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REVIEW

COVID-19, ENVIRONMENT, CLINICOPATHOLOGIC FEATURES, LABORATORY FINDINGS AND DIAGNOSIS, TREATMENT, VACCINES, ANIMALS, AND CANCER

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ABSTRACT

SARS-CoV-2 (COVID-19) belongs to the same coronavirus group (Beta-coronavirus) as SARS and MERS viruses that caused two of the more severe epidemics in recent years. Horseshoe bats (genus Rhinolophus) have been identified as the natural reservoirs of SARS-related coronaviruses (CoVs) and the likely origin of SARS-CoV-2. The intermediate host is thought to be the pangolin. The purpose of this review is to draw attention to the relationship between COVID-19 and different malignancies, and to discuss the similarities in their pathogenesis, and the possible repurposing of cancer drugs for the treatment of COVID-19. Along with antiviral and anti-inflammatory drugs, several anti-cancer drugs can be potentially repurposed in the management of COVID-19. The pathogenesis of COVID-19 and cancer shares certain similarities, including inflammation, immunological dysregulation, and coagulopathy. Blood parameters in COVID-19 patients upon admission show lymphocytopenia, and elevated C-reactive protein (CRP), ferritin, lactate dehydrogenase (LDH), and D-dimer levels in most of the patients. Currently, RT-PCR is the gold-standard laboratory test for COVID-19 confirmation in suspected cases.

KEY WORDS

COVID-19; SARS-CoV-2; cancer; environment; animals.

IMPACT STATEMENT

This review wants to address some aspects of COVID-19, such as environment, pathophysiology, laboratory findings, diagnosis, therapeutic and preventive treatment, role of different animals in transmission, with particular attention to cancer.

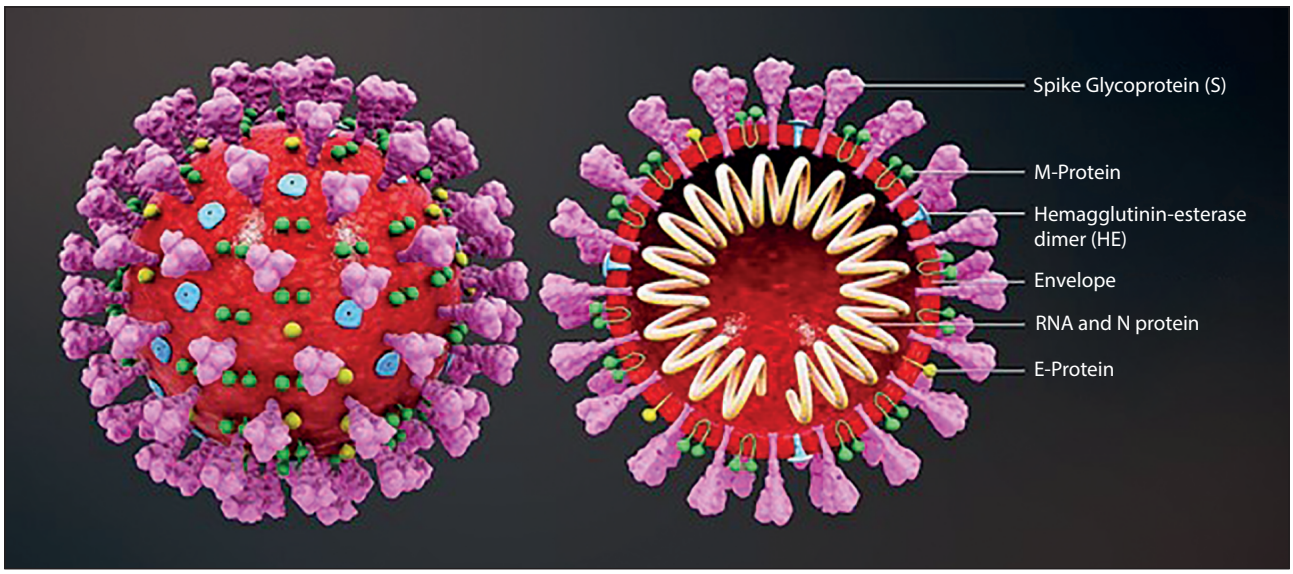
INTRODUCTION

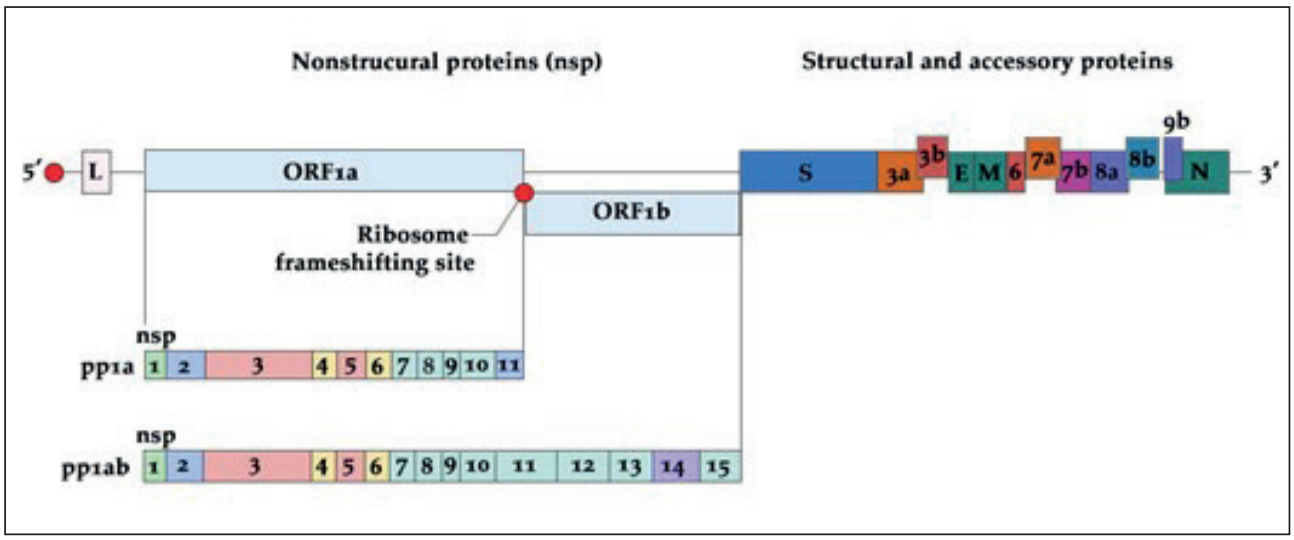
Coronaviruses are members of the *Coronaviridae* family in the Nidovirales order. The coronavirus family is divided into four subgroups: alpha (*α*), beta (*β*), gamma (*γ*), and delta (*δ*). Alpha- and beta-coronaviruses are found in mammals, particularly bats, while gamma- and delta-coronaviruses are found in pigs and birds (1). SARS-CoV-2 is a member of the same coronavirus family (Betacoronavirus) as the SARS and MERS viruses, which were responsible for two of the most devastating epidemics in recent years (2). Horseshoe bats (*genus Rhinolophus*) were discovered to be natural reservoirs of SARS-related CoVs and the likely source of SARS-CoV. Fruit bats (*Rousettus aegypticus*) can become infected and transfer the disease to other bats (3). Malayan pangolins have also been shown to have closely similar sequences (4). The inclusion of an intermediary, such as the pangolin, is suggested by the fact that SARS-CoV-2 was initially detected in Wuhan, China, far from where the horseshoe bat is found (5). These are enveloped viruses. The capsid is made up of the nucleocapsid protein N, which is surrounded by a membrane composed of three proteins: the membrane protein (M), the envelope protein (E), which are involved in the virus budding process, and the spike glycoprotein (S) (6). The SARS-CoV-2 virus is 50-200 nm in diameter and contains a + ssRNA genome of approximately 29.9 kb in length, making it the biggest known RNA virus. It has a 5'-cap structure and a 3'-poly-A-tail, and 14 putative open reading frames (ORFs) encoding 27 proteins (7). The SARS-CoV-2 genome has ten genes. The genes are organized in the following order: 50-replicase-S-E-M-N-30, with genes for accessory proteins inserted among structural genes (S, E, M, N). The polymerase gene, which has two overlapping open reading frames (ORFs), **figures 1 *a*** and ***b***, takes up around two-thirds of the total RNA(8). SARS-CoV-2 uses ACE2 as an attachment receptor and TMPRSS2 for spike protein priming, membrane fusion, and cell entry. TMPRSS2 cleaves ACE2 at Arginine 697-716 (9). The ACE2 gene is an escape gene that is found in the Xp22.2 region of the X chromosome. In principle, females get a double dose of ACE2, which might compensate for the loss of membrane ACE2 caused by SARS-CoV-2 (10). (**figures 1 *a*, *b***).

