation of the same, with anti-cytokine medicines or immunomodulators, appear promising for improving COVID-19 patient outcomes. Endogenous surfactant system changes have been observed in ARDS patients due to type-2 epithelial cell injury and severe inflammation. Exogenous surfactant has yielded mixed effects in 7 clinical trials in ARDS [3,1]. Surfactant protein has also been demonstrated to be helpful in the treatment of viral pneumonia produced by the Influenza A virus [4,5,2].

One of the suggested pathways for disease pathophysiology is virus-induced ACE2 downregulation. Deprivation of the expression of ACE2 leads to increased vascular permeability, increased lung edema, neutrophil buildup, and deterioration of lung function. One of the prospective treatment strategies against SARS-CoV-2 is to block the host target ACE2 receptor [1,2]. In lung tissue, microvascular thrombosis has been seen. Pause-inflammatory septal capillary damage with substantial mural and luminal fibrin deposition and neutrophil penetration of the interalveolar septa has been shown in COVID-19 patients' lung tissue. Hypercoagulability, direct endothelial damage, and complement activation may all be involved in the underlying process of pulmonary

microvascular thrombosis. Clinical studies must investigate treatment strategies for the prevention and remedy of pulmonary microvascular thrombosis [6,1].



**Fig. 1. Coronavirus Biology & Replication: Implications for SARS-CoV-2; V’kovski et al., Nature**

**Table 1. Clinical symptoms of COVID-19**

Dry cough	60–70%
Fatigue	40–60%
Productive cough	30–40%
Fever	80–90%
Dyspnoea	20–30%
Nausea/emesis	5–10%
Diarrhea	5–15%
Sore Throat	10–20%
Loss of appetite	30–40%
Palpitations, thoracic oppression	5–15%
Myalgia	20–30%
Chills	10–20%
Headache	10–20%
Nasal congestion	5%

(Source: Kurz DJ, Eberli FR. Cardiovascular aspects of COVID-19. Swiss Med Wkly. 2020 Dec 14;150:w20417.)

Acute Respiratory Distress Syndrome occurs in almost half of COVID-19 pneumonia patients. According to the ARDS spectrum, patients subdivided into type-L and type-H. Patients with type-L have distinctive characteristics such as low lung elasticity and limited lung recruitability, but they also have significant hypoxemia. Hypoxemia is most likely caused by a lack of hypoxic vasoconstriction and a reduction in pulmonary blood flow [1]. High PEEP is effective in Type-H patients because they have a high pulmonary elastance and weight. A few case studies and anecdotal evidence support this idea. Continued clinical research is needed to understand better ARDS and the best ways to manage it with ventilators [1,7].

Respiratory distress is only experienced when there is significant hypoxia or respiratory muscle exhaustion in the patient. Silent hypoxemia affects around 14 percent of patients. Patient self-inflicted lung injury occurs when a hypoxic patient breathes spontaneously and the increased respiratory drive causes lung damage [8,1].

### **Cytokine storm**

Patients with SARS-CoV have increased circulating chemokines (CXCL8, CCL2, and CXCL10) and inflammatory cytokines (IL-1, IL-6, and IL-12). This was also thought to be a good prognostic indicator for SARS. SARS-CoV might also infect [9] Macrophages and dendritic cells. As a viral entry in these cells can lead to an abortive infection, this looked to be essential. Die Autoren hypothesises that chemokine up-regulation might be an additional immune evasion mechanism for the lack of responsiveness to antiviral interferons [9]. A new study has found that the SARS-CoV-2 virus can replicate more easily and induce fewer IFNs in human lung tissue than SARS-CoV. This suggests that the two viruses may have different abilities to influence the production of pro-inflammatory chemokines and cytokines. Initial reports from China had indeed suggested of the involvement of chemokine system. Studies of transcriptome sequencing discovered up-regularization [9].

