Multiple Organ Failure in COVID-19 Patients: A Narrative Review of Pathophysiology and Clinical Outcomes

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***Abstract*—Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), has emerged as a global health emergency with clinical manifestations that extend far beyond the respiratory system. Although acute respiratory distress syndrome is the primary cause of mortality, increasing evidence indicates that COVID-19 is a multisystem disorder leading to dysfunction of the cardiovascular, renal, hepatic, neurological, and hematological systems. This narrative review aims to summarize and critically analyze the current understanding of the pathophysiological mechanisms underlying multi-organ involvement in COVID-19 patients. Key mechanisms include dysregulation of the immune response, cytokine storm, endothelial dysfunction, coagulopathy, and direct viral invasion mediated by angiotensin-converting enzyme-2 receptors expressed in multiple organs. Clinical outcomes associated with multi-organ failure, including increased morbidity, prolonged hospitalization, and higher mortality rates, are also discussed in this review. Furthermore, this review highlights the importance of early identification of organ dysfunction, integrated clinical management strategies, and the need for multidisciplinary therapeutic approaches to improve patient outcomes. Understanding the systemic nature of COVID-19 is essential for optimizing treatment protocols and reducing long-term complications in affected patients.**

***Index Terms*—coronavirus disease (COVID-19), organ failure, SAR-CoV-2, cardiovascular system, kidney, lungs, immunity.**

I. BACKGROUND

The latest surveys recommend that coronavirus disease was first reported in Wuhan, China, in October–November 2019 [1]. The results of continuous research development, including the investigation of available genome grouping information from SARS-CoV-2 (Figure 1) [1] and related infections, have no authentic evidence that the infection was contracted in a research center or was human-made. The novel coronavirus is a large family of viruses that can cause serious illness, leading to death [2].

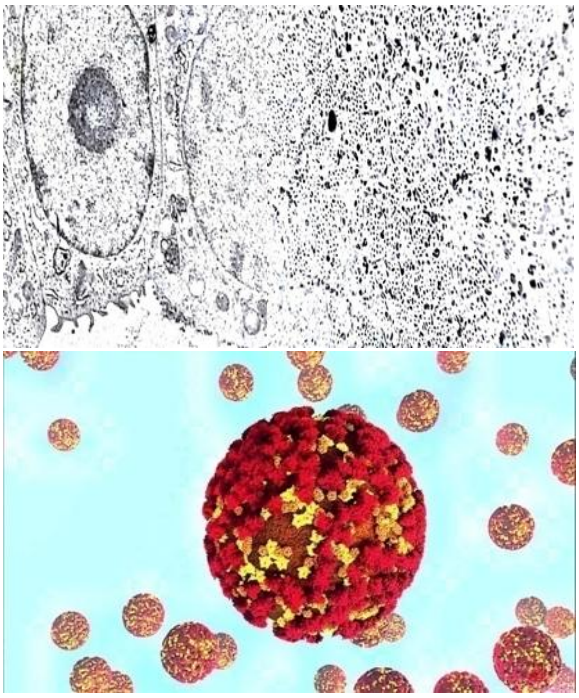

Figure 1: Shows microscopic view of Corona Virus (Source: Cynthia Goldsmith/Maureen Metcalfe/Azaibi Taemin)

The primary observation was the extreme sickness caused by the coronavirus that developed in 2003, SARS, a pestilence in China. The next phase of serious sickness was initiated in 2012 in Saudi Arabia with MERS [3]. Last year, in December, Chinese experts

warned the WHO of a coronavirus incident causing serious sickness, which was named SARS-CoV-2 [4]. Patients suffering from mild COVID-19 symptoms easily recover without hospitalisation in 7-14 days [5]. The coronavirus has a single-stranded positive RNA structure protein, which is made up of different parts, such as Spike(S), Nucleocapsid(N), Envelope(E), Membrane(M), and Hemagglutinin Esterase (HE) (Figure 2).