Quite recently, due to its importance, considerable attention has been paid to, and many publications have been released about the different features of COVID-19. The purpose of this review is to draw attention to the relationship between COVID-19 and different malignancies, and to discuss the similarities in their pathogenesis, and the possible repurposing of cancer drugs for the treatment of COVID-19. The remainder of the paper is organized into ten sections, starting with Section II, which discusses the role of the environment, and ending with Section X, which is devoted to cancer.

COVID-19 AND ENVIRONMENT

The origins of emerging infectious diseases (EIDs) are strongly linked to socioeconomic, environmental, and ecological factors. Changes in the manner and intensity of land use around the world are creating more dangerous interfaces between people, animals, and wildlife, which are a zoonotic disease reservoir (12). Because of the loss of habitat, animals are forced to move, where they may come into touch with other animals or people and spread germs (13). Humans and cattle are more likely to come into touch with wildlife, particularly in regions where forest cover has been reduced by more than 25% (14). Pathogen transmission from wild animals to domestic animals and humans, and vice versa, has resulted in major epidemics and pandemics around the world (14). Large livestock farms can also serve as a source for spillover of infections from animals to people (13). People are infected directly or indirectly by zoonotic viruses when they touch live primates, bats, and other wildlife (or their meat) or farm animals such as chickens and pigs (15). Live and dead wild animals come into contact with hunters, traders, customers, and everyone else involved in the wildlife trade at wildlife markets and in the legitimate and criminal wildlife trade (15). Air pollution, particularly NO2 and PM2.5 (particles with a diameter of less than 2.5 micrometers), may increase the susceptibility to infection and mortality from COVID-19 (16). PM2.5 and NO2 have a strong relationship with COVID-19 (17). Climate change is caused by carbon dioxide (CO2) emissions. Pandemic risk is increased by several of the core causes of climate change. For centuries, carbon dioxide persists in the atmosphere and oceans. CO2 emissions have fallen globally owing to coronavirus lockdown. According to scientists, this will be the largest reduction in manmade CO2 emissions since World War-I





Figures 1 ***a****. Schematic presentation of the SARS-CoV-2;* ***b****. its genome structure. SARS-CoV-2 has a spherical structure. The virus has an outer lipid envelope, covered with spike glycoprotein. The RNA genome has a replicase complex (comprised of ORF1a and ORF1b) at the 5'UTR. The ORF1a encodes for nsp1-nsp11, while ORF1b encodes for nsp1-nsp15. Four genes that encode for the Structural proteins: Spike gene, Envelope gene, Membrane gene, Nucleocapsid gene and a poly (A) tail at the 3'UTR. The accessory genes are distributed in between the structural genes. (****a****: credit to https://www.scientificanimations.com/wiki-images/;* ***b****: modified from (11)).*

(18). According to NASA researchers, ozone concentrations above the polar parts of the planet declined by roughly 240 Dobson units on March 12, 2020, compared to March 12, 2019. Low levels like these are extremely unusual, occurring just once every ten years or so (19).

PATHOPHYSIOLOGY

The spike glycoprotein-S enhances the virus's attachment to the angiotensin-converting enzyme 2 (ACE2) receptor and allows it to fuse with the host cell's membrane (7). There are two functional subunits in the S glycoprotein. The S1 subunit, which contains the RBD, is important for binding to the host cell receptor, while the S2 subunit is important for fusing of the viral and cellular membranes (20). SARS-CoV-2 then infects target cells by using serine proteases TMPRSS2 (transmembrane protease serine 2) for S protein priming (7). This protein is used for cell entrance by the influenza virus and the human coronaviruses HCoV-229E, MERS-CoV, SARS-CoV, and SARS-CoV-2 (COVID-19 virus) (21). Type 2 alveolar cells, nasal goblet cells, nasal ciliated cells, corneal cells, and intestinal epithelial cells are all likely SARS-CoV-2 host cells since they show high amounts of both ACE2 and TMPRSS2. SARS-CoV-2 appears to infect mononuclear phagocytes but not lymphocytes among

