Current Trends in Biotechnology and Pharmacy
Vol. 16 (4) 577 - 602, Oct 2022, ISSN 0973-8916 (Print), 2230-7303 (Online)
10.5530/ctbp.2022.4.90

COVID 19: A New Insight Into Organ Failure and Complications Caused by Novel SARS-CoV-2 Virus and Discussion on the Role of Nanotechnology in Detection, Treatment and Prevention of the Disease

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Abstract

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus, which first appeared in Chinese individuals in December 2019, is now causing the COVID-19 pandemic, with 5,79,319 deaths and 13,338,364 confirmed cases as of January 31st, a total of 56.7 lakhs. COVID-19 causes dysregulated immunological responses, metabolic dysfunctions, and negative consequences on a variety of organ functions. Significant risk factors are typically connected with older people who have medical comorbidities including cancer and diabetes. Scientists and doctors have battled to understand the unique virus and its pathogenesis in order to develop suitable treatment drugs and vaccines for COVID-19. The spike protein SARS-CoV-2 has recently been discovered to attach to the enzyme that converts human angiotensin I. The purpose of this study was to examine the involvement of many organs in COVID-19 patients, particularly in severe cases. We also wanted to know what was driving the multiorgan failure caused by SARS-CoV-2. Multi-organ dysfunction manifests itself in a variety of ways, including acute lung failure, acute liver failure, acute kidney damage, cardiovascular disease, a variety of haematological abnormalities, and neurological problems. The most important processes are associated to SARS-direct coV-2's and indirect pathogenic features. Although SARS-CoV2 receptor angiotensin-converting enzyme 2 (ACE-2) was found in the lung, heart, kidney, testis, liver, lymphocytes, and nervous system, the presence of SARS-CoV-2 RNA in these organs was unknown. These epidemics have strained healthcare systems and prompted serious concerns about how to deal with them using traditional drugs and diagnostic tools. In this regard, the application of nanotechnology opens up new avenues for the creation of ground-breaking preventative, diagnostic, and treatment solutions. We examine how nanotechnology can be applied to control the COVID-19 virus by designing nano-based materials such as disinfectants, personal protective equipment, diagnostic systems, and nanocarrier systems for treatments and vaccine development, as well as the challenges and drawbacks that must be overcome.

Keywords: COVID-19, SARS-CoV-2, Multi-organ failure, Nanotechnology

Introduction

The world is currently experiencing a pandemic sickness (COVID-19) caused by SARS-CoV-2, a newly discovered coronavirus [1]. At the time of writing, SARS-CoV-2 had infected almost 12 million people worldwide, resulting in 6,362,614 deaths (WHO, 2022). The disease causes mild to severe respiratory symptoms, with the latter being more common in the elderly and individuals with serious medical diseases such as heart disease, chronic lung disease, cancer, and diabetes [2]. Minor gastrointestinal, cardiovascular, and even neurological issues have been reported in COVID-19 individuals who have been admitted to the hospital [3].

Coronaviruses (CoV) are transmitted by bats and infect humans via an intermediate animal host before overcoming the species barrier. Different bat populations in China have coronaviruses with complex genetics,several of them are the SARS-direct CoV's ancestors. [4], [5]. SARS-CoV in Chinese *Rhinolophus* bats that seemed to adapt to the wild Himalayan palmcivet before spreading to humans [6]. It is most likely that interaction with sick camels caused people to contract the Middle East Respiratory Syndrome Corona Virus (MERS-CoV), which was generated from a *Pipistrellus* bat CoV. [7], [8]. It was confirmed shortly after the initial human SARS-CoV-2 outbreak that this novel virus was connected to a bat-borne coronavirus discovered in the *Rhinolophusaffinis* bat species [9]. The search for antransitional animal host has centred on the pangolin (Manisjavanica), which is thought to be the intermediate host for SARS-CoV-2[10]. The SARS-CoV-2 receptor ACE2 was discovered to be similar to human receptors in bats, pangolins, and a variety of other animals [11].

Over the last two decades, seven coronaviruses that cause more or less severe respiratory disorders have been discovered in humans. SARS-CoV-2, for example, can cause lung damage in patients as well as multi-organ dysfunction, including unfavourable cardiac remodelling, myocardial stress, and congestive heart failure [12]. SARS-CoV-2 has been identified as a human angiotensin I enzyme converting enzyme 2 (ACE2)-tropical virus [13], capable of binding alveolar pneumocytes with ACE2 on their surface [15].

COVID-19 aetiology is complicated, especially in patients with severe disease, due to various organ failures. The angiotensin-converting enzyme 2 (ACE 2) is thought to be a cell entrance receptor for SARS-COV-2 [16]. However, ACE2 mRNAs were found to be expressed in practically all organs in humans, including the brain, heart, kidneys, and testes, indicating that the virus might infect tissues other than the lungs [17,18]. ACE2 is a known peptidase that controls blood pressure by modulating the renin-angiotensin-aldosterone system (RAAS). Pathogenicity of SARS-CoV-2 may be influenced by the host immune system, resulting in tissue damage and, in some cases, death. Lympopenia, reduced lymphocytes, and cytokine storms have all been observed in COVID-19 individuals [19,20-24].

Effects of SARS-CoV-2 on human health

SARS-CoV-2 is distinguished from SARS-CoV by the appearance of an unique spike glycoprotein with a distinct binding affinity to the angiotensin-converting enzyme 2 (ACE2) receptors; it should be noted, however, that SARS-CoV-2 has a 10–20 fold higher binding affinity to ACE2 receptors than SARS-CoV[25,35]. ACE2 can be found in a variety of organs in the human body (figure 1), including the lung, colon, small intestine, testis, kidney, duodenum, oesophagus, gallbladder, and urinary bladder [36,37], making these organs a potential SARS-CoV-2 target [36][37].