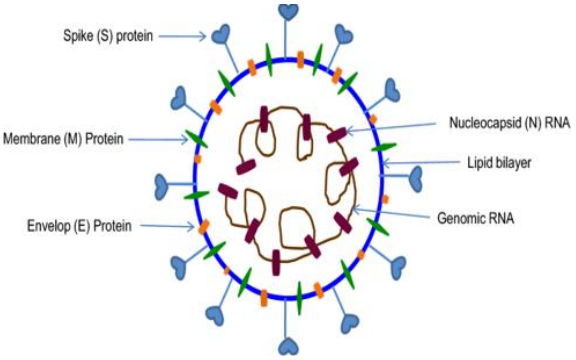

Figure 2: Basic structure of coronavirus (Source: https://link.springer.com/article/10.1007/s12291-020-00919-0)

Table 1 reveals a description of the coronavirus and its associated features.

- It is a 5-structural protein.
- Its genome ranges from approximately 26-34 kbs.
- Its structural size is approximately 80-160 nanometers.
- This is a single-stranded largest positive RNA virus.

Table 1: Taxonomical description of SARS-CoV-2

REALM	Roboviria
PHYLUM	Incertae Sedis
ORDER	Nidovirales
FAMILY	Coronaviridae
SUB-FAMILY	Orthocoronaviridae

There are few similarities in the symptoms of COVID-19 and different betacoronaviruses, for example, SARS and MERS [6]. Table 2 shows the symptoms of COVID-19 in patients. Nonetheless, COVID-19 presents other clinical highlights that it mainly targets the lower respiratory system with high gastrointestinal side effects; for example, loose belly and chest radiography shows invasion in the upper projection of the left lung, which causes dyspnea. Reports indicate that COVID-19 patients are asymptomatic and not detected in any clinical reports. SARS-CoV-2 contamination includes a two-stage safe reaction (Figure 3). The primary reaction period is defensive and is seen during the hatching time frame. Multiple resistant reactions attempt to fight the infection and prevent the infection movement at the initial stages [7]. The next stage starts when the introductory period of safe reaction weakens. This stage targets immune cells favorable to harmful macrophages, leukocytes, and cytokines, eventually leading to lung injury.

Further, COVID-19 does not only affect the lungs. However, it also influences other fundamental organs where ACE 2 is profoundly expressed and may encourage the infection entrance that causes organ damage with additional viral burden and cytokine storm [8]. Hence, this study reveals insights into the expanding effect and death rate in COVID-19 patients due to multi-organ collapse.

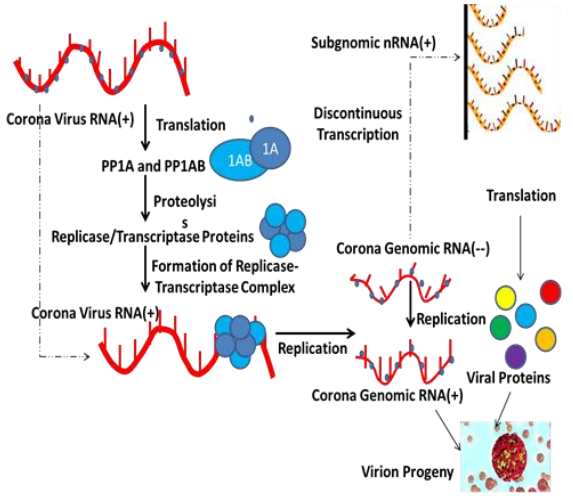

Figure 3: Shows the replica system of the coronavirus (Source: https://www.researchgate.net/figure/Shows-the-replica-system-of-coronavirus-9_fig1_354535258)

Table 2: Symptoms of COVID-19

Initial symptoms	Confirmed case symptoms	Serious symptoms
Fever	Intense pain	Breathing difficulty
Dry cough	Weakening of smelling power	Chest pain
Tiredness	Diarrhoea	Loss of speech
Sweating	Ski n Rashes	Sleeping sickness

Patients with minor symptoms stay at home [9]. On normal, it takes 5–6 days to show the symptoms when somebody is contaminated with the infection. Further, it can take as long as 14 days. It has protein spikes on its head and is divided into four groups: alpha, beta, gamma, and delta. Human coronaviruses were first distinguished during the 1960s in various forms (Figure 4).