COVID-19 and high altitude pulmonary edema have been found to share similarities concerning the presentation, pathogenesis, and radiological observations. Hypoxemia may be improved with alternative therapeutic techniques such as hyperbaric oxygen therapy (HBOT) [1,7,8].

Patients with COVID-19 pneumonia have been shown to have co-infections with different pathogens. The presence of the new coronavirus may not be ruled out by the identification of another disease [10]. Resistant bacteria were found in 12 percent of intubated patients who developed hospital-acquired pneumonia [1,3].

A greater knowledge of the pathophysiology behind organ involvement can lead to safer patient care and a better outcome for the patient as a result. It may also be used to plan future clinical trials that are well-designed. Recently released guidelines have a dearth of solid recommendations due to the constant evolution of our understanding of illness [3] [6].

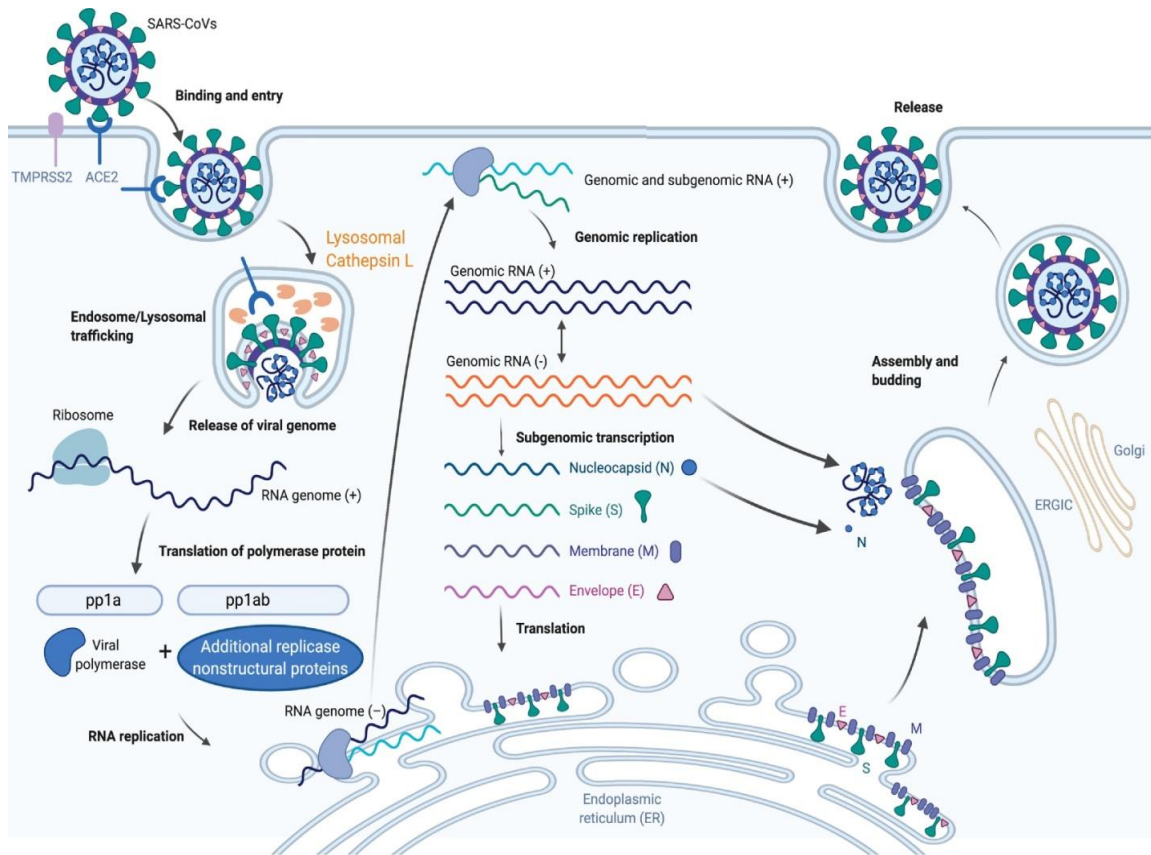
### **B. Cardiovascular System**

While the pulmonary machinery and the respiratory system is the primary possible target of COVID19, recent reports have shown that COVID19 severely affects the cardiovascular system and the kidneys as well. Autopsy observations have depicted that direct heart and kidney damage is often seen in patients who die from COVID19 infection. Contrarily, a structural or functional impairment of the heart and consequently of the cardiovascular system can impair the kidney and vice versa [11].

