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Review article

Insight into COVID-19's epidemiology, pathology, and treatment

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ABSTRACT

The newly emerged 2019 coronavirus disease (COVID-19) has urged scientific and medical communities to focus on epidemiology, pathophysiology, and treatment of SARS-CoV-2. Indeed, little is known about the virus causing this severe acute respiratory syndrome pandemic, coronavirus (SARS-CoV-2). Data already collected on viruses belonging to the *coronaviridae* family are of interest to improve our knowledge rapidly on this pandemic. The current review aims at delivering insight into the fundamental advances inSARS-CoV-2 epidemiology, pathophysiology, life cycle, and treatment.

1. Introduction

On October 12, 2020, up to 37,423,660 cases of coronavirus disease 2019 (COVID-19) and 1,074,817 deaths were reported by the World Health Organization (WHO) (https://COVID19.who.int/). This new pandemic has urged the world, especially the scientific community, to understand epidemiology and pathogenesis and develop adequate treatments quickly. The first suspected human infection by a *Coronaviridae* family member dates back to the last century's third decade (Almeida and Tyrrell, 1967; Henry, 2020). The virus causing severe acute respiratory syndrome coronavirus two (SARS-CoV-2) shares several common features with known coronaviruses (Cascella et al., 2020), especially its zoonotic origin, infection route, and genetic organization. Epidemiological, clinical, and pathophysiological findings reveal the characteristics of stars-CoV-2 that make it the family's most virulent and contagious coronavirus.

2. Historical aspects and common features

2.1. Historical insight into coronaviruses

In 1937, Fred Beaudette and Charles Hudson identified a coronavirus, avian bronchitis virus (IBV), isolated from birds (Henry, 2020). Thirteen years later, in 1967, June Almeida and David Tyrrell isolated two strains from human nasal epithelium and trachea, HCoV229E and B814, that share significant identities with the IBV(Almeida and Tyrrell, 1967). The term "coronavirus" was firstly introduced by Almeida because of the "solar corona" shape disposition due to the surface viral glycoprotein spikes, as revealed under electronic microscopic examination. HCoV 229E and HCoV OC43, known as beta coronaviruses, are the first human coronaviruses to be identified: they cause mild respiratory tract infections (Bradburne et al., 1967; McIntosh et al., 1967; Medicine, 1962). Since the late sixties, the pace of research on coronaviruses has slowed down, settling only for some routine monitoring on humans. As a result, information on human coronavirus's (HCoVs) effect on the respiratory

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tract is underestimated, and epidemiological data were scarce. In 2003 new studies on the clinical features of HCoV infections were launched, following the emergence of new HCoVs causing severe acute respiratory syndrome (SARS, induced by SARS-CoV). These have emerged in Guangdong, China, in 2002 and then quickly spread worldwide, causing 8437 infections and 813 deaths (Zhong et al., 2003). Two new HCoV family members were after that further identified, HCov-NL63 in New Haven in 2004 (Fouchier et al., 2004; Van Der Hoek et al., 2004) and CoV-HKU1 in 2005, in a 71-year-old man with pneumonia after returning from Shenzhen, China (Woo et al., 2005). These viruses spread worldwide with a short incubation time during the winter (Gerna et al., 2006). The most vulnerable targets for these viruses are newborns, infants, immunosuppressed and elderly patients (Falsey et al., 2002). Another outbreak occurred in Saudi Arabia in September 2012, implying a Betacoronavirus genus member and causing the Middle East respiratory syndrome (MERS) (Assiri et al., 2013). Since 30 November 2019, the WHO reported 2494 infections related to MERS-CoV with 858 associated fatalities (https://www.who.int/). On December 31, 2019, a new cluster of pneumonia developed in Wuhan city in Hubei Province, China. Laboratory analyses reported the emergence of a new CoV species that was not genetically related to MERS-CoV, influenza, avian influenza, adenovirus, or other common respiratory pathogens, SARS-CoV. The virus was named 2019-nCoV, but subsequently, the International Committee on Taxonomy of Viruses (ICTV) termed it the SARS-CoV-2 virus, as it shows similarities to SARS-CoV (Cascella et al., 2020).