Figure 4: Other human coronaviruses

People worldwide are generally contaminated with human coronavirus families, such as HKU, NL63, OC4, and 229E. New coronaviruses that contaminate people differ from the old structure due to mutation. Understanding the working process of a new coronavirus is challenging for all researchers; therefore, Figure 5 depicts the basic idea of the working process of coronavirus.

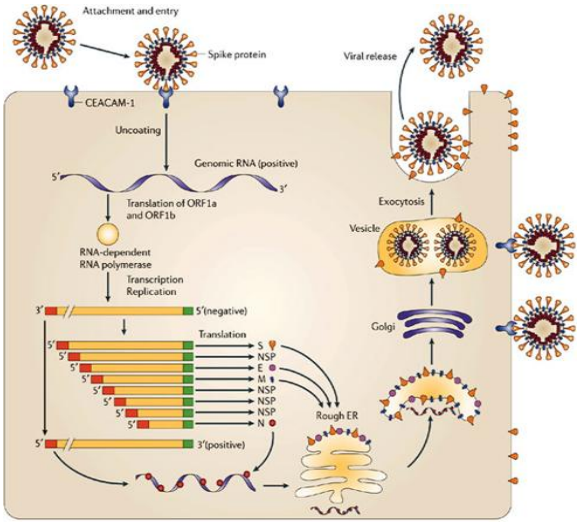

Figure 5: Shows the working process of the Coronavirus (Source: https://www.sinobiological.com/research/virus/coronavirus-replication)

II. MAIN TEXT

2.1 Impact on different age groups of humans as per immunity standardsThe side effects of COVID-19 appear at approximately 5.1 long periods of the middle hatching period; however, in 99% of cases, the period from the onset of COVID-19 symptoms varies from 6 to 41 days, with an average of 14 days. This periodic symptom can vary from individual to individual because of the age of the patients and their immunity status; the older the patient, the shorter the brooding period. According to the latest survey, death rate and hospitalised cases are higher among the more established COVID-19 patients [10]

2.2 COVID-19 impact on children and newly born babies

In this pandemic, which had a low number of cases in youngsters while it was more significant in adults, the rate of children infection with COVID-19 has expanded significantly, as the way that kids couldn't wear protective kits and couldn't take other preventive measures which are essential during this pandemic. As per the updated COVID-19 case data, there is insufficient proof of the methodology for pediatric patients and infants, the impact of COVID-19 on the embryo, and the wellbeing of breastfeeding, and clinical investigations are continuing [11]. As per the latest studies, contrasted with grown-ups, the quantity of pediatric cases analyzed is insufficient. In China, the latest study by Zhonghua Liu and Xing Bing, it is found that in an investigation, a total of 44672 cases determined to have COVID-19 test positive, 1022 patients with serious sickness died (2.3%) among 43.707% of patients more infected than 20 years of age. Just a single failure among 549 patients matured 10-19 years (% 0.2) and no failure among 416 patients between the ages of 0-9 (0%) were watched (10). Korea Center for Disease Control and Prevention expressed that 6.3% of all cases tested positive for COVID-19 by March 20 were kids under 19. Yet, China Disease Control and Prevention Centre detailed that after assessing 72,314 cases, under 1% of the cases were youngsters below 10 years of age. Information distributed in Italy on March 18, 2020, announced that 1.2% of 22,512 COVID-19 Italian cases were youngsters, and there was no downfall in kids. 5% of 4,226 COVID-19 cases analyzed in the USA until March 16 are kids. Kids represented under 1% of all COVID-19 hospitalizations in the USA [12]. This disease influenced patients from all age groups in the Chinese pediatric case arrangement (with 2143 cases), while 171 kids detailed from the Wuhan pediatric medical clinic was an age of 6-7. Nine newborn children with COVID-19 were determined to have

COVID-19 in China from December 8, 2019, to February 6, 2020, and the least age was one month. Information distributed in Turkey announced that just 1% of 11535 COVID-19 cases were children by 30.03.20. There were three genital cases. Another possible hypothesis for COVID-19 contaminations in youngsters is about the distinctions in the COVID-19 cases infected by the ACE 2 receptor. Treatment with ACE inhibitor starts ACE 2 receptor articulation. Though the two medicines are usually utilized in grown-ups with hypertension, it is an uncommon treatment in youngsters, which depicts the seriousness of SARS-Cov2 in grown-ups with high ACE2 articulation. [13]