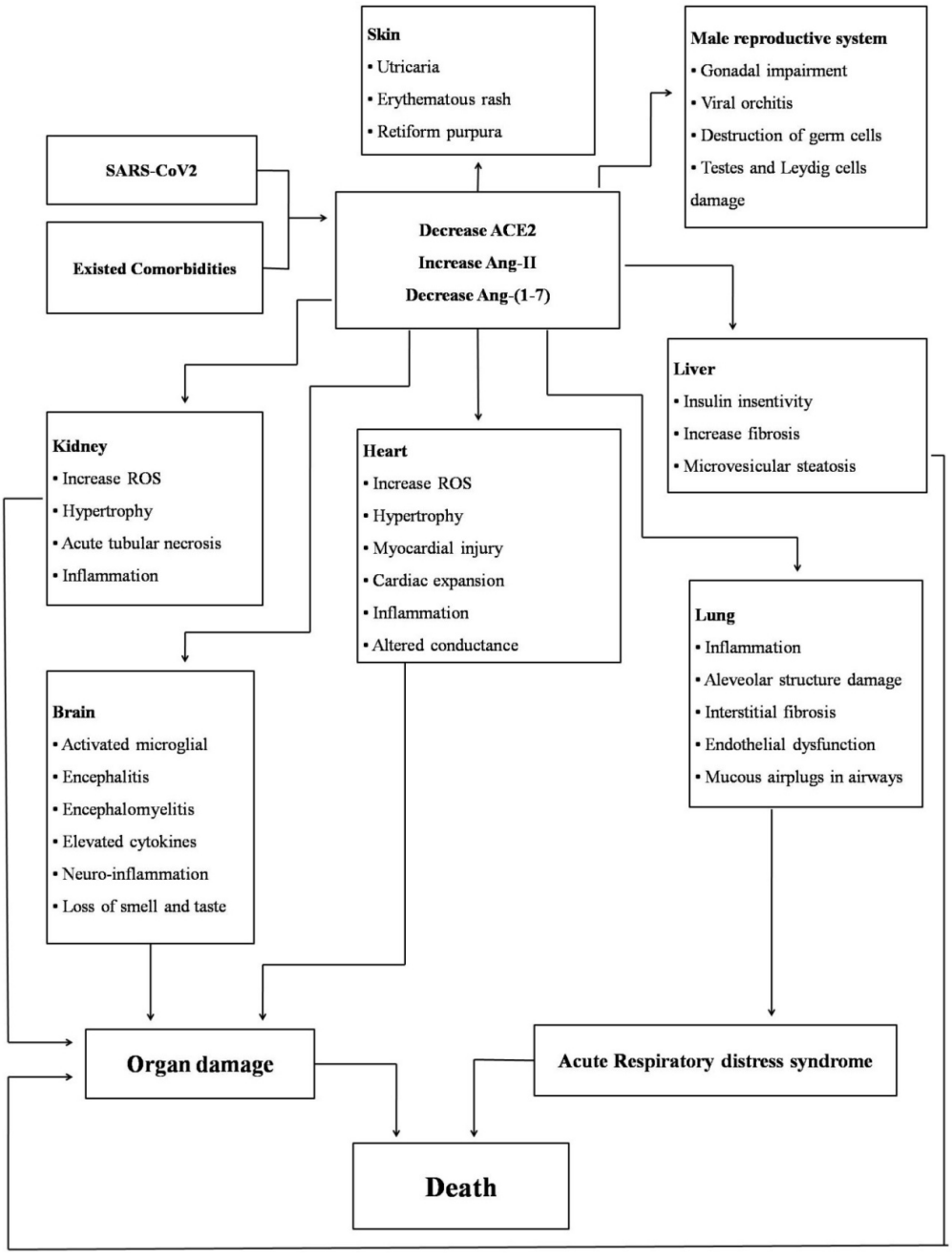

Fig. 1 The impact of SARS-CoV-2 on the human body's various organs.

Covid 19: A new insight into organ failure and complications

Lung damage

Coronaviruses like SARS-CoV-2, MERS-CoV, and SARS-CoV can cause serious morbidity and mortality in those who are infected. Lung infection appears to be the most common location of infection for all three viruses, resulting in acute respiratory distress syndrome and death. SARS-CoV pathogenesis is often initiated by the virus attaching its envelope protein (spikes) to the appropriate receptor, angiotensin-converting enzyme 2 (ACE2). Because ACE2 is widely expressed on the surface of lung and intestinal epithelial cells, these cells are vulnerable to SARSCoV [38]. According to several case studies, the chest imaging and histological observations of the lung caused by SARSCOV2 are similar to those seen in patients with SARSCoV and MERSCoV. A report from Italy [39] and another from China [40] both found significant pathological abnormalities in the lungs caused by new coronavirus pneumonia. Involvement of the lungs is also caused by a strong viral transmission. In respiratory viral infections, interstitial inflammation, disseminated alveolar destruction, and necrotizing bronchitis/ bronchiolitis are common histological findings in the lungs. In both the acute and late (organising) stages of respiratory virus infections, diffuse alveolar damage is the most common. Acute diffuse alveolar injury is characterised by intra-alveolar edoema. The creation of hyaline membranes that line the alveolar walls is followed by the deposition of fibrin. Type II pneumocytes, granulation tissue formation, and collagen deposition characterise the late phases of widespread alveolar injury [40].

Based on the examination of released patients for lung injury, there are widespread concerns. Huang et al. discovered that about three-quarters of COVID-19 patients had pulmonary dysfunction during early convalescence, with the most common symptoms being decreased diffusing ability and a decrease in the FEV1/ FVC ratio (forced expiratory volume in the first, second, and third/forced vital capacity). More than half of COVID-19 cases had abnormal carbon monoxide diffusion capability (DLCO), indicating that intra-alveolar diffusion channels were disrupted [41]. MEO et al. discovered that acute severe respiratory syndrome (SARS) and COVID-19 have the same biochemical and clinical aspects [42]. Previous studies on SARS survivors indicated that impaired DLCO was the most common anomaly, ranging from 15.5 percent to 43.6 percent [3, [43], [44]. The autopsy of COVID-19 patients revealed varying degrees of alveolar structural destruction as well as lung interstitial fibrosis [45]. Few extreme COVID-19 patients had mucous plugs in restricted airways, according to pathological findings [45], which may help to explain the decreasing breathing function. Neuromuscular dysfunction, in addition to acute lung injury, is a common cause of diminished lung capacity. In a few patients with a decreased FEV1 or FEV1 / FVC ratio, it could be due to long-term smoking or significant hyperresponsiveness of the airways [41].

Neurological dysfunctions

It has been proposed that SARS-CoV-2 virus enters the central nervous system via the synapse-connected route found in other coronaviruses like SARS-CoV, which may contribute to a variety of neurological abnormalities such as ataxia, epilepsy, neuralgia, unconsciousness, severe cerebrovascular disorder, and encephalopathy [46]. Mao et al. found neurological symptoms in 36.4 percent of the population, with the severe group being more likely to have significant cerebrovascular dysfunction, reduced cognition, and skeletal muscle injuries [47]. As previously stated, viruses that bind to ACE2 receptors can result in excessively high blood pressure and raise the risk of a brain haemorrhage. However, the virus may be able to cross the blood-brain barrier and enter the central nervous system (CNS) via the vascular system if SARS-spike CoV-2's protein interferes with ACE2 generated in capillary endothelium [48].