Alert monitoring of micro and macro-hemodynamics would permit rapid diagnosis and understanding of any persistent circulatory dysfunction and may be much critical to prevent renal injury. In addition, the variant and volume of fluid therapy can aid in the management of these patients with or without mechanical ventilation assistance under critical conditions [11][12].

Since it was recognized as a global epidemic in December 2019, COVID19 has spread rapidly worldwide, creating a pandemic. Pre-existing comorbidities, which are common in stressful lifestyles amid the modern environment and settings, such as high blood pressure, diabetes and associated heart diseases, post infection, emerge with greater severity. [13].

In addition, COVID19 contributes to many diverse cardiovascular complications of progressive severity, including acute myocardial infarction due to coronary ischemia, arrhythmias, myocarditis, cardiogenic shock, stress cardiomyopathy and finally cardiac arrest, to name a few. The CVS proceedings of COVID19 show many resemblances with those of SARS, MERS and Influenza - H1N1 [14].



Trends in Immunology

Fig. 2. Mechanisms of SAES-CoV-2 Transmission & Pathogenesis; Harrison et al., Cell

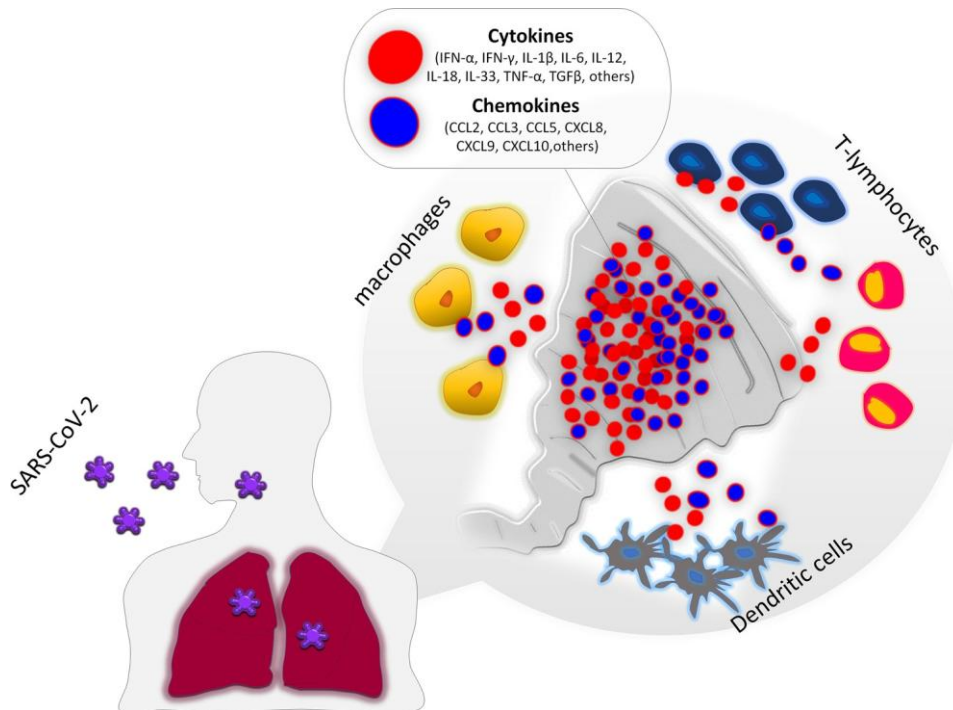


Fig. 3. Schematic Representation of "Cytokine storm"

Some particular considerations for the cardiovascular system are also essential with supportive anticoagulant therapy (heparin injection), continued use of the renin-angiotensin-aldosterone system or the "RAAS" mechanism inhibitors, continuous monitoring of arrhythmia, immunosuppression or modulation, and mechanical circulatory support for critically ill people [15][16].