CT scan of Thorax: According to the most recent proof, the CT examination discoveries of COVID-19 pneumonia show themselves from the presence of multifocal, one-sided, or ground glass opacification regularly to inside and outside the ground-glass opacification. In an investigation in China, five children with PCR-positive COVID-19 were analyzed. In comparison, the chest CT was normal in two children with tested COVID-19 contamination; the other three patients had unpredictable ground glass opacification (Figure 6).[14]

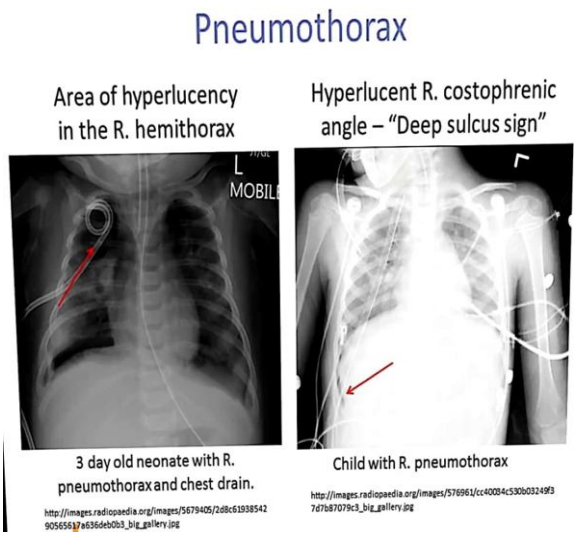

Figure 6: The CTs of Pneumothorax

Chest radiography: When the announced cases regarding the infant were inspected, comparative discoveries in imaging were seen with the youngsters. However, due to the insufficient information regarding the matter, the radiographic highlights of babies with lower respiratory diseases identified with SARS-CoV-2 are not enough to distinguish the matter. According to further investigations, discoveries of pneumonia were distinguished on chest radiography of 3 infants determined to have early neonatal COVID – 19 (Figure 7). The affectability of chest radiography is low in children. In the beginning phases, chest radiography might be ordinary and doesn't show ground-glass injuries, yet in extreme cases, advance to respective multifocal union might be watched [15].

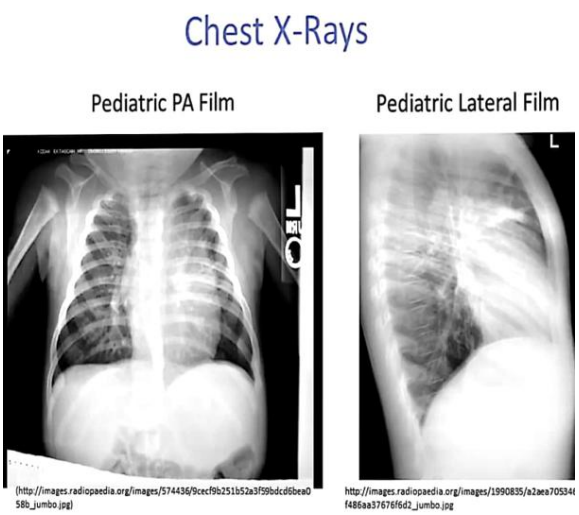

Figure 7: The Chest CT scan

2.3 COVID-19 impact on Adults and High Aged people

The COVID-19 cases have demonstrated solid age-reliance, with hardly any cases in youngsters [16], which could be because younger ages are fewer casualties of the contamination or potentially are less inclined to indicate clinical side effects when examined. We utilized unique transmission models fitted to a scope of accessible information on the age dissemination of announced cases [17]. We find that those under 20 years are generally half as powerless to disease as those over 20 years old, and 79% of contaminations are asymptomatic or paucisymptomatic (subclinical) in 10- 19-year-olds, contrasted and 31% in those more than 70 years old. Age-wise COVID-19 infection risk is given in Table 3. Similarly, as with all examinations, further information created during the disease could change our boundary parameters.

Table 3: Age-wise COVID-19 infection risk [18].