Indeed, some people first develop COVID-19 symptoms after experiencing neurological symptoms [47]. Beijing Ditan Hospital has reported a case of viral encephalitis caused by a new CoV that first attacked the CNS. The presence of SARS-CoV-2 in cerebral fluid was confirmed through genome sequencing, strengthening the idea that this modern pneumonia virus can also affect the nervous system [47]. Furthermore, pathogenic germs, such as influenza, are more likely to disrupt the blood-brain barrier in individuals with severe COVID-19 symptoms, resulting in headaches, profuse vomiting, visual loss, and limb convulsions.

SARS-CoV-2 infection causes a variety of neurological symptoms, including cerebrovascular problems, leukoencephalopathy, and other CNS illnesses. While certain types of diffuse white matter injuries (such as post-hypoxic leukoencephalopathy or leukoencephalopathy associated with sepsis) are mimicked by COVID-19-related white matter anomalies, all of these are significant differences that are distributed by neuroanatomic means of the white matter lesions. The pathophysiology of COVID-19 white matter abnormalities is unknown, but it is thought that “silent hypoxia” may play a role in their development. According to Otto Repalino’s cohort study, decreased NAA/Cr ratios were associated with neuronal dysfunction and axonal damage [49].

A significant number of COVID-19 patients have reported a loss of smell or taste. As a result, anosmia and dysgeusia are likely to be observed in COVID-19 patients [50]. Streeck, a German virologist, presented the first report of scent and taste deficiency on March 16th, 2020, identifying this ailment as a significantly more frequent disease (66.7 percent of COVID-19 patients). In February and March of 2020, the first reports of smell and taste abnormalities in COVID-19 patients surfaced. These studies were first anecdotal, but articles soon began to reliably show an increased prevalence of chemosensory impairments [51].

According to numerous case investigations of MERS coronavirus, neurological symptoms such as meningoencephalitis, hyporeflexia, and ataxia have also been reported [52]. Neuronal infection in SARS-CoV-infected hACE2 transgenic mice has been demonstrated to cause mortality [53]. According to accumulating evidence, the virus has been discovered in the cerebrum [54] as well as in the CSF as a result of SARS-CoV infection [55]. Coronaviruses were found in the cerebrum and cerebrospinal fluid of patients with epilepsy, encephalitis, and encephalomyelitis [56]. The average age of meningoencephalitis-related COVID-19 patients was 50.8 (19.09) years, with males being more frequently infected, according to clinical characteristics (70 percent). Chronic seizures, slurred speech, and cognitive impairments, including hearing and motor perseverance, are among the less well-known neurological symptoms [57].

Coagulation disorder

SARS-CoV was found to have similar thrombotic and haematological symptoms to COVID-19 [58]–[60]. Four patients with pulmonary embolism, three patients with deep vein thrombosis, and two patients with significant multi-organ infarctions due to thrombi were detected in a Singapore report involving postmortem investigations of eight known cases of SARS-CoV [61]. In a retrospective study of 157 SARS-CoV-infected patients, thrombocytopenia (55%) was discovered with the lowest platelet count one week after the onset of symptoms, reactive thrombocytosis (49%) was discovered at its peak during the third week (median = 17 days), and extended partial activated thromboplastin time (63%) was discovered throughout the first two weeks [62]. Thrombotic consequences and comparable haematological symptoms of COVID-19 and SARS-CoV illness have also been linked to MERS-CoV. In comparison to COVID-19 and SARS-CoV, there is a scarcity of data. Moderate thrombocytopenia was identified by Kim et al. as a common observation during the first week,

with no distinction made between individuals with mild or severe sickness [63]. MERS-CoV caused disseminated intravascular coagulation (DIC), intracerebral haemorrhage, and multi-organ failure in an apparently healthy patient two weeks after admission, according to Algahtani et al. [64].

Thrombotic issues appear to be a common occurrence in COVID-19 patients. Early research on the COVID-19 pandemic indicated that infected patients typically have thrombocytopenia (36.2 percent) and may have low D-dimer (46.4 percent) [2]. However, these rates are substantially greater in patients with COVID-19 severe illness (57.7% and 59.6%, respectively) [2]. Emerging evidence suggests that patients infected with this new coronavirus may develop DIC [65]. Both thrombocytopenia and increased D-dimer could be explained by an overactive coagulation cascade and platelet activation. Infectious disorders generate a mismatch between the procoagulant and anticoagulant homeostatic mechanisms, resulting in a systemic inflammatory response [66]. In patients infected with the new coronavirus, increased rates of D-dimer and fibrin breakdown, as well as prolonged prothrombin length, were linked to a poor prognosis [65]. In accordance with the diagnostic guidelines of the International Society on Thrombosis and Haemostasis, 15 of the 21 non-survivors (8 percent of the entire cohort) manifested evident DIC (>5 points) [67]. Lippi and colleagues found slightly lower platelet counts in patients with acute disease in a meta-analysis, and thrombocytopenia was connected to a five-fold increased risk of severe disease [65].

Hypokalemia

In the general population, diuretics are primarily employed as pharmacological medicines to treat hypertension and prevent fluid overload. Hypokalemic patients have a considerably higher prevalence of hypertension, cardiovascular illness, and renal impairment than normovolemic patients, which could explain why they require more diuretics. Long-term use of diuretics has been shown to cause hypokalemia and other electrolyte abnormalities [68]. This side effect in the patients could have been the primary cause of several electrolyte imbalances. In comparison to patients with normokalie, hypokalemia was associated with hypocalcemia and a lower plasma magnesium level. While female gender is associated with hypokalemia, early experimental investigations conducted in the 1950s [69] and later confirmed in the 1990s [70] found that women, particularly the elderly, have less exchangeable body potassium than other popular subsets. As a result, women are more likely than males to develop hypokalemia because their potassium deposits have been drained due to differences in body composition, with women having less extracellular water than men.