Due to its association with the resulting increased mortality, cardiovascular disease is an obvious and significant co-morbidity of COVID19 and other respiratory viruses; becoming one of the leading difficulties in management of the case and happen to be amongst the leading causes of total mortality in critically ill COVID19 patients. The mechanisms causing the various cardiovascular manifestations due to COVID19 and their relationship to the corresponding antecedent conditions could not have yet been elucidated and are probably be multi-factorial to a large extent. There is currently only limited evidence of direct cardiac viral toxicity, and the direct and indirect mechanisms are likely to combine and contribute synergistically to cardiovascular damage, working together. [17][18].

The emergency clinicians serving in the Covid healthcare centers should be well aware and informed of these aforementioned cardiovascular complications when evaluating and consequently managing the patients with COVID-19 or presenting the same symptoms.

### C. Central Nervous System

In the hematogenous pathway, a few infections taint endothelial cells of the Blood Brain Barrier or epithelial cells in the choroid plexi and consequently attacking neuronal tissue by breaking the blood-cerebrospinal liquid obstruction or utilizing leukocytes as a vector for dispersal inside the CNS. When the infection gets away from these actual obstructions and attacks the CNS, the principal line of protection is the initiation of microglia [19].

Covid might gain access to the CNS through a few courses. Covies may contaminate the neurons and neuroglia. Most probably by intranasal entry and then using the trans-synaptic pathways. Neural cells show the passage protein ACE2, albeit undeviating endocytotic

contamination (like the ones showed for ZIKA and TBEV infections), can't be prohibited [20].

Diverse Covies have a fondness for various receptors. As expressed, SARS-CoV-2 communicates with the ACE-2 receptor [21]. CoVs-seropositivity is accounted for in a relationship with a few neurological issues with assorted resistant provocative cycles like e intense spread of demyelination from encephalomyelitis, various encephalitis, sclerosis, and optic neuritis [22].

CoVs-seropositivity is accounted for in a relationship with a few neurological issues with assorted insusceptible incendiary cycles like intense spread encephalomyelitis (ADEM)- like demyelination, various sclerosis, optic neuritis, and encephalitis. The limit concerning neurovirulence in Covies, including SARS-CoV-2, may add to the somewhat high commonness of neurological complexities in COVID-19 patients, especially among hospitalized patients with extreme or basic sicknesses [22].

### D. Renal System

Upon being infected by the covid19 virus, a significant number of patients have complained of experiencing acute kidney injury. Patients who have been decreased due to the progressed infection, most notably, have shown diffused acute tubular injuries upon postmortem analysis. Also, kidney biopsy in the subjects already suffering from proteinuria and haematuria did showcase a pattern of injuries, mainly around the glomerulus. Although there have been many hypotheses regarding the same, the actual chronology of renal infection still remains unclear and uncertain.

Autopsy studies have demonstrated a range of persistent abnormalities and indicated that kidney cells were more likely to be infected with the virus. A significant number of ATIs have been observed, with the incidence of microvascular lumen occlusion, mainly due to RBC with corresponding damage to the endothelial layer, and also, significant vascular & glomerular alterations suggesting possible have diabetes or high blood pressure. A handful of these findings directly agree with previously studied mechanisms of renal coronavirus infection. The results suggest that distinct mechanisms of infection with the novel coronavirus, with the involvement of direct infection of the renal parenchyma and most likely secondary

endothelial injury, are also to be considered [23].

It was observed that there were many cases of injury in the proximal tubule with isostatic vacuum aspiration, as evidenced by ultrastructural evaluation and immunostaining. Most of the observed cytoplasmic tubular vacuoles vary in size [23].