Age(years)	1-20	21-50	Above50
Immunity	Moderate	High	Low
COVID-19 infection risk	Moderate	Low	High
COVID-19 Cases	16%	36%	47%
Death report	0.8%	3%	6.25%

2.4 COVID-19 effect on Lungs, Kidney, and Cardiovascular system

The theory behind multi-organ damage by SARS-CoV-2 contamination in co-infection is the contact of ACE 2 on the digestive system, heart, kidney, liver, pancreas, cerebral neurons, vascular endothelial cells, testicles, insusceptible cells, uterus, placenta, and hatchling (Figure 8) [19].

The proof is disturbing that there is an expanded death rate in more infected COVID-19 patients with prior diseases, for example, hypertension, cardiovascular infections, diabetes, ongoing kidney ailment, cerebrovascular sickness, ceaseless obstructive pneumonic disease, and cancer.

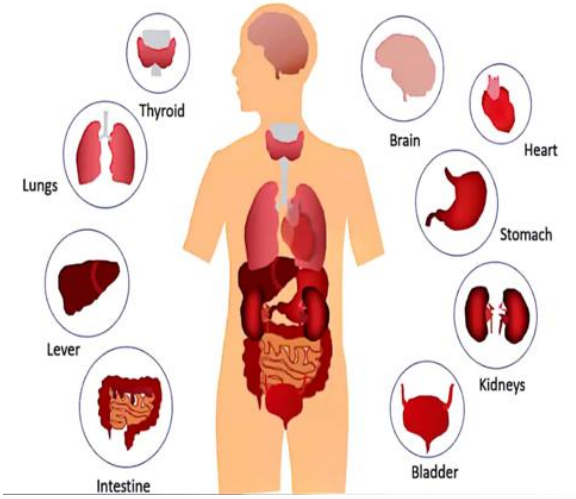

Figure 8: The multi-body organs (Source: https://www.pixtastock.com/illustration/57126526)

2.5 COVID-19 effect on human lungs

SARS-CoV-2, the virus that causes COVID-19, is a member of the coronavirus family. When contamination enters the human body, it encounters the mucous layers lining the nose, mouth, and eyes. Contamination enters with multiple strong cells, and the infected cells produce new disease parts. This increases the total production of the virus cells and dominates the WBC inside the body. An upside-down tree affects the windpipe initially in the respiratory system.

Furthermore, the virus attacks the lungs because of breathing problems. In the lungs, the infected cells damage the alveoli responsible for exchanging oxygen with CO_2 [20]. The new coronavirus can damage the upper or lower parts of the respiratory system. Specialists are currently learning about lung disorders due to the new coronavirus, and several researchers are continuing to understand the actual action of COVID-19 inside the human lungs. They acknowledge that the effect of COVID-19 on the body is similar to that of two distinctive coronavirus infirmities, such as SARS and MERS. Illness with SARS-CoV-2 begins when the respiratory system containing the disease enters the upper respiratory part (Figure 9). As contamination increases, the sickness can cause more lung damage due to pneumonia [21].

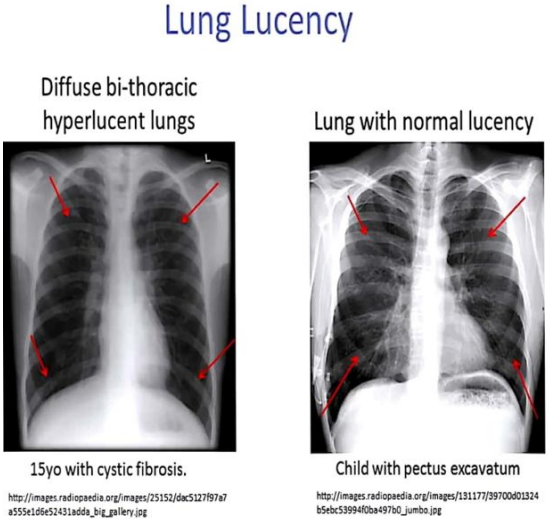

Figure 9: The Lungs Disorder

As per the recent survey on infected COVID-19 patients, most suffer from breathing shortness due to the low oxygen exchange rate inside the lungs. In any case, a disease with SARS-CoV-2 can damage the alveoli and surrounding tissues. Individuals with COVID-19 pneumonia can cause acute respiratory distress syndrome (ARDS), a dynamic type of respiratory failure that occurs when the air sacs in the lungs fill with liquid, which makes it difficult to relax. Several reasons infections, similar to seasonal infection or SARS-CoV-2, can be dangerous. [22].