immune cells (22). SARS-CoV-2 infects pulmonary capillary endothelial cells in addition to epithelial cells, amplifying the inflammatory response and triggering an influx of monocytes and neutrophils (23). 15-30% of persons who are hospitalized with COVID-19 will develop COVID-19-associated acute respiratory distress syndrome (ARDS) (24). Patients with COVID-19-related ARDS who have decreased respiratory system compliance and elevated D-dimer concentrations have a high death risk (25). Two genetic susceptibility loci at Chr3p21.31 and Chr9q34.2 were discovered in the first genome-wide association study (GWAS) of severe COVID-19 with ARDS. The locus Chr3p21.31 spans the genes SLC6A20, LZTFL1, CCR9, FYCO1, CXCR6, XCR1, CCR1, and include several chemokine receptors (CCRs, CXCR6, and XCR1) that mediate chemokine signaling pathways for leukocyte chemotaxis and cause lung injury (26). The presence of high levels of ACE2 in the intestine makes the small bowel and colon particularly vulnerable to SARS-CoV-2 infection. According to the Human Protein Atlas database, the expression of ACE2 messenger RNA and protein in the gut is 100 times higher than in the lung (27). SARS-CoV-2 is largely spread from person to person through close contact (about 2 m) and aerosol respiratory droplets with a diameter of less than 5 μm in diameter (17). Longer exposure to an infected person (at least 15 minutes within 6 feet) and shorter exposures to symptomatic individuals are linked to a higher probability of transmission (28). Both TMPRSS2 and ACE2 are found in human corneal epithelial cells, implying that ocular surface cells could be viral entry sites as well (29). Another mechanism of transmission is contact surface spread. Aerosols may also be a cause of infection in humans outside of a laboratory setting, however it is unknown if this is a substantial cause of infection in humans (28). Viral shedding can begin 5 to 6 days before the first symptoms occur, and infectiousness can drop dramatically 8 days after the first symptoms occur (30). The median incubation period was calculated to be 5.1 days among 181 confirmed cases with known exposure and symptom start dates, and 97.5 percent of those who develop symptoms go through with within 11.5 days following infection (31). The most prevalent symptoms in hospitalized patients are fever (up to 90% of patients), dry cough (60%-86%), shortness of breath (53%-80%), fatigue (38%), nausea/vomiting or diarrhea (15%-39%), and myalgia (15%-44%). Non-classical symptoms, such as isolated gastrointestinal complaints, can also be present. In 64% to 80 of patients, olfactory and gustatory dysfunctions have been recorded (28). The underlying pathophysiology of the loss of these olfactory and gustatory perceptions has been linked to direct damage to the olfactory epithelium's supporting cells, the olfactory bulb, and altered olfactory neuron function, altered ACE2 signal transmission, and intensified gustatory particle degradation by sialic acid (32). Hypertension (56.6%), obesity (41.7%), and diabetes (33.8%) were the most common comorbidities in 5700 hospitalized patients, according to clinical research (33). Acute renal injury (9%), liver dysfunction (19%), bleeding and coagulation dysfunction (10%-25%), and septic shock (6%) are all possible complications for hospitalized patients (28). It is unclear why children are less likely to contract COVID-19. The following are some possible explanations: Children's immune responses are less vigorous (no cytokine storm), they have partial immunity from prior viral exposures, and they have lower rates of SARS-CoV-2 exposure. SARS-CoV-2 infection has recently been linked to a rare multisystem inflammatory illness similar to Kawasaki disease in children in Europe and North America (34). RNA viruses have a higher rate of mutation than DNA viruses. Coronaviruses, on the other hand, create fewer mutations than most RNA viruses because they encode an enzyme that corrects some replication errors (34). In the global pandemic, a SARS-CoV-2 variant with the Spike protein amino acid mutation D614G has become the most common type. The transition from D614 to G614 happened asynchronously in different parts of the world, starting with Europe, then North America and Oceania, and finally Asia (35). This dominant strain is ten times more infectious than Wuhan-1 strain. In both Denmark and the Netherlands, a mink-related variation Y453F has been discovered (36). Y453F is found in the RBD and is most likely a mink ACE2 adaptation, but it also boosts affinity for human ACE2 and replicates as well as the wildtype (37). In the United Kingdom, a SARS-CoV-2 variant B1.1.7 with a mutation Δ69/70 has spread fast (38). This variant accounted for around 28% of SARS-CoV-2 infection cases in England as of December 28, 2020, and population genetic models imply it is spreading 56 percent faster than other lineages (34). The E484K mutation can be found in different variants including, the South African (B.1.351), Brazilian (B.1.1.28), and UK B.1.1.7 var-

iants (39). The SARS-CoV-2 B.1.617 lineage was identified in October 2020 in India (40). The lineage includes three main subtypes (B1.617.1, B.1.617.2 and B.1.617.3), harbouring diverse Spike mutations in the N-terminal domain (NTD) and the receptor binding domain (RBD) which may increase their immune evasion potential. B.1.617.2, also termed variant Delta, is believed to spread faster than other variants. Sera from individuals having received one dose of Pfizer or AstraZeneca vaccines barely inhibited variant Delta. Administration of two doses generated a neutralizing response in 95% of individuals, with titers 3 to 5 fold lower against Delta than Alpha(B.1.1.7) (41). The Lambda (C.37) lineage was classified as a variant of interest (VOI) by the World Health Organization on June 15th, 2021. The C.37 variant, which lies within the B.1.1.1 lineage, has already been reported as highly prevalent in Peru and has also been identified in many countries across the Americas, Europe and Oceania (42). The Omicron variant, also known as B.1.1.529, is a novel extensively mutated SARSCoV2 variant that was identified as a variant of concern (VOC) by the World Health Organization on November 26, 2021 (43).

LABORATORY FINDINGS

The average range of laboratory abnormalities identified in COVID-19, according to a systematic evaluation of 19 studies involving 2874 patients included elevated serum C-reactive protein (increased in > 60% of patients), LDH (increased in approximately 50%-60%), alanine aminotransferase (elevated in approximately 25%), and aspartate aminotransferase (approximately 33%) (28). According to Huang *et al.* (44) a serum albumin level of < 35 g/L at presentation increased the risk of death in COVID19 by at least 6 times. According to Khourssaji *et al.* (45), blood parameters in COVID-19 patients upon admission indicated elevated C-reactive protein (CRP) (100%), ferritin (92%), LDH (80%), white blood cell (WBC) count (26%) with lymphocytopenia (52%) and eosinopenia (98%). Yao *et al.* (46) showed that D-dimer elevation (≥ 0.50 mg/L) was found in 74.6% (185/248) of the patients, and D-dimer level of > 2.14 mg/L predicted in-hospital mortality with a sensitivity of 88.2% and specificity of 71.3%. Al-Samkari *et al.* (47) described that in a multicenter retrospective study of 400 hospital-admitted COVID-19 patients, additional markers at initial presentation predictive of thrombosis during hospitalization included platelet count > 450 × 109/L, CRP > 100 mg/L, and erythrocyte sedimentation rate (ESR) > 40 mm/h. COVID-19-associated coagulopathy (CAC) has characteristics that are unique from bacterial sepsis-induced coagulopathy (SIC) and disseminated intravascular coagulation (DIC) (48). COVID-19-induced coagulopathy (CIC) is characterized by a significant increase in D-dimer and fibrin split products but little or no change in activated partial thromboplastin time and prothrombin time upon presentation (49). Neutrophil extracellular traps (NETs), including cell-free DNA, are higher in severe COVID-19 patients requiring mechanical ventilation, according to Zuo *et al.* (50), and have a substantial correlation with acute phase reactants such as CRP, D-dimer, and LDH. These NETs have the capacity to spread inflammation and microvascular thrombosis. The occurrence of the virus-induced "cytokine storm" has been related to mortality in COVID-19 patients (51). Guo *et al.* (52) showed that, D-dimer rises before the cytokine storm reflected by the IL-6 rise, implying that coagulopathy could operate as a signal to intensify a cytokine storm. COVID-19 infection appears to cause a worse cytokine storm, culminating in widespread micro- and macrovascular thrombosis and organ failure (49). Calprotectin, CRP, IL-1, IL-10, and tumor necrosis factor (TNF-) are all up to 200-fold higher than normal, while IL-6 can be up to 1000-fold higher than normal in recorded cases (26). In the event of SARS-CoV-2, higher innate immune system cytokine levels, such as IL-8 and IL18, are linked to greater severity in men. Females, on the other hand, had a lower severity in line with a larger T-cell activation (10). Within 3 weeks of the onset of symptoms, patients with Covid-19 develop kidney dysfunction, primarily acute kidney injury (AKI), hematuria, and proteinuria. The pathogenesis of AKI can be linked to COVID-specific mechanisms (direct viral entry, unbalanced RAS activation, virally induced proinflammatory cytokines, and thrombotic state) as well as nonspecific pathways (right heart failure, hypovolemia, nosocomial sepsis, nephrotoxic drugs, high PEEP in cases demanding mechanical ventilation and hemodynamic changes) (53). The GI signs seen in COVID-19 are caused by SARS-CoV-2 infection of intestinal enterocytes, which leads to ileum and colon dysfunction. According to multiple studies, people with severe COVID-19 have increased liver enzymes and a higher rate of