Hypokalemia was found to be a common electrolyte imbalance among COVID-19 patients, according to Riccardo etalfindings. .'s During hospitalisation, 41 percent of patients with severe symptoms of SARS-CoV-2 infection had hypokalemia. Hypokalemia's incidence and causes are unknown at this time, as it has only been documented as a probable COVID-19 symptom. Hypokalemia, on the other hand, has the potential to cause life-threatening arrhythmia in people infected with SARS-CoV-2 [71]. In this study, for the first time, the clinical features of hypokalemic SARS-CoV-2 patients are presented [71]. They tracked the various causes of hyperkalemia in a sample of hospitalised patients, including diuretic treatment, acid-base dysfunction, and corticosteroid therapy, despite the fact that urine analysis was only available in a small number of patients. Their findings indicate the necessity to frequently measure blood potassium levels in COVID-19 patients, as well as the urine K-to-creatinine ratio or 24-hour potassium excretion, in order to improve patient care. Depending on the severity of the urine loss, potassium should be supplemented, and the electrocardiogram (ECG) should be carefully evaluated, especially if you're using

any potentially arrhythmogenic medications.

In a small percentage of patients, the cause of tubular potassium shortage was unknown (22.2 percent). Hypokalemia was usually minor, unrelated to bad outcomes, and easily treated with potassium supplements. Although hypokalemia was not linked to death in their patient group, it is a potentially fatal illness if left untreated [71].

Kidney damage

SARS-CoV-2 may infiltrate the lungs and cause cytopathic consequences in a variety of organs, including renal tissue [70]. It has been discovered that the kidneys express the SARS-CoV-2 cell-entry receptor ACE2 around 100 times more than the lungs do [33,71]. The pathophysiology of kidney illness in COVID-19 patients is likely multifaceted, involving direct cytotoxic effects on renal tissue, immune complex deposition, and virus-induced cytokines or mediators [72,73]. COVID-19 patients' postmortem data were analysed by Su et al., who discovered proof of COVID-19's severe cytopathic influence on kidney tissue [74]. Hirsch et al. investigated 5449 patients with acute kidney injury (AKI) and proposed COVID-19 ischemic acute tubular necrosis as a significant cause of AKI [75].

They found a significant risk of AKI (29.1%) and a high death rate in patients with AKI (34.6 percent). According to earlier clinical trials, the detection of AKI in COVID-19 patients ranged from 0.5 percent to 36.6 percent [75] [70]. COVID-19 was thought to be unrelated to AKI by Wang et al. [76]. AKI was not documented in that study, even in patients who died in the intensive care unit. AKI was found in 5.1 percent of 701 patients by Cheng et al. [74]. In that study, the among-hospital death rate was 16.1%, but it was estimated that in patients with elevated baseline blood creatinine levels, the rate may reach 33.7 percent. Another Chinese study looked at 1,099 patients and discovered that patients with high creatinine levels (9.6%, n=52) had a greater death or ICU admission rate than patients with normal creatinine levels (1%, n=700) [77].

Acute renal failure appears to be a common complication of COVID-19, since it occurs in one-fifth of SARS-COV-2 pneumonia hospitalised cases. AKI is often recognised in symptomatic elderly people as a severe systemic inflammatory response to the ongoing illness. Size, male sex, and Chronic Kidney Disease (CKD) were all characteristics in our patient sample that contributed to AKI. Because AKI is a standalone risk factor in COVID-19 for all-cause mortality [78], it is critical to determine the etiological mechanism, as well as a technique to prioritise AKI prevention and early detection.

Liver injury

According to recent epidemiological studies, 16–53 percent of COVID-19 patients experienced varying degrees of hepatic injury [78] [79], with some patients developing serious liver injury. The coagulant system anomaly caused by hepatic damage can result in substantial bleeding, especially in patients receiving continuous renal replacement or extracorporeal membrane oxygenation. The deterioration of liver function can lead to hepatic failure and death. In COVID-19 patients, liver damage need immediate care [81]. Existing studies have linked SARS-CoV-2 transmission, hepatotoxic medication treatment, virally mediated cytotoxic T cells, and a dysregulated innate immune response to liver damage in COVID-19 [82]. COVID-19 [83] patients' liver tissue showed moderate microvesicularsteatosis and minor lobular activity. According to preliminary studies, SARS-CoV-2 can bind directly to ACE2-positive cholangiocytes, causing liver function dysregulation.

According to the data, liver damage occurred more frequently and more quickly in very ill COVID-19 patients, advanced more quickly, and healed later than in non-critical patients. In non-critically ill COVID-19 patients, drug characteristics such as lopinavir/ritonavir and arbidol therapy, as well as the number of

concomitant drugs, were predictive predictors of liver damage, which could be attributable to metabolic interactions with the drug. Liver injury was linked to a longer hospital stay and delayed virus eradication in all of the enrolled patients.

SARS-CoV-2 may directly dysregulateliver function by binding to ACE2-positive cholangiocytes [84]. ALT (Alanine aminotransferase) and AST (Aspartate aminotransferase) were found to be the primary markers in COVID-19 patients with serious illness, rather than TBL (Total bilirubin). Immune interactions involving virally mediated cytotoxic T cells and Kupffer cells can cause hepatocyte injury [82]. Researchers speculated that, in addition to the obvious damage caused by SARS-CoV-2, a virus-induced cytokine storm might also play a significant role in critically ill patients with liver damage. Specifically, unlike other studies, Jiang et al. discovered that drug factors, rather than the severity of the disease, may play a larger role in the liver injury of non-critically ill COVID-19 patients [81].

Cardiovascular dysfunction

Patients with chronic cardiovascular disease (CVD) are more likely to develop severe COVID-19 and have a poor prognosis. The most common comorbidities among COVID-19 patients were hypertension (17%), diabetes (8%), and CVD (5%), according to a meta-analysis of 46,248 individuals [85]. CVD and hypertension have grown more prevalent in the extreme patient group than in the non-serious cases [85]. There is also a link between existing CVDs and increased mortality. COVID-19, on the other hand, is well acknowledged to have negative effects on circulatory function, potentially harming or exacerbating the heart. There have been reports of cardiogenic connection in patients who have no history of CVD[86], as well as cases with exclusively cardiac manifestations [86] [87].