2.6 COVID-19 effect on Human Kidney

Kidney infection has been reported in a new survey of patients with different degrees of SARS-CoV-2 contamination (Figure 10). As information advances, specialists have acknowledged the actual occurrence of Acute Kidney Injury (AKI). Numerous inquiries are yet to be replied to concerning the impact of epidemiological factors and co-morbidities on the event of AKI. A few reports have observed the occurrence of hematuria and proteinuria in affected patients. Additionally, serious kidney disease has not been found in certain reports, which adds to the adverse results, an angle that benefits further investigation. Patients on normal hemodialysis may feel weak against the virus due to the lower invulnerability status and requirement for visit participation to human services offices. As per the existing research on COVID-19, SARS-CoV-2 infection among the poor population establishes a significant test [23]. A great significance has been given to the requirement for ventilators, and all establishments were approached to achieve much higher quantities of ventilators facilities in their place. However, it needs to understand that a critical extent of grown-up patients with serious COVID-19 was affected with acute kidney injury (AKI) with a prerequisite for kidney substitution treatment (KST)].

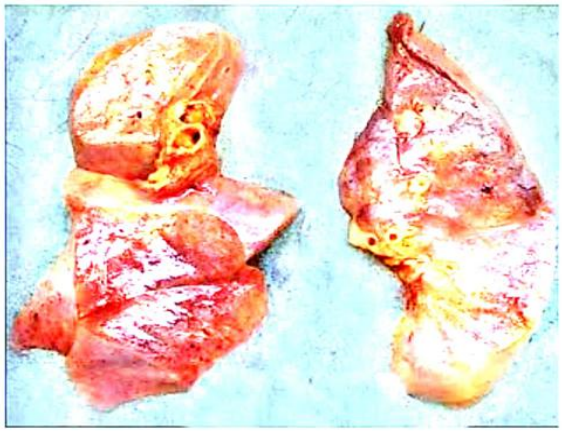

Figure 10: Shows kidney failure due to COVID-19

Even though AKI less seriously influences youngsters with COVID-19 illness and the underlying rates of AKI in these kids have been discovered to be low, due to the expanded interest for KST in grown-up patients and redirection of KST assets to the grown-up COVID-19 patients, a procedure should be arranged for children in the setting of restricted resources. Moreover, AKI occurs with higher frequency in the recently analyzed hyperinflammatory condition in children, which spread a typical Kawasaki disease or harmful stun disorder, Pediatric Inflammatory Multisystem Syndrome: Temporally Associated with SARS-CoV-2 (PIMS-TS). Cytokine storm, hyper-inflammatory state, hyper-coagulability, lack of hydration, and vasculitis are part of the hypothesized explanations for multisystem involvement, including AKI [24]. This review will focus on extraordinary transformations (in hyper-coagulability and expanded channel coagulating) or deviations from the "standard" to be made during the delivery of KRT to patients with COVID-19-induced AKI, which is moreover significant for the future with more COVID-19 patients anticipated and pediatricians overseeing either grown-up patients in PICU or being redeployed to the grown-up ICUs to deal with grown-up patients. Critically, suppose pediatric patients require KST during the pandemic. In that case, similar standards will apply as the majority of the resources (originating from a similar normal pool) would have been occupied by the grown-up patients.

2.7 COVID-19 effect on Human Cardiovascular System

The latest survey reports were released by Dr. Ashesh Parikh, a cardiologist at Texas Health Presbyterian Hospital Plano and Texas Health Physicians Group. The three basic reasons are co-contamination with another germ and respiratory distress when the ailment weakens the lungs. Cytokines are proteins that control a wide cluster of biological capacities, including inflammation and repair. The inflammatory response of cytokines can lead to heart damage through the mechanism of cardiovascular breakdown (Figure 11) [25].