Electron microscopy revealed the presence of spherical viral fragments, iconic of the coronavirus, near the epithelium of the proximal tubule. The identified viral-like particle diameter and point length had resemblances to the covid viruses found earlier in the Middle East.

Coronavirus-like particles have also been vividly illustrated in the podocytes, associated with occasional vacuolation and clearance of the foot process and disengagement and consequent separation of the layer of the podocyte cells from the basement membrane of the glomerulus. These results clarify that the SARSCoV2 virus can straightaway cause infection to the tubular epithelium and podocytes of the kidney directly, comorbidity that was strongly associated with acute renal injury and persistent proteinuria in the patients with COVID19 [24].

Yet another more observed morphological observation is the case of stagnation of erythrocytes inside the lumen of the peritubular and glomerular capillaries, but with no presence of platelets. Interestingly, in occurrences of predominantly glomerular loop obstruction, RBC accumulation was much less in the peritubular capillaries and hence correlated to a comparatively longer time of prolonged hypotension. [23][24].

### 3. DISCUSSION

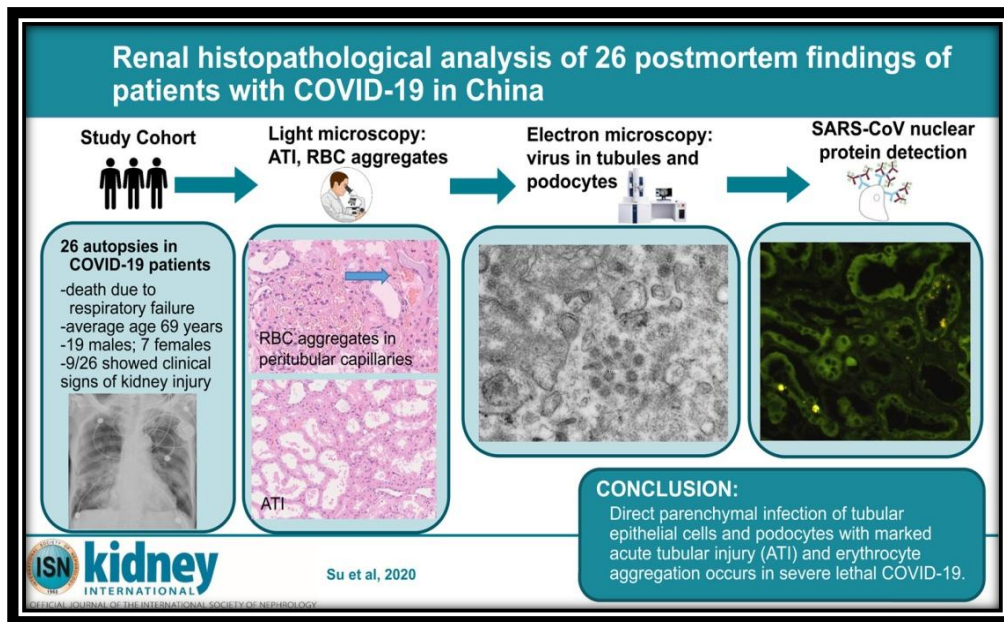
SARSCoV2 shows an approximate similarity of almost 79% to the SARS-CoV, the causative agent of the SARS epidemics 20 years or so ago in the Chinese peninsula. They both hail from the  $\beta$ -CoV line and use the same cellular ACE2 receptor to enter the target host cells.

The Renin Angiotensin Aldosterone System or 'RAAS' plays many essential roles in treating kidney disease, by converting angiotensin to angiotensin, mediated by the angiotensin-converting enzyme (ACE). ACE2 is expressed in the kidneys in the apical brush edges of the proximal convoluted tubules and the podocyte layer with relatively more minor intensity. Renal endothelial cells only express ACE, with no detectable presence of ACE2 [23].