Although the exact function of cardiovascular activity in COVID-19 remains unknown, increased cardiac biomarker rates are common. According to Wang et al., 7.2 percent of patients exhibit high troponin levels, as well as electrocardiographic or echocardiographic abnormalities that indicate heart damage [89]. Because ACE2 is highly concentrated in the heart, it raises the risk of a myocardial infection. Both a cytokine storm caused by systemic inflammation and a hypoxic situation caused by ARDS (Acute Respiratory Distress Syndrome) that causes high extracellular calcium rates and contributes to myocyte death are probable harm mechanisms [90]. Increased myocardial demand, as a result of hyperinflammatory reactions or secondary hemophagocyticlymphohistiocytosis, may contribute to atherosclerotic plaque instability and myocardial damage, increasing the risk of acute myocardial infarction [91]. Blood pressure abnormalities are frequently observed as a result of the condition. Arrhythmia-related palpitations were also seen [90] [91]. Arrhythmias can take many different forms, and their causes might range from hypoxic circumstances to ARDS-induced myocarditis. Patients with reduced ejection fraction and cardiac enlargement have been documented by Hu et al. and Zeng et al. [87][92]. As a result, the long-term effects of COVID-19 on cardiovascular function, such as the risk of heart disease, should be observed and investigated further.

Male reproductive system

SARS-CoV-2 is a betacoronavirus with symptoms that are similar to SARS-CoV and MERS-CoV. COVID-19 can cause symptoms that are similar to pneumonia in some persons. Male reproductive systems are similarly susceptible to infection; COVID-19 patients have substantial fluctuations in sex hormones, indicating a gonadal dysfunction [94]. Viruses like HIV, hepatitis B and C, mumps, Epstein-Barr, and papilloma can induce viral orchitis, which can lead to infertility and tumours in the testicles [95]. SARS-CoV can cause orchitis, according to an examination of testis postmortem materials from six patients who died from the virus [95]. In all six specimens, pathological findings included

spermatogenic cell death, germ cell destruction, few or no spermatozoa in the seminiferous epithelium, thicker basement membrane, and leukocyte infiltration. As a result, SARS-CoV-2 may have an effect on the testes. New research on SARS-CoV-2 infection sheds light on impaired male gonadal function [96]. The ratio of testosterone to luteinizing hormone (T to LH) in 81 COVID-19 patients fell considerably when compared to 100 healthy men of the same age (COVID-19 patients: 0.74; healthy men: 1.31, P 0.0001). The serum T/LH ratio (as a measure of male gonadal function) has been suggested as a possible marker of SARS-CoV-2 reproductive dysfunction [97].

SARS-CoV particles have been found in the epithelial cells of testicular seminiferous tubules and Leydig cells, indicating that testicular injury has occurred [97]. ACE2 is highly expressed in the epithelial cells of seminiferous testis ducts, adult Leydig cells, and the prostate gland. The testis cannot be detached from the immune system, despite its special immunological status. Interferons are produced when leukocytes, CD3+ T cells, and CD68+ macrophages infiltrate the interstitial tissue of the testes, inhibiting steroidogenesis and testosterone production [98]. These cells produce inflammatory cytokines that stimulate an autoimmune response and damage the seminiferous epithelium, resulting in autoimmune orchitis [99]. High cytokine levels associated with viral or bacterial infection cause sickness or injury, which can lead to sperm loss and steroidogenesis, both of which have negative impacts on fertility [98]. COVID-19 is not protected by the blood-testis barrier, and inconsistent sex hormone production may be linked to reduced gonadal function. Young adults who want to start a family after recovering from COVID-19 should seek a fertility consultation.

Female reproductive system

To date, no harm to the female reproductive system has been recorded in COVID-19 patients. The involvement of renin–angiotensin (Ang)–aldosterone (RAS) in female reproductive processes like folliculogenesis, steroidogenesis, oocyte maturation, and ovulation has been researched. Reis and colleagues [100] confirmed the presence of an Ang-(1–7)–Mas receptor–ACE2 axis and ACE2 markers at all stages of follicle maturation in the human ovary [101]. However, earlier studies have shown that ACE2 is expressed in granulosa bovine and rat ovarian cells, regulated by gonadotropins, nd involved in folliculogenesis [101] [102].

SARS-CoV-2 could kill endometrial epithelial cells and affect early embryo implant by targeting ovarian tissue and granulosa cells and reducing ovarian function and oocyte production, causing to female infertility or miscarriage. The effect of SARS-CoV-2 on the fallopian tube is currently unknown, however it is something that should be investigated more in the future [104]. During this time, further research is needed to assess the long-term consequences of SARS-CoV-2 infection in men and women on human reproduction, pregnancy outcomes, and offspring growth and development in order to obtain more evidence on the reproductive impacts of associated disorders.

Dermatological manifestations

An old study by Hamming et al. [105] showed the existence of ACE2 in the epidermis basal cell layer extending to the hair follicle basal cell layer, the smooth muscle cells comprising sebaceous glands and eccrine glands.

In the same context, Goren et al. [106] postulated a theory that androgen receptors could play a role in COVID-19 patient's severity. This finding was focused on the increased frequency of extreme COVID-19 in children and adult females relative to adult males. Furthermore, with the reduction of the androgen hormones, the ACE2 activity has shown a decrease. However, this theory is not yet proven.

Patients have been observed to have

cutaneous signs such as Urticaria [107] in addition to the traditional respiratory symptoms, acralischaemia [108], morbilliform [109], livedoreticularis [110], vasiculitis petechial exanthems[111], erythematous rash [112], chilblains-like lesions [113], Pernio-like lesions [114], maculo-papularexanthems [115], croischaemia, retiformpurpura [116], erythema multiforme [117], pityriasisrosea [118], etc. The figure 2 and 3 demonstrates distinct skin signs seen in COVID-19 confirmed patients in a study conducted by Galvan casas et al. [119].

One of the most recent articles released by Recalcati et al., addressing largely to skin reactions connected to COVID-19, finds the existence of various cutaneous illnesses in 18 out of 88 individuals. Of them, 14 (15.9% of the total) patients had an erythematous infection, three (3.4%) had urticarial infection, and one (1.13%) had chickenpox-like symptoms. Young asymptomatic patients with this illness were also observed to have purpuraraynaud's syndrome, chilblain-like, and erythema multiforme-like lesions [116]. According to Henry et al., COVID-19 patients may experience urticarial eruption without any respiratory symptoms. [120].

Because the predominant symptoms were petechiae skin rash and low platelet count, a COVID-19 patient in Thailand was misdiagnosed with dengue [121]. The first retrospective investigation by Galva Casas et al. [119] classified COVID-19 cutaneous symptoms into five separate clinical forms: pseudo-chilblain (19%), vesicular eruptions (9%), urticarial lesions (19%), maculopapular (47%) and livedo or necrosis (19%). (19 percent). 6% of the population. Our goal is to promote awareness of COVID-19 viral infection's cutaneous manifestations and to help dermatologists better understand the skin rash caused by this unique virus. Furthermore, dermatologists should pay extra attention to patients with infectious skin rash in these settings to ensure that COVID-19 cases are not missed.