liver injury. Patients with abnormal liver function tests, particularly raised alanine aminotransferase (ALT) and aspartate aminotransferase (AST), were also more likely to develop severe pneumonia (54). Wang *et al.* (55) found that, the rate of pancreatic damage was not actually low (17%) among the 52 patients with COVID-19 pneumonia. COVID-19 appears to exacerbate diabetic problems, most likely due to viral-induced pancreatic dysfunction, along with immunological dysregulation, vasculopathy, and coagulopathy (56).

DIAGNOSIS

Antibody tests use lateral flow assays to quickly identify antigens (spike, membrane, or nucleocapsid proteins) or antibodies for COVID-19. Rapid diagnostic tests (RDT), enzyme-linked immunosorbent assays (ELISA), neutralization assays, and chemiluminescent immunoassays are the four main types of antibody tests (57). The companies have centered their efforts on developing ELISA kits for detecting serum antibodies against two S protein domains (S1 and S2). In detecting antibodies from mildly infected COVID-19 patients, the RBD and N ELISA tests were found to be more sensitive than the S1 ELISA test (58). When compared to other testing methods, molecular diagnostic procedures are more appropriate since they target the pathogen's genome or proteome, making them more specific and precise (59). Currently, the gold-standard laboratory test for COVID-19 confirmation in suspected patients is RT-PCR (60). Eight of 13 studies evaluating SARS-CoV-2 viral load in serial upper respiratory tract samples showed peak viral loads calculated based on cycle threshold values within the first week of symptom onset (61). Among 1070 specimens collected from 205 patients with COVID-19, bronchoalveolar lavage fluid specimens showed the highest positive rates (14 of 15; 93%) by RT-qPCR testing followed by sputum (72 of 104; 72%), nasal swabs (5 of 8; 63%), fibro-bronchoscope brush biopsy (6 of 13; 46%), pharyngeal swabs (126 of 398; 32%), feces (44 of 153; 29%), and blood (3 of 307; 1%). None of the 72 urine specimens tested positive (62). Droplet digital PCR (ddPCR) is the most extensively utilized method among different partitioning methods (microwell plates, capillaries, oil emulsion, miniaturized chambers) (63). In the detection of low-viral load samples, digital PCR (dPCR) surpasses RT-qPCR and can be used as a complement (64). Notomi *et al.*[65] created a new method called loop-mediated isothermal amplification (LAMP) in the year 2000, which amplifies DNA with high specificity, efficiency, and rate under isothermal conditions. They used a DNA polymerase and a set of four specially designed primers that recognize a total of six distinct sequences on the target DNA. Rabe *et al.* (66) recently established a sensitive (RT-LAMP) assay compatible with current reagents that used a colorimetric readout in as fast as 30 minutes for SARS-CoV-2 detection. Lau *et al.* (67) designed and optimized a sensitive reverse transcription recombinase polymerase amplification assay (RT-RPA) for the fast detection of SARS-CoV-2 utilizing SYBR Green I and/or lateral flow (LF) strips. In experimental systems, four classes of Clustered regularly interspaced short palindromic repeats (CRISPR)-derived genome editing agents are currently available: nucleases, base editors, transposases/recombinases, and prime editors (68). Cas12a (CRISPR-associated protein 12a) or Cas13a (CRISPR-associated protein 13a) nucleases are used in the most innovative forms of these researches that take advantage of collateral cleavage of single-stranded DNA (Cas12a) or RNA (Cas13a) (63). Broughton *et al.* (69) used the Cas12a method for COVID-19 diagnosis. The assay was created to detect regions in the SARS-CoV-2 E and N genes, and the human RNase P gene as a control (63). the SHERLOCK (specific high-sensitivity enzymatic reporter unlocking) COVID-19 detection methodology based on CRISPR-Cas13 screens for unique nucleic acid targets (SARS-CoV-2 ORF1ab and S genes) and employs a dipstick as a visual readout in less than an hour. Other molecular methods, like microarray assays and viral sequencing (next-generation sequencing) can be utilized for the detection of SARS-CoV-2, however, their application is still restricted (58) (**figure 2**).

PATHOLOGICAL FEATURES

The main target organ of COVID-19 is the lung. The pathological features of COVID-19 are comparable to those of Middle Eastern respiratory syndrome (MERS) coronavirus infection and SARS (70). The lungs are heavy and congested with bilateral interstitial edema. Grossly visible pulmonary emboli and a distinctive patchy gross appearance of the lung parenchyma have been reported (71).