2.2. Coronavirus family, common features

Coronaviruses, such as SARS-CoV, MERS-CoV, and the newly identified SARS-CoV-2, are highly contagious pathogens. They cause lethality in humans. Thus, they become pathogens responsible for outbreaks of respiratory diseases, with a solid ability to cross species barriers and spread human-to-human infection. All human-infecting CoVs have a zoonotic origin. Bats are believed to be their evolutionary reservoir hosts for 229E, NL63, SARS-CoV, MERS-CoV, and SARS-CoV-2 (Zhou et al., 2020b). However, OC43 and HKU1 would originate from rodents, and the ancestors of OC43 were also isolated in swine and cattle (Kissler et al., 2020).

Moreover, bovine CoV (BCoV) and OC43 share a common ancestor dating to 1890, suggesting a recent zoonotic transmission (Vijgen et al., 2005). Similarly, it is suggested that MERS-CoV and 229E are transmitted to humans from dromedary camels. Nonetheless, it is supposed that humans and camels may have both acquired 229E from a host yet to be identified (Corman et al., 2018). Although SARS-CoV-2 is of animal origin namely, *Rhinolophus affinis* (bat) or *Manis javanica* (Malayan pangolins), genomic analysis demonstrates that no identified coronavirus present a sufficient level of identity with SARS-CoV-2 to be its direct ancestor (Andersen et al., 2020; Liu et al., 2020b). Habitats of pangolins are close enough to human living areas, outweighing the possibility of direct infection from bats to humans. Therefore, an intermediate animal host might have transmitted SARS-CoV-2 to humans, proposed as pangolin, since the pangolin CoV shares 85.5%–92.4% sequence similarity with SARS-CoV-2 (Lam et al., 2020). The same transmission scenario is thought to have occurred in previous CoV pandemics, i.e., the intermediate animal host might be civet for SARS-CoV and camel for MERS-CoV (Corman et al., 2018).

2.3. Genetic material

Coronaviruses (CoVs) are single-stranded, positive-sense RNA viruses that belong to Nidovirales, the Coronaviridae family, the Coronavirinae subfamily (De Groot et al., 2012). Data from molecular biology showed that the CoVs genome is the largest among the other RNA viruses with 26–32 kilobases (Woo et al., 2005, 2007, 2009). The coronavirinae subfamily is split into three genera, namely alpha-CoVs, beta-CoVs, and Gamma-CoVs (Figure 1) according to the variation of the genetic makeup and antigenic reactivity (Cleri et al., 2010; Gorbalenya et al., 2004; Shereen et al., 2020; Woo et al., 2010). In addition, other new Coronaviruses are documented in birds and pigs. While the human pathogenic strains are: alpha-CoVs (HCoV-229E and HCoV-NL63), beta-CoVs (HCoV-HKU1, HCoV-OC43, SARS-CoV), and MERS-CoV (Cortellis, 2020). Oher alpha and beta-CoVs such as Swine acute diarrhea syndrome (SADS-CoV), porcine transmissible gastroenteritis virus, and porcine enteric diarrhea virus (PEDV), may present a risk for livestock (Brian and Baric, 2005; Lin et al., 2016; Zhou et al., 2018).

The CoVs single-stranded RNA molecule's consists of 5′-capped of 26–32 kb with at least six open reading frames (ORFs) for which the first one, ORF1a/b, contains approximately two-thirds of the genetic information and codes for replicase proteins (Figure 1). The other one encodes the structural proteins S, E, and M, along with nucleocapsid (N) proteins (Fung et al., 2020). Also, proofreading exoribonuclease (ExoN) ensures the fidelity of RNA synthesis by reducing replication errors (Ogando et al., 2019).