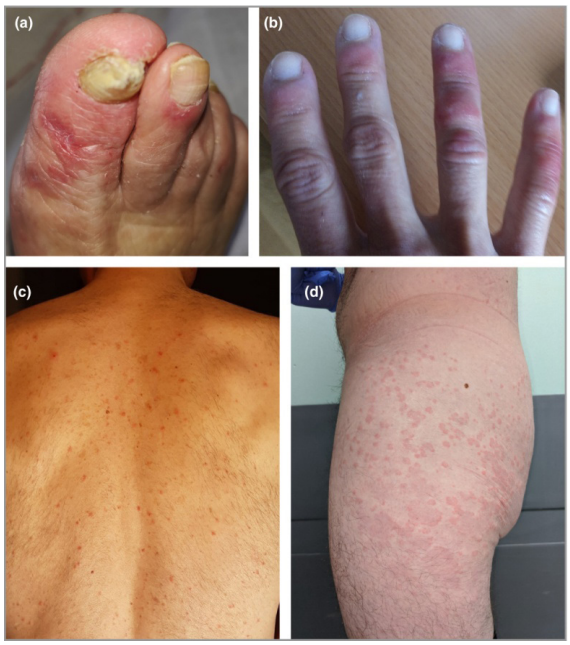

Fig. 2 All of the patients shown had confirmed COVID -19. (a, b) Acral areas of erythema–oedema with vesicles or pustules (pseudo-chilblain). (c) Monomorphic (i.e. at same stages) disseminated vesicles. (d) Urticarial lesions.

Source: Reproduced from Galvan casas et al. [119]

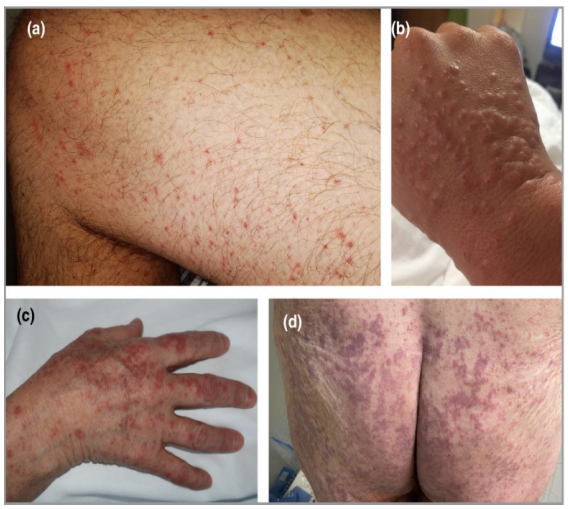

Fig. 3 All of the patients shown had confirmed COVID -19. (a) Maculopapular eruption. Some of the lesions are perifollicular. (b) Acral

infiltrated papules (pseudovesicular). (c) Acral papules (erythema multiforme like). (d) Livedoid areas.

Source: Reproduced from Galvan casas et al. [119]

Skin damage in healthcare workers managing COVID-19

Many skin problems arise as a result of repeated usage of personal protection equipment [122] due to hyperhydration, rubbing, and allergic contact reactions. Protective equipment caused 97.0 percent of skin injuries among health-care professionals, with lesions on the nasal bridge (83.1 percent), hands, cheeks, and forehead [123]. Hand washing or glove decontamination should be confined to the following times: before handling the patient or performing any aseptic therapy, and after contact with body fluids, touching the patient or some of the patient's objects.They also recommended using ethanol for hand hygiene and, if possible, applying hand cream after each hand hygiene session. Furthermore, a cotton glove should be worn beneath the latex gloves, and topical moisturisers including glucocorticoid cream should be used. A properly fitted mask, goggles, and the application of moisturisers or cream to contact areas are also recommended [122] [124]. When utilising N95 masks.

Role of nanotechnology in detection, treatment and prevention of Covid-19

Nanotechnology has sparked a lot of interest in recent years, and it's now widely employed in fields including health [125], agriculture [126], and bio-labelling [127]. Nanotechnology has been employed in numerous fields of medical research, including gene transfer [128], selective drug delivery [129], artificial implants [130], and public health sensing systems and other biosensors [131]. It can also be utilised for cancer treatment and detection [132] as well as the development of active antiviral, antibacterial, and antifungal medicines. The nanoscale scale of the material, which allows entrance into the cells of living systems, particularly the human body, is the basis for this interest in employing nanotechnology in medicine. Due to the shielding capabilities of some nano-sized materials, nanomaterials may serve a defensive role, preventing degradation of the enclosed product or anti-infection agent [133].

Detection

Diagnostics may play a key role in COVID-19 containment, enabling for the rapid implementation of control measures that limit the spread of the virus by identifying and isolating cases as well as tracking links (i.e. recognising individuals who might have come into touch with an infected patient). COVID-19 is typically diagnosed using reverse transcription polymerase chain reaction (RT-PCR) and screened using CT scans, although each method has drawbacks. Because they can monitor and identify different infections, molecular techniques are more reliable than syndromic testing or CT scans in detecting illnesses [134]. Nanotechnology opens up new possibilities for making low-cost, high-efficiency identification systems, secure personal protection gadgets, and cutting-edge, effective medications. Nanosensors are already a reality, capable of detecting low levels of bacteria and viruses and alerting clinicians when symptoms appear in patients with low viral loads. To diagnose COVID-19, many nano-based methodologies have been developed, which have advantages over molecular procedures. The methods that are currently being tested are listed below.

Reverse transcription loop-mediated isothermal amplification (RT-LAMP) coupled with a nanoparticle-based biosensor (NBS) assay

Covid 19 is now diagnosed by RT-PCR in real-time detection of SARS-CoV-2 nucleic acid [135]. Many types of gene amplification have been employed in comparison to this method, but their main disadvantages are that they are complex, require experienced

personnel, and take a long time. Yang et al. devised an RT-LAMP test for the identification of three genes to diagnose SARS-CoV-2 fast in order to overcome these limitations. In 2003, this method was employed to test for the coronavirus SARS, and it was shown to be quick and simple [136]. Since then, an RT-LAMP NBS assay has been developed to swiftly and accurately detect COVID-19 [137]. This RT-LAMP-NBS test combines LAMP amplification, reverse transcription, and multiplex inspection with nanoparticle-targeted biosensors to diagnose COVID-19 in a single-tube, one-step response. A one-step, one-tube RT-LAMP-NBS assay was designed to identify COVID-19. This technique takes 30 minutes to amplify nucleic acid at a temperature of 60–650 degrees Celsius. The impacts of identification can be seen macroscopically in the form of a colour transformation.