Consistent with the above distribution of ACE2, the presence of virus-like particles was much observed in the tubular epithelia and the podocytes, which are marked spots of known pronouncement of ACE2. In synergy, the visceral glomerular epithelial cells and the visceral tubular epithelial cells of the kidney are primarily affected by infection with SARSCoV2. Therefore, it is believed that the endothelium should not be directly infected with SARSCoV2. However, the possibility that SARSCoV2 infects other resident kidney cells cannot be completely ruled out because the expression of ACE2 might be impaired in persisting diseases or by drug administration [23-30].

Finally, adding to the straight virulence factors of SARSCoV2, several other secondary injuries, such as most notably cytokine storms, hypoxic injury, consequent infection by bacteria or other fungi, viruses, and drug-induced nephrotoxicity may all pave the way to the genesis of the AKI [31,32].

To finally summarize the elucidated results and observations mentioned above, the discovery of the extensively widespread ATI and a surprising pattern of endothelial damage, accompanied by sufficient evidence of direct viral infection and resulting infiltration of the ductal parenchyma and podocyte epithelium in severe cases of COVID19, which can be highly fatal in due course of time, are noticed. However, there are quite a few gaps in current ongoing research and do demand further research, which is essential for a complete and fully deciphered understanding of COVID19, including its side effects on the kidneys and the renal system whole.



**Fig. 4. Renal histopathological analysis of 26 postmortem findings of patients with COVID-19 in China**

Source: Su H, Yang M, Wan C, Yi L-X, Tang F, Zhu H-Y, et al. Renal histopathological analysis of 26 postmortem findings of patients with COVID-19 in China. *Kidney Int.* 2020 Jul;98(1):219–27

#### 4. CONCLUSION

The COVID19 pandemic has emerged to be the most significantly lethal and disrupting public health crisis of the century. Due to the isolation and quarantine restrictions, which are also having different schedules in different countries and even in different provinces of the same country, the COVID19 pandemic has been a significant challenge to the well-being of the population and health services, especially in large COVID19 epidemic areas, and in low and middle-income countries that have not been developed very well both in terms of living standards of the majority of the population and health care. This can potentially delay the needed treatment for cardiac emergencies, like stroke or acute myocardial infarction. Therefore, there is a need to strengthen awareness and protection ideas to reduce morbidity and mortality in people with CVD and similar states.

Adding to those above, the advent of technology and telemedicine offers another potential way to utilize healthcare in isolated and rural communities and enable scheduled follow-up for people. Currently, treatments for COVID19 are limited to steroids and remdesivir (and potentially vital plasma from cured Covid patients, with questionable results) with unsatisfactory and persistent complications of

prevention, treatment, and reduction of effects of COVID19. The symptoms being displayed associated with SARSCoV2 infection should therefore be thoroughly expedited and closely monitored, and managed at all times to avoid additional death from cardiovascular complications.

Meanwhile, solid and vigorous efforts must be made to develop a cost-effective yet safe vaccine against COVID19 and make them widely available and affordable to the public in the shortest time possible, having cleared all the necessary tests for its viability and operational safety post-administration. Also, it is a must to reduce the amount of skepticism present in some portion of the population and to provide valid scientific explanations to the rumors and false information that have been circulated highly through electronic media from unverified and unauthorized sources, raised over concerning the safety and functional capabilities and long term effects on the population.

Although the Covid virus is adapting and evolving gradually and presenting with new strains at an increased frequency, yet vaccination is of high and immediate importance as it is expository to the critical situation and effective to some extent, even for the newer strains and imparts much the necessary protection to the population.



Therefore, vaccination against COVID-19 should be prioritized in patients with cardiovascular diseases as a part of the prevention strategy, especially in those with cardio-metabolic diseases, to decrease the risk of consequent and other cardiovascular events in due progression.

## CONSENT

It is not applicable.

## ETHICAL APPROVAL

It is not applicable.

## COMPETING INTERESTS

Authors have declared that no competing interests exist.

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