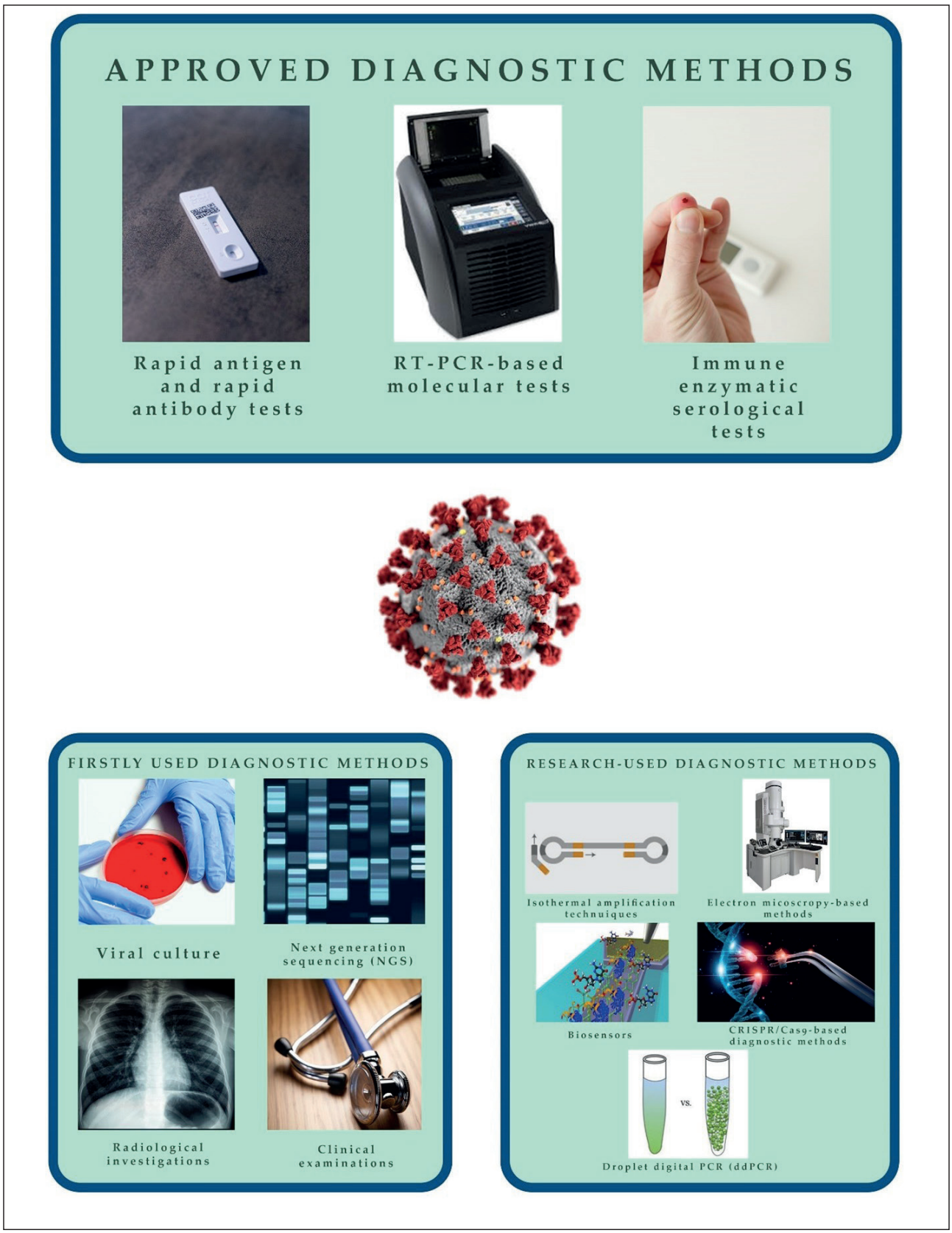


Figure 2. *Overview of the available clinical, diagnostic and research strategies for the effective diagnosis of COVID19 infection.*

Elsoukkary *et al.* (72) showed that the average total lung weight was 1,851 g (reference range = 685-1,050 g) in a postmortem study on 32 patients with COVID-19. Exudative and proliferative diffuse alveolar damage (DAD) were present in most of the patients (n = 24, 75%). The acute stage of DAD, as in other conditions, is marked by the presence of hyaline membranes, while the organ-

izing phase is characterized by variable degrees of the proliferation of fibroblasts and myofibroblasts (73). Pronounced fibroblastic proliferation, partial fibrosis, pneumocyte hyperplasia leading to interstitial thickening and collapsed alveoli, and patchy lymphocyte infiltration were the predominant findings in 10 confirmed cases of COVID-19 in the organizing-stage diffuse alveolar damage according to Schaller *et al.* (74). In areas with organized diffuse alveolar damage, reactive osseous and squamous metaplasia were seen (74). Xiao *et al.* (75) performed gastrointestinal endoscopy for a confirmed COVID-19 patient. Histological examination revealed damage to the mucosa in esophagus, and infiltration of numerous plasma cells and lymphocytes in the lamina propria of the stomach, duodenum, and rectum. The cytoplasm of gastric, duodenum, and rectal glandular epithelial cells were marked with viral nucleocapsid protein, but not in the esophageal epithelium, since ACE2 is rarely expressed in the esophageal epithelium. Lagana *et al.* (76) examined the liver sections of 40 COVID-19 autopsies. Grossly, two livers showed fibrosis and one had abscesses, the remaining livers showed varying degrees of steatosis, congestion, and ischemia. The most common histological findings were, macrovesicular steatosis, mild acute hepatitis, and minimal-to-mild portal inflammation. Santoriello *et al.* (77) showed that, acute tubular injury (ATI) was the most notable renal histologic finding in a group of 42 autopsied patients dying with COVID-19. The degree of ATI was most commonly mild, and ischemia, hypoxia, sepsis-associated factors, and toxin exposure could be suggested as the etiologic factors. Giavedoni *et al.* (78) showed that COVID-19 related cutaneous lesions could be classified into six patterns: Generalized maculopapular (20.7%), Grover's disease and other papulovesicular eruptions (13.8%), livedo Reticularis (6.9%), Other eruptions (22.4%), Urticarial (6.9%), and CHilblain-like (29.3%). In acral chilblain-like lesions, a diffuse heavy lymphoid infiltrate of the dermis, and the hypodermis, with a predominant perivascular pattern are seen (79). Fox *et al.* (80) detected the major gross and microscopic findings of 22 hearts from COVID-19 infection confirmed deaths. The hearts weighed 340-1010 gm. The most significant finding was severe right ventricular dilatation. Marked diffuse single myocyte necrosis was seen on microscopic examination. The endothelial cells of the small arterioles, venules, and capillaries were plump, and immunostaining showed diffuse perivascular infiltration of CD4 and CD8 lymphocytes. Lymphocytopenia, neutrophilia, eosinopenia, mild thrombocytopenia, and less frequently, thrombocytosis (81) are the most frequent hematological findings. Lymphocytopenia appears to be the most important change in the peripheral blood, and it can be used as a marker of severity of the infection (82). Harris *et al.* (83) investigated the bone marrow of 19 autopsied cases. They were all normocellular to hypercellular, with a myeloid shift, and hemophagocytic histiocytes were detected. Xu *et al.* (84) performed postmortem needle biopsies from the spleen on 10 patients who died from COVID-19 in Wuhan. The histopathological examination showed decreased cellularity of the spleen with atrophic white pulps at various ranges. The lymphoid follicles were diminished or nonexistent at all, and the ratio of red pulp to white pulp was variably increased. Liu *et al.* (85) noticed that the 12 postmortem spleens were all contracted and had shrinking capsules. The contracted spleens showed, mixed thrombi, anemic infarction, and hemorrhagic areas. Bryce *et al.* (86) studied the microscopic findings of the thoracic lymph nodes of 60 cases. Sinus histiocytosis was detected in 50 cases, 34 of which showed foci of hemophagocytosis. Germinal centers were lacking in 52 of the 60 lymph nodes. In 142 autopsies, gross brain findings were reported. The most remarkable abnormality was hemorrhage ranging from petechial bleedings to punctate subarachnoid hemorrhages (n = 9), and to massive cerebral or cerebellar hemorrhage (87). SARS-COVID-2 viral particles were found in the frontal lobe of the brain and endothelial cells of the capillaries. Perivascular acute disseminated encephalomyelitis (ADEM)-like picture, and neocortical microscopic infarcts were also observed in autopsy findings (88). Iuga *et al.* (89) revealed adrenal gland findings who described small vessels with acute fibrinoid necrosis, subendothelial vacuolization, and apoptotic bodies. Furthermore, Yang *et al.* (90) studied the 12 post-mortem testicular biopsies, and observed Sertoli cell swelling and detachment from tubular basement membrane, reduced Leydig cells, mild lymphocytic inflammation, and intratubular cellular sloughing. They reported immunohistochemical positivity to markers such as CD3, CD20, CD68, CD138, and ACE-2 as well (91). In another study, the olfactory bulbs were edematous and oval, and microscopic examination showed diffuse edema, inflammatory cell infiltration, severe neuronal degeneration, and