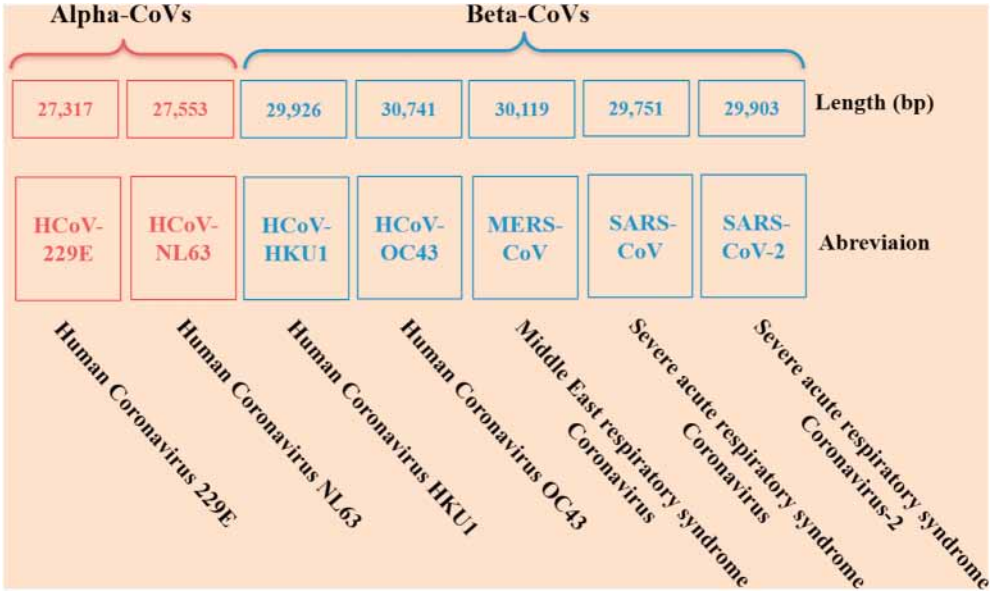

Figure 1. Genetic comparison of the various coronavirus (modified according to Kaur et al., 2020).

3. COVID-19 epidemiology, diagnosis, and clinical features

3.1. COVID-19: from silence to pandemic

At the end of December 2019, many people were hospitalized with unknown etiology pneumonia. Diagnosis and epidemiological analysis linked their infection to the seafood and wet animal market in Wuhan, Hubei Province, China (Bogoch et al., 2020). Subsequently, reports presumed a potential outbreak caused by a new coronavirus, called SARS-CoV-2, with a reproductive number ranging from 2.24 - 3.58 (Zhao et al., 2020). The initial timeline of the SARS-CoV-2 infection in China is described (Rothan and Byrareddy, 2020). Initially, five patients (one died) with acute respiratory distress syndrome were admitted to the hospital between December 18–29, 2019 (Ren et al., 2020). The WHO China country Office received the first report on the cluster on December 31, 2019. On January 2, 2020, 41 patients from the same hospital were diagnosed positive for COVID-19, among whom more than half had underlying diseases such as cardiovascular diseases and diabetes (Huang et al., 2020). Hence, a nosocomial infection of SARS-CoV-2 is presumed to have occurred in this hospital (Rothan and Byrareddy, 2020). By January 22, the total number of reported infections reached 571 positive cases and 17 deaths in 25 Chinese provinces (Lu, 2020). A few days later, on February 12, 2020, this number increased exponentially to reach 52, 526 cases, of which 1367 died, according to the reports from 31 Chinese provinces. By 23 March 2020, the number of newly confirmed cases decreased to 78 in the 31 mainland Chinese provinces (National Health Commission of People's Republic of China, 2020).