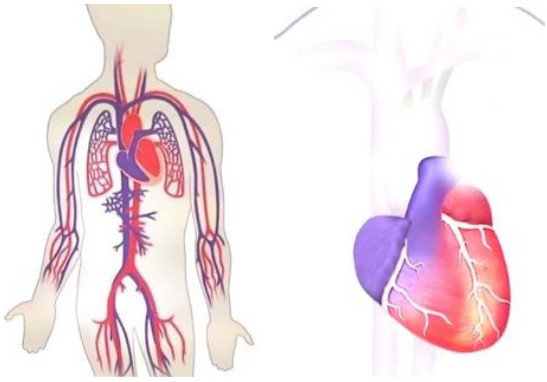

Figure 11: Shows the cardiovascular system

Dr. Sreenivas Gudimetla released another survey report. A cardiologist at Texas Health Fort Worth and Texas Health Physicians Group, a patient can encounter a possibly lethal condition called myocarditis. Myocarditis is the irritation of the heart muscle [26]. It can result in weak pump capacity of the heart muscle, known as cardiovascular breakdown with decreased discharge division (HFrEF) or systolic cardiovascular breakdown; in the above research report, attention is given to ongoing research trusted sources in JAMA Cardiology that ended up heart injury is a common condition in hospitalized patients with COVID-19 in Wuhan, China. The American College of Cardiology (ACC) recorded the following heart recommendations from Chinese COVID case reports in late February 2020.

These focus come into consideration because the first case was related to heart disorder in American and European case reports:

- Asymptomatic patients are at a higher risk of mortality from COVID-19, and up to 50% of hospitalized patients have an interminable clinical illness [27].
- 40% of COVID-19 patients have cardiovascular or cerebrovascular disorders.
- 16.7 % of patients were affected by arrhythmia.
- 7.2% were infected with intense cardiovascular injury.
- 8.7 % of patients were infected with a stun, and 3.6% caused AKI.
- Rates of confusion were generally higher for ICU. Patients.
- Some COVID-19 patients are affected by myocarditis.

2.8 Developments in COVID-19 treatments

Treatment is fundamentally organized by utilizing clinical involvement in adult patients. COVID-19 does not have a particular medical treatment in adolescents. Indicative and strong treatment, oxygen treatment, and liquid electrolytes are recommended. For infants, high-portion pneumonic surfactant breathed in nitric oxide, HFO (high-frequency oscillations) treatment, and ECMO (extracorporeal membrane oxygenation) can be valuable. Oxygen treatment and mechanical ventilator uphold must be given to patients with respiratory misery and SARS with oxygen treatment immersion above 94%. The nasal cannula is suggested in youngsters. Antiviral can be considered in clinical investigations on a case premise. All antiviral use should be considered tentatively because of the nonattendance of antiviral that has demonstrated viability for treatment and ought to be tried in clinical preliminaries to guarantee adequacy and wellbeing [28].

Hydroxychloroquine and chloroquine, which repress SARS-CoV-2 in vitro (hinder cell access), are FDA-approved and widely used to treat and prevent intestinal illnesses when they are not confused. Hydroxychloroquine is FDA-approved for discoid lupus erythematosus, foundational lupus erythematosus, and rheumatoid joint pain. There is no satisfactory evidence of its use in the treatment of pediatric COVID-19. However, it has paediatric clinical experience attributable to its worthy symptom profile and different signs. Along these lines, even though it is invaluable, the combination of azithromycin is not suggested because it increases heart reactions. The pediatric dose is 13 mg/kg/portion (maximum: 800 mg/portion) PO followed by 6.5 mg/kg/portion (maximum: 400 mg/portion) per oral, to be taken 6, 24, and 48 hours after the underlying portion. Given that intense jungle fever has a 3-day therapy period, it is prescribed not to be given longer than 5 days in COVID-19 concerning clinical preliminaries [29].

Remdesivir is a simple nucleotide prodrug that restrains viral RNA polymerase. It has been found to be compelling in SARS-CoV-2 in vitro investigations. Remdesivir is suggested to be used as a preliminary clinical feature [30].