neuronal necrosis. Microglial nodules and scattered degenerative neurons were also observed in the ganglion cell regions (32).

TREATMENT

The most important symptomatic treatment for COVID-19 patients is oxygen therapy (92). The classes of drugs being evaluated or developed for the management of COVID-19 include antivirals, antibodies, anti-inflammatory agents, targeted immunomodulatory therapies, anticoagulants, and antifibrotics (28). The list of drugs for instance, in Tongji Hospital, Wuhan for the treatment of COVID-19 patients was as follows: Interferon-alpha (IFN-α), Lopinavir/ritonavir (LPV/r), Ribavirin, Chloroquine or hydroxychloroquine, Arbidol (93). Long *et al.* (93) showed that starting oxygen treatment less than 2 days following onset of hypoxic symptoms and the using of IFN-alpha among critically ill patients were both linked to a lower risk of COVID-19 mortality. Oral antivirals do not have the side effects of monoclonal antibodies, which must be administered in a hospital setting, and they are far less expensive (94). Remdesivir is a direct-acting antiviral drug that inhibits RNA-dependent RNA polymerase(RdRP) (95). It is an FDA-approved intravenous drug for use in adult and pediatric patients both older and less than 12 years of age for the treatment of COVID-19 requiring hospitalization (96). A 3-day regimen of remdesivir showed a tolerable safety profile among nonhospitalized patients at high risk for Covid-19 progression, and resulted in an 87 percent lower chance of hospitalization or mortality than placebo (97). The US Food and Drug Administration (FDA) issued an emergency use authorisation for Pfizer's COVID-19 antiviral, Paxlovid, on Dec 22, 2021. Paxlovid is a combination of two drugs: ritonavir plus the novel protease inhibitor PF-07321332. Paxlovid inhibits a protease that is needed for replication (98). On December 23, the FDA approved Merck Sharp & Dohme's (MSD) molnupiravir, an oral antiviral. Molnupiravir causes the replicating virus to accumulate mistakes until it can no longer survive (99). Monoclonal antibodies (mAbs) have emerged as valuable tools for treating and detecting a variety of diseases due to their high specificity and reliability. The receptor-binding domain (RBD) of the SARS-CoV-2 spike protein has become a primary target for therapeutic Ab development since it is critical for viral infection (100). Bamlanivimab is a strong neutralizing mAb (IgG1 with an unmodified Fc region) to the S protein that was generated from the convalescent plasma of a patient who had COVID-19 (100). The use of inhaled adenosine in COVID19 patients has resulted in a 6-day reduction in duration of stay. The modifying and regulating activities of adenosine on macrophages could explain its effectiveness (101). Purinergic receptors are important in understanding the COVID-19. P2X7 is one of the receptors recently discussed in COVID-19. It is ionotropic and has an affinity for ATP. P2X7R has been identified as a possible treatment target for COVID-19102 (102). Multiple drugs acting on different signaling pathways such as angiotensin-II receptor antagonists, blockers of RAS pathway, ACE inhibitors, inhibitors of serine protease such as TMPRSS2, and Tocilizumab, and Baricitinib inhibitors of the JAK/STAT pathway have been studied (103). Researchers are interested in the development of JAK inhibitors as a therapeutic intervention in COVID-19. The JAK/STAT pathway is involved in the release of cytokines and chemokines which regulate inflammation in organisms (104). The small molecular inhibitors are known to prevent the interaction of SP with ACE2 and other proteases. Arbidol, a membrane fusion inhibitor authorized for the influenza virus is currently being tested against COVID-19 in clinical trials (105). FDA has approved the emergency use of baricitinib (an oral JAK1/JAK2 inhibitor) (106), in combination with remdesivir, for the treatment of certain hospitalized patients with suspected or laboratory-confirmed COVID-19 (107). Compared with those who received standard treatment alone, 129 patients hospitalized for COVID-19, received tocilizumab (an IL-6 receptor-targeted antibody), in addition to standard treatment, were significantly less likely to need ventilation or die within 2 weeks (92). IL-6 is a major signal transducer and activator of transcription 3 (STAT3) stimulator, particularly during inflammation, and Hojyo *et al.* (108) hypothesize that IL-6-STAT3 signaling is a promising therapeutic target for the cytokine storm in COVID-19. Thromboembolic prophylaxis with subcutaneous low molecular weight heparin is recommended for all hospitalized patients with COVID-19 (28). Studies show that, the use of dexamethasone is associated with a lower risk of invasive mechanical ventilation and, for those already receiving invasive mechanical ventilation, a greater likelihood of early cessation (109). The hospitalized patients in New

York with COVID-19 who were treated with hydroxychloroquine, azithromycin, or both, did not have significant differences in in-hospital mortality compared to those with neither treatment (110). To decrease the virus-ACE2 connection, researchers are using the CRISPR-Cas9 technique to generate point mutations in human ACE2 (111) (**table I**).

Drug	Mechanism of action
Arbidol	Targets S protein/ACE2 interaction Inhibits membrane fusion of the viral envelope
Camostat mesylate	Inhibits TMPRSS2 Prevent viral cell entry
Tocilizumab **Sarilumab**	Bind IL-6 receptor Prevent IL-6 receptor activation Inhibit IL-6 signaling
Chloroquine **Hydroxychloroquine**	Inhibit viral entry and endocytosis by multiple mechanisms as well as host immunomodulatory effects
Lopinavir **Darunavir**	Inhibit 3-chymotrypsin-like protease
Ribavirin **Remdesivir** **Favipiravir**	Inhibit viral RNA-dependent RNA polymerase (RdRp)

Table I. *SARS-CoV-2 Potential Drug Targets* (112).