Point-of-care testing

Point-of-care People are diagnosed without having to send samples to national labs, and conclusions are produced without the need for a testing network to classify infected patients. SARS-CoV-2 lateral flow antigen testing is being investigated as a point of care for COVID-19 diagnosis [138]. In commercial lateral flow tests, a paper-like membrane strip is coated with two lines: one that carries antibody conjugates to gold nanoparticles, and the other that collects the antibodies. The membrane collects patient samples (such as blood and urine), and the protein is pushed over the line by capillary action. The antigens bind to the gold nanoparticle-antibody conjugate as the first line goes across the membrane, and the complex flows across the membrane. When the trapped antibodies reach the second side, where the red or blue side is visible, the complex is immobilised. Due to connected plasmon bands, individual gold nanoparticles are red, while the fluid containing clustered gold nanoparticles is blue [139]. The lateral flow test's clinical sensitivity, specificity, and accuracy for IgM were 57 percent, 100 percent, and 69 percent, respectively, and 81 percent, 100 percent, and 86 percent for IgG. A test that detects both IgM and IgG has an 82 percent clinical sensitivity [139].

Optical biosensor nanotechnology

A new device based on optical biosensor nanotechnology could identify the coronavirus directly from patient samples in roughly 30 minutes, removing the need for centralised laboratory testing. The most recent studies will swiftly determine whether a person is afflicted with the coronavirus or influenza virus. The project could be used for purposes other than the present pandemic and human care. The most recent biosensor technology could also be used to investigate various varieties of coronavirus found in reservoir animals like bats, in order to identify and track the virus's potential evolution and avoid future human pandemics. [140].

Nano-based treatment

Experts have been studying the possibility of using nanoparticles to treat bacterial and viral diseases for some years. For example, gold nanoparticles are designed to bind to viruses like Ebola or influenza, and then heat the particles using infrared wavelengths to disrupt the virus's structure. COVID-19 infections have recently been linked to a hyperinflammatory state characterised by a fulminant cytokine storm (hypercytokinemia) prior to the onset of ARDS and death [32]. A better understanding of the biology of acute inflammation can aid in the development of new inflammatory disease treatments [19]. Death may be linked to virally mediated hyperinflammation, according to research on confirmed cases of COVID-19. These unregulated pro-inflammatory systems are typically guided by constant positive feedback loops between pro-inflammatory signalling and oxidative stress, according to evidence and observations. According to the researchers, there is currently no effective way to target counteract this activity.

According to the research of Dormont et al., multidrug nanoparticles could be utilised to monitor and alleviate the effects of uncontrolled inflammation. The nanoparticles of adenosine, an endogenous immunomodulator, were created by conjugating squalene, an endogenous lipid, and encapsulating -tocopherol, a natural antioxidant. This resulted in high drug loading, biocompatible, multidrug nanoparticles, according to the researchers. The researchers discovered that the nanoparticles might deliver therapeutic medicines in a tailored manner by targeting vascular endothelial barrier failure at high-inflammatory sites. In animal models, endotoxemia testing revealed a "significant survival" benefit. As a result, scientists believe that administering adenosine and antioxidants in a targeted manner could be a novel way to treat acute COVID-19 inflammation with few side effects and reliable therapeutic applications. [141].

Vaccination is one of the most important therapy methods for improving the immune response to infectious disorders [142]. Meanwhile, because nanoparticles have been proven to exhibit immunostimulatory properties [143], substantial attention has been focused on developing nano-based medicinal medicines or vaccines against various coronaviruses. In inoculated mice and rabbits, Staroverov et al. evaluated the defensive immunological response elicited by gold nanoparticles (AuNPs) mixed with a type of coronavirus discovered in 2011 as swine transmissible gastroenteritis virus (TGEV) [144]. In vaccinated specimens, TGEV-conjugated colloidal gold was observed to elicit greater IFN- concentrations and neutralising antibody titers. In comparison to the free antigen reaction, vaccination with the antigen-colloidal gold complex increased T-cell proliferation tenfold, and the authors of the study also found that complex administration resulted in reciprocal enhancement of respiratory macrophage function and enhanced protective immunity against TGEV. Gold nanoparticles coupled to a virus could also be considered an antiviral option for vaccine development.

In mice, Sekimukai [145] evaluated the efficacy of two types of adjuvants (AuNPs and Toll-like receptor agonists) in combination with recombinant S protein against SARS-CoV infection. In contrast to a Toll-like receptor agonist-adjuvanted vaccine, vaccination with AuNP-adjuvanted protein elicited a high IgG response but did not develop protective antibodies or reduce eosinophilic infiltration. Gold nanoparticles, spike protein nanoparticles, and hollow polymeric nanoparticles have all been shown in animal models to have great potential to trigger an immune response against coronavirus [146]–[148]. For SARS-COV-2, a messenger RNA (mRNA) lipid nanoparticle vaccination is being explored. It is based on previous SARS-CoV and MERS reports [149].

Prevention

SARS-CoV-2 is disseminated mostly through minute droplets of virus particles that enter the body through the eyes, mouth, or nose as a result of breathing, speaking, sneezing, or coughing. Preliminary research also suggests that these germs can survive for days when stuck to countertops, handrails, and other hard surfaces. Nanoparticles will destroy certain diseases long before they enter the body, according to Webster, because they cling to numerous things and structures. His lab has developed nanoparticle-forming materials that may be sprayed on goods to combat viruses. He claimed that the virus was inactive even if it was on a table, a countertop, or an iPhone [150].

Many modern masks fail to maintain their air filtration function, and their electrostatic activity vanishes when exposed to water. As a result, their filtering capability is greatly reduced, making re-use almost impossible. Professor Kim's nanofilter mask, on the other hand, is made by crossing and aligning thin nanofibers to generate small air holes that keep viruses out while allowing people to breathe easily. That is, unlike traditional masks, the filter produces

a physical barrier rather than relying on static electricity. The material has been demonstrated to retain more than 94 percent of its filtration ability after 20 regular washings with soap and is safe to use for up to a month. In fact, it showed no deformations in its nano-fibre framework after three hours of soaking in ethanol and resisted 4,000 mechanical crumples and strains [151].