Favipiravir (FPV) is another medication that is undergoing clinical exploration for the treatment of COVID-19, yet there is no evidence of its use in pediatric patients with serious COVID-19. This medication is an RNA-subordinate R.N.A. polymerase inhibitör, and it has been discovered to be successful in the Ebola episode. It is contraindicated in children younger than 1 year [31].

The use of Lopinavir/Ritonavir (LPV/RTV), a protease inhibitor utilized in HIV disease, has an extremely low job in treating SARS-CoV-2 contamination, and it has been seen in past examinations that it has some action against SARS CoV and MERS-CoV. The use of LPV/RTV, the main tablet structure that can be utilized securely in HIV-tainted pregnant ladies, is available to discuss

regarding infants and youngsters. Antiviral medications suggested in SARS-CoV-2 contamination can be considered in treating infants and youngsters after the hazard advantage proportion is deliberately assessed in clinical preliminaries [32]. The issue of iatrogenic concealment of resistance because of cytokine storm in COVID - 19 has been arranged, and it isn't prescribed to give corticosteroids, particularly in the light of current restricted logical proof because of the lower safe reaction in youngsters contrasted with adults. If there is proof of auxiliary bacterial disease, the important anti-infection agents should be utilized. Kids with an expanded danger of apoplexy can be treated with low sub-atomic weight heparin in the beginning phases, and anticoagulant treatment can be controlled if vital. Table 3 shows the Treatment dosage and clinical trial stage. Healing plasma treatment can be utilized in youngsters whose clinical condition disintegrates quickly and who have genuine and basic illnesses.

Table 3: The Treatment dosage and clinical trial stage

Treatments	Dosage	Clinical stage	Ref
Hydroxychloroquine	400 mg	Initial	[33]
Remdesivir	200 mg	Initial	[34]
Favipiravir	200 mg	Phase 2	[35]
Lopinavir/Ritonavir	LPV-800mg RTV-200mg	Initial	[36]

III. CONCLUSIONS

It is assumed that the ACE 2 interaction and its upregulation in various neurotic conditions make patients more helpless to SARS-CoV-2 contamination and can add to an expansion in mortality. COVID-19 is a worldwide concern, and its pathophysiology is exceptionally intricate; doing research towards the utilization of first-line drugs in the treatments of toxemia, cardiovascular illnesses, pneumonia, acute kidney injury, diabetes and its difficulties, asthma, NASH, safe-related maladies, and malignant growth. Thus, there is an essential requirement for care for those patients who have SARS-CoV-2 contamination fundamental with various ailments. It may expand the seriousness and mortality in co-morbid conditions due to multi-organ damage due to contamination with infection and cytokine storm. Hence focusing on the cooperation of SARS-CoV-2 to ACE 2 could be the future novel, vital way to reduce multiple organ transmission and damage. Clinical experience of kids and babies with COVID - 19 is a step-by-step expansion, and the methodologies suggested here depend on accessible proof. Even though continuous research in pediatric patients contrasted with grown-up patients in the COVID-19 pandemic, it is necessary to consider during the treatment choice that kids infected with heart and respiratory illness may advance extreme dependent on clinical experience from other viral contaminations. Concerns remain due to COVID-19 mother-child vertical transmission and the absence of proof of possible fatal results; further investigations are required.

LIST OF ABBREVIATIONS

COVID-19	Corona Virus Disease
SARS-CoV-2	Severe Acute Respiratory Syndrome coronavirus 2
RNA.	Ribonucleic acid
A.C.E. 2	Angiotensin-Converting Enzyme 2
RAAS	Renin-Aldosterone Angiotensin System
HE	Hemaglutin Esterase
AKI.	Acute Kidney Injury
WHO	World Health Organization
CT Scan	Computed tomography Scan
ARDS	Acute Respiratory Distress Syndrome
KST.	Kidney substitution treatment
PIMS.	Paediatric Inflammatory Multisystem Syndrome
HFO.	high-frequency oscillations
ECMO	extracorporeal membrane oxygenation
FDA.	Food and Drug Administration
ACC.	American College of Cardiology
FPV.	Favipiravir
LPV/RTV	Lopinavir/Ritonavir

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