COVID-19 VACCINES

In the development of vaccines for viral diseases antigens are delivered to induce virus-specific neutralizing antibodies. Additional immunological responses may be needed for effective vaccine-induced immunity for many viruses, including CD4 and CD8 T cells with specific characteristics and positioning (113). Traditional immunization against viral infections is based on the use of the entire pathogen in a weakened or inactivated condition by chemical or physical alterations. To create immunological memory to a particular vaccine antigen, or even a toxin, inactivated vaccines which are replication-deficient or killed viruses or bacteria are administered (114). However, they typically give less protection for a shorter time and induce modest immunological responses, particularly cell-mediated immunity. As a consequence, inactivated vaccinations are given with a powerful adjuvant and require boosters to produce satisfactory and long-lasting immunity (115). Another method for vaccine development is to isolate viral proteins like the spike rather than the entire virus. The immune system reaction to the isolated protein is generally not as strong as it is to the full virus particle, but it is safer and easier to produce. Protein subunit vaccines have a low immunogenicity, and to produce a more robust immune response, an adjuvant must be included in the vaccine formulation (116). In SARS-CoV-2, the T cell response against the S, M, and N subunit proteins was found to be the most prominent and long-lasting (117). Injecting patients with RNA or DNA encoding viral proteins is a more advanced method of vaccine development (118). DNA vaccines are extremely stable and require no refrigeration, making them ideal for use in endemic areas (119). mRNA vaccines are an attractive alternative to traditional vaccine technologies because of their high potency, ability to generate quickly, and potential for low-cost manufacturing and safe delivery. However, owing to the instability and inefficiency of mRNA distribution in vivo, their usage was limited until recently (120). Adenoviruses (Ad) are one of the most widely used vectors for vaccine production, with Ad5 being the most frequently employed non-replicating Ad vector (121). The S protein or RBD subunit of SARS-CoV-2 is expressed in most of the vaccines based on non-replicating Ad5 viral vectors S (117). Because of its safety and lack of pre-existing immunity in humans, the chimp adenovirus (ChAdOx1) is a viable alternative to the human Ad vector (122). Virus-like particles (VLPs) have the same structure as viruses but lack the viral genome and are therefore non-infectious (123). S protein spikes on the exterior of the produced SARS-CoV-2 VLPs make them excellent for vaccine development (124). Unlike subunit vaccines, VLPs are unable to connect directly to B cell receptors to produce (117). Low productivity and high costs limit the use of cell-based vaccinations. For example, a "synthetic mini-gene" producing the SARS-CoV-2 viral proteins S, M, E, N, and polyprotein protease (P) was constructed using a lentiviral vector (LV-SMENP) and transmitted to artificial APCs (APCs) (NCT04276896) (117). Currently, more than 200 COVID-19 vaccine candidates are being developed using a variety of technologies. The two front-runner vaccines based on mRNA platforms, Pfizer/BioNTech BNT162b2 and Moderna mRNA-1273, have been approved by the US Food and Drug FDA for emergency use in mid-December 2020, with reported overall efficacy rates of 95 percent and 94.1

percent, respectively (125).

COVID19 AND ANIMALS

Based on the biological features of bats and the high identity sequence between bat-nCoV and SARS-CoV-2, bats are considered as the natural reservoir of SARS-CoV-2 for now. The intermediate host is thought to be the pangolin. Snakes, minks, and turtles, as well as ferrets and domestic animals, should not be overlooked (126). Hamsters are susceptible to SARS-CoV infection with comparable viral replication in the upper and lower respiratory tract (127). Rosenke *et al.* (128) found that the SARS-CoV-2 RBD has a strong functional interaction with the hamster ACE2 receptor. The pathological features of SARS-CoV-2 infected hamsters' lungs are like those seen in COVID-19 patients. Syrian hamsters are an excellent small animal model for testing vaccinations, immunotherapies, and antiviral medications (129). Mathavarajah and Dellaire (130) used the recently reported crystal structure of ACE2 and the RBD of the SARS-CoV-2 spike protein to try to figure out why dogs are less susceptible to SARS-CoV-2 than cats. They discovered that a mutation at amino acid H34 found solely in dogs (H34Y) and not in feline ACE2 was the fundamental distinction between these domestic pets. As a result, H34 appears to be a crucial residue linked to the species' susceptibility to the SARS-CoV-2 virus. H34Y is thought to reduce ACE2 and SARS-CoV-2 binding affinity. Strong ACE2 expression is found in tracheal and bronchial goblet cells, tracheobronchial submucosal gland serous epithelial cells, and type I and type II pneumocytes in cats. Cats can contract SARS-CoV-2 from their owners and are susceptible to experimental infection. They shed virus in the nasal turbinates, soft palates, tonsils, tracheas, lungs, and small intestines, with the live virus in all these tissues except the intestines and feces, implying minimal virus shedding via that route. There is currently no evidence of *cat-to-human transmission (131).* Other SARS-CoV-2 infections in pigs, dogs, chickens, and tree shrews have shown limited findings, with none demonstrating illness symptoms and only dogs shedding in feces but not tissue. Chickens have a high level of resistance to SARS-CoV, MERS-CoV, and SARS-CoV-2. In ferrets, the pattern of ACE2 expression resembles that in cats, except that it is absent in type I pneumocytes and tracheal and bronchial goblet cells (132). The ferret is a great small animal model that can mimic many of the manifestations of human influenza virus infection (133). Ferrets are a COVID-19 infection and transmission animal model that could aid in the development of SARS-CoV-2 therapeutics and vaccines (134).

COVID-19 AND CANCER

The pathogenesis of COVID-19 and cancer share certain similarities, with both expressing inflammation, immunological dysregulation, and coagulopathy (135). Hematological cancer, lung cancer, and breast cancer patients have more vulnerability toward getting infected with Sars-CoV2 (136). Inflammation is linked to the development of cancer and promotes carcinogenesis (137). Angiotensin-converting enzyme 2 plays an important role in the development of cancer (138). The expression of ACE2 is higher in some cancers such as lung, cervical, pancreatic, and renal carcinomas, while the expression is decreased in breast, prostate, and liver cancers. Patients, particularly with prostate cancer, have higher expression of TMPRSS2 as compared to patients with renal, lung, colorectal, or pancreatic cancers, while other cancers have no significant expression of TMPRSS2 (139). COVID-19 cancer patients had much higher mortality and severe disease than the general population, according to data from the COVID-19 and Cancer Consortium (CCC19) cohort study, which comprised 1,018 patients (92). A year after the COVID-19 outbreak and the initial lockdown, it is apparent that the disease has taken a high toll on cancer patients, affecting every stage from screening to diagnosis, and treatment (140). Around 40000 fewer people than normal started cancer treatment in the UK last year, and US hospitals have been deluged by COVID-19 cases, rendering patients with cancer unable to obtain timely care. WHO has reported that one in three European countries had partially or completely interrupted cancer care services early in the pandemic (141). The COVID-19 diagnostic delay in the UK is expected to result in a 9.6% rise in breast cancer deaths, 16.6% increase in colon-rectal cancer deaths, 5.3 percent increase in lung cancer deaths, and 6.0 percent increase in esophageal cancer deaths during the following 5 years (142). A survey of 155 countries by WHO found that 42% of countries had disruption of services for cancer prevention and treatment; the degree of disruption