Antiviral nature of nanoparticles

Nanoparticles could be an interesting treatment option. Against the alphacoronavirus porcine epidemic diarrhoea virus (PEDV), Du et al. first revealed a new treatment method based on silver nanoparticles in 2018 [152]. They discovered that Ag2S nanoclusters (NCs) can stop PEDV from multiplying in treated Vero cells. Treatment with Ag2S NCs decreased viral budding and viral negative-strand RNA synthesis, which could explain why. Furthermore, the Ag2S NCs have been demonstrated to favourably control the proliferation of IFN-activating genes and the generation of pro-inflammatory cytokines, resulting in resistance to PEDV infection, making them a viable therapeutic candidate for further research.

To combat human coronavirus NL63, Ciejka et al. created a biopolymeric material for the creation of nano/microspheres (NS/MS) with a high potential for adsorbing coronaviruses [153]. When N-(2-hydroxypropyl)-3-trimethyl chitosan (H-HTCC)-NS/MS was added to viral suspensions, the number of copies of viral RNA dropped, and this was found to have a strong link with the amount of H-HTCC-NS/ MS employed. According to their findings, 2.5 mg/500 l H-HTCC-NS/ MS could reduce the amount of H-HTCC-NS/ MS by 99.60 percent. The decrease was 99.92 percent when 10 mg/500 l of HHTCC-NS/MS was introduced.

In a patent discovered in 2014 by Cho et al., a mixture of silver colloid, titanium dioxide (TiO2) nanoparticles, a dispersion stabiliser, binder, and water displayed antibacterial, antifungal, and antiviral properties (US 8,673,331 B2) [154]. At a 100-fold dilution of the formulation concentration, antiviral efficacy against PEDV and TGEV was demonstrated at a rate of 99.99 percent or greater, according to antiviral research findings. When the formulation concentration was diluted 1000 times, the viruses' development was reduced at a rate of 99.9% for PEDV and 93.0% for TGEV, respectively. As a result, Cho et alproposed .'snanomaterials' antiviral activity was dependent on the composition's concentration, implying that dose should be changed to achieve optimal inhibition [133].

Antiviral activity of zinc

Antiviral activity of zinc against rhinoviruses, common cold virus infections, and influenza viruses is excellent. Zinc can also be utilised to treat COVID-19 infections and reduce the risk and severity of infection [140]. In vitro, zinc nanoparticles inhibit influenza virus multiplication, and zinc oxide nanoparticles appear to be effective against H1N1 influenza virus infections. SARS coronavirus replication is also inhibited by zinc [155]. The virus's respiratory syncytial replication is inhibited by zinc salts, and viral replication of hepatitis C is reduced. Zinc supplementation has significantly reduced the prevalence of pneumonia in children in underdeveloped nations. Although the antiviral activity of zinc is unknown, it may hinder the virus from adhering to the mucosa and multiplying later. Zinc has been shown to have antiviral activity in vitro by promoting the production of antiviral interferon-alpha or gamma and reducing inflammatory reactions [156]. Zinc also affects immune cell function and aids in the activation of enzymes involved in a variety of cellular processes [157].

Zinc deficiency has been linked to an increased vulnerability to bacterial and viral illnesses, according to new research. Zinc deficiency has been demonstrated to impact B-cell development in vivo, resulting in insufficient antibody production and macrophages with low phagocytic activity against parasites [158]. Zinc may have antiviral effects by either limiting virus

replication or increasing the immune response, according to research. Consuming roughly 50 mg of zinc per day strengthens the host immune system, reduces the host's sensitivity to viral infection, and provides additional defence against infection with COVID-19 to lower disease risk [159], [160]. The usage of ionic zinc oxide nanoparticles in a mask covering has antiviral and antibacterial properties. Zinc oxide nanoparticles can be included into these materials to stabilise them and kill microorganisms on contact [140].

As a result, the nanomaterials may have antiviral properties against a wide range of coronaviruses. Antiviral nanomedicines against SARS-CoV, MERS-CoV, and SARS-CoV-2 should be studied even more urgently.

Conclusion

There is a global health concern that is affecting people all over the world. COVID-19 has surpassed the infection-to-mortality ratio's upper limit, separating it from other viral illnesses. To build a firm foundation for averting prospective pandemics, doctors and scientists must collaborate to eliminate the SAR-CoV-2 menace. Science and technology development and implementation are our primary weapons in the fight against COVID-19. The involvement of comorbidities and impairment of extrapulmonary organs have the greatest impact on disease progression. ARDS, cardiac arrest, renal failure, trauma, and multi-organ failure are all causes of death. When enforcing prevention and protective measures, thorough awareness of the comorbidities and potential organ damage is crucial. Recognizing this may make it easier to prioritise individual patient care and reduce the danger of decompensation. Apart from the rapid publication of study findings, this report seeks to provide medical information about COVID-19. Clinical symptoms induced by SARS-CoV-2 infection should be closely monitored to determine whether the virus has impacted internal organs and, if so, how effective treatment can be administered. For the formulation of an effective treatment approach, an individual's demographic records and previous medical history are required. In this review, we focused on the impact of COVID-19-induced human body impairments in order to provide researchers with a more detailed explanation of COVID-19's clinical implications. The role of nanotechnology approaches in managing, detecting, and preventing COVID-19 spread was also discussed. Nanotechnology offers a unique combination of capabilities that will dramatically advance our understanding of viral illnesses and the development of critical diagnostic and therapeutic technologies. It has been suggested that nanoparticle-based vaccines have a higher potential for eliciting a stronger defensive immune response than standard antigen-based immunizations. Furthermore, results demonstrated that nano-assays have the potential to give improved sensitivity and specificity when used for early phase quick detection of viral infection when compared to current approaches.

Abbreviations

SARS-CoV-2: **S**evere Acute Respiratory Syndrome Coronavirus 2; **ACE-2**: angiotensin-converting enzyme 2; **MERS-CoV**: Middle east respiratory syndrome-related Corona virus; **DPP4:**dipeptidyl peptidase 4; **ECG:** Electrocardiogram; **DIC**: Disseminated Intravascular Coagulation; **AKI:** Acute Kidney Injury; **CKD:** Chronic Kidney Disease; **CVD:** Cardio Vascular Disease; **ARDS**: Acute Respiratory Distress Syndrome; **TGEV**: swine transmissible gastroenteritis virus; **PEDV**: porcine epidemic diarrhea virus

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