was proportional to the extent of the pandemic in that country. The possible cause of this high risk to cancer patients with COVID-19 is surely the immunocompromised state of the patient (143). Coronavirus pneumonia brought about a 24% mortality in individuals with cancer while a 3% mortality was observed with noncancer patients (144). Most cytotoxic agents used in chemotherapy cause bone marrow suppression which could ultimately result in thrombocytopenia and neutropenia, this further makes cancer patients more susceptible to infections (144). Radiation therapy has also been reported to damage lymphocytes resulting in lymphopenia (145). In Northern Italy, the study conducted on 25 patients with cancer and COVID-19 showed a high mortality rate of about 36% compared to 16.13% in non-cancerous COVID-19 patients, and lung cancer was prominent among cancer patients (146). A study in a New York hospital system and a multicenter study in China demonstrated that patients with lung cancer had a higher risk of adverse outcomes when compared with other cancer types (147). According to Dai *et al.* (148), lung cancer was the most common cancer histology in infected patients (20.95%), followed by gastrointestinal cancer (12.38%), breast cancer (10.48%), thyroid cancer (10.48%), and hematologic cancer (8.57%) of 105 patients. The incidence of mortality in lung cancer patients infected with SARS-CoV-2 was reported to be up by four times (146). Although patients receiving chemotherapy appeared to be at a higher risk of severe illness from COVID-19, delaying chemotherapy is not advised, whereas individuals receiving only radiotherapy showed no significant differences in severe events when compared to individuals without cancer (92). The likelihood of radiotherapy being preferred by clinicians to other forms of cancer treatment is supported by the fact that in the UK, radiotherapy services decreased by only 10% during the 10-week lockdown from March to May 2020, compared with a 40% reduction in surgery (143). Data from both Italy and Latin America suggest that delivery of radiotherapy services was less affected than other modalities (143). Depending on the stage of illness, the progression of cancer can be a challenge for delaying procedures in cancer patients. Delays in the case of prostate, breast, cervical, or skin cancer in early stages can be tolerated but pancreatic, lung and hematological cancers such as leukemia require treatment as soon as possible (146). To avoid more suffering to patients from the deadly pair of COVID-19 and cancer, oncologists along with cancer societies, advise putting cytotoxic chemotherapy on hold and waiting until the SARS-CoV-2 virus becomes negative in the body (149). Cancer treatment regimens that do not affect outcomes of COVID-19 in cancer patients may not need to be altered (150). The presence of COVID-19 with malignancy makes diagnosis extremely challenging. Diagnosis of radiographs can be similar in both COVID-19 and cancer which may deceive the healthcare professional in making an accurate diagnosis (146). Carbohydrate antigens (CA) 125 and 153, carcinoembryonic antigens (CEA), human epididymis protein 4 (HE4), CRP, and cytokeratin-19 fragment (CYFRA21-1) are common markers in both COVID-19 and cancer; these markers are raised in both COVID-19 and cancer (146). Cancer patients are at a higher risk of both arterial and venous thromboembolism, especially if they are undergoing systemic chemotherapy (151). Cancer affects one's immune system and physiology through higher D-Dimer, lower levels of albumin, longer prothrombin time, and higher neutrophil counts (152). Sallah *et al.* (153) evaluated the occurrence of DIC in 1117 patients with solid tumors. Of these patients, 76 (6.8%) were diagnosed with DIC. Thrombocytopenia, hypofibrinogenemia, elevated D-dimer and, fibrinogen degradation products were the most common coagulation abnormalities encountered in patients with DIC. Tumoral factors such as tissue factor (TF), podoplanin, plasminogen activator factor (PAI-1), cytokines, NET, and mucins trigger the risk for thrombosis (146). The type of cancer changes with the severity of coagulation, *e.g.*, adenocarcinomas, lung cancer, pancreatic cancer, gastrointestinal cancer, and ovarian cancer have elevated risk for coagulation, while the risk is lower in breast and renal carcinoma compared to no risk associated with prostate cancer and melanoma (146). Cancer and COVID19 treatments generally have similar goals, and several anti-cancer medications are being examined in clinical trials to see whether they might be repurposed for COVID-19 (154). Recombinant IFNγ and IFNα2b have been widely utilized to treat cancer, and IFN administration has emerged as a promising treatment for COVID-19 (155). Cancer immunotherapy includes pharmaceuticals such as immune checkpoint inhibitors and monoclonal antibodies (MAbs), immunogene therapy, cell therapy, and vaccines (156). The same treatment regimen that is utilized to prevent or lessen cytokine storm in cancer patients receiving CAR-T cell therapy could be

used to lower the risk of cytokine storm in COVID-19 patients. As a result, antibodies that target the IL-6 receptor (tocilizumab and sarilumab), IL-6 (siltuximab), and other receptor antagonists (α1-adrenergic receptor antagonist, prazosin) for preventing cytokine storm are useful therapeutic options for the treatment of cancer patients with COVID-19 (157). PD1 inhibitors are immune checkpoint inhibitors (ICI), which have gained potential importance in solid cancer treatment (158). Reduction in sepsis or infection after pneumonia and inflammatory response syndrome was observed in COVID-19 patients administered with PD-1 inhibitors (146). ICIs would likely to be a protective factor against the onset of COVID-19 infection (159). Ruxolitinib a Janus-associated kinase (JAK) inhibitor has been reported to reduce cytokine-mediated inflammation, reducing severe events such as ARDS in COVID-19 infected patients, and many trials are currently active (146).

CONCLUSIONS

The results of COVID-19 imply that heavy polluters must act quickly and strongly on climate change to prevent a far more hazardous future and a more difficult recovery course (160). The COVID-19 dilemma teaches us a lot about what to expect in the forthcoming global climate crisis. Global emergencies are not new, but our ability to understand, avoid, and respond them has never been better (161). The only safe method to deal with COVID is to develop a vaccination, and the only way to combat climate change is to convert to a low-carbon system (162). Medications now being evaluated for COVID-19 repositioning can be divided into two categories: 1) medications that may impede one or more steps of the coronavirus lifecycle, and 2) drugs that may counteract the consequences of SARS-CoV-2 infection, such as the heightened immune response and massive cytokine release (163). More effective vaccines will need to be developed specifically for immunocompromised individuals. Several anti-cancer medications, in addition to antiviral and anti-inflammatory medications, could be repurposed to treat COVID-19 (154). SARS-CoV-2 can infect a wide range of animals. Several animal models, including the mouse, hamster, cat, ferret, and monkey, have been identified as suitable for evaluating the efficacy and safety of antiviral medicines or testing experimental vaccinations against SARS-CoV-2 (164).

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Authors' contribution

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