SARS-CoV-2 infections have drastically spread worldwide to become a global pandemic (Zhang et al., 2020a). As of January 30, 2020, the WHO reported 82 new confirmed cases outside China, including Japan, the Republic of Korea, Vietnam, Singapore, Australia, Malaysia, Cambodia, the Philippines, Thailand, Nepal, Sri Lanka, India, the United States of America, Canada, France, Italia, Finland, Germany, and the United Arab Emirates. Since then, the occurrence of COVID-19 cases has grown exponentially, reaching on March 22, 2021, a total of 122 992 844 confirmed cases with 2 711 021 death worldwide, distributed as 54 127 466 in the Americas, 42 674 788 in Europe, 14 236 990 in South-East Asia, 3 006 474 in Africa and 1 786 689 in Western Pacific (https://www.who.int/).

3.2. Clinical features and diagnosis of COVID-19

Symptoms of COVID-19 are multiple and highly heterogeneous in their distribution. Hence, the large majority of patients experience fever (83–99%), cough (59–82%), fatigue (44–70%), anorexia (40–84%), shortness of breath (31–40%), sputum production (28–33%) and myalgia (11–35%) (Guan et al., 2020; Huang et al., 2020; Pan et al., 2020). Among minor symptoms expressed at the early stage of the infection, 2/3 of COVID-19 patients develop a sudden onset of many smells and taste impairment, a phenomenon stated to be reversible after recovery (Moratto et al., 2020). These characteristics of anosmia and ageusia appear to be specific to COVID-19, unlike the other symptoms indicative of a viral infection. Infrequently, these symptom manifestations are mild, with heart palpitations and thoracic tightness instead of respiratory distress. In many cases, symptoms of COVID-19 can be atypical or may show a delay in the presentation of fever and respiratory symptoms, especially in older people (Zhou et al., 2020a) or patients with medical comorbidities (Yang et al., 2020a, b). A study performed in China demonstrates that out of 1099 patients, only 44% present fever at hospital admission, but it reaches 89% during hospitalization (Guan et al., 2020). Some studies point that less than 10% of patients presented headache, sore throat, rhinorrhea, diarrhea, confusion, hemoptysis, and vomiting (Chen et al., 2020a, b, c; Guan et al., 2020). Additionally, gastrointestinal symptoms such as nausea and diarrhea occur before lower respiratory tract symptoms and fever (Pan et al., 2020). A plethora of characteristics regarding the host genetic impacting the immunology may relate to such diversity in clinical signs. The incubation period varies among patients but reaches up to 14 days with a median time of 4–5 days (Guan et al., 2020; Lauer et al., 2020).

4. Host cell entry, infection routes, transmission, genetic variation, and risk factors

4.1. SARS-CoV-2 entry to the host cells

A body of evidence sustains the functional similarities between SARS-CoV and SARS-CoV-2 interaction with the host receptors. Both viruses can recognize the human angiotensin-converting enzyme ACE2 (hACE2) (Letko et al., 2020; Li, 2013; Wan et al., 2020). However, X-ray crystallography of the SARS-CoV-2 binding receptor domain (RBD)-hACE2 complex revealed critical functional differences between the two SARS-CoV viruses regarding the receptor recognition affinities (Shang et al., 2020). Accordingly, SARS-CoV-2 RBD shows a higher binding affinity to hACE2 than SARS-CoV RBD (Shang et al., 2020).

Protease activators for SARS-CoV-2 entry were studied as well. Indeed, the TMPRSS2 and lysosomal proteases have been qualified as necessary for the virus entry (Hoffmann et al., 2020; Ou et al., 2020). Moreover, studies reported that the SARS-CoV-2 spike contains a proprotein convertase (PPC) motif at the S1/S2 boundary, associated with increased pathogenicity for influenza viruses (Tse et al., 2014). However, PPC cleavage does not appear to interfere with SARS-CoV-2 host cell entry (Walls et al., 2020).

4.2. Shedding and human-to-human routes of SARS-CoV-2 transmission

4.2.1. Shedding

Understanding the dynamics of SARS-CoV-2 shedding is essential for public health policy to design appropriate strategies to control the COVID-19 pandemic. However, only a few studies reported the presence of SARS-CoV-2 RNA in the respiratory tract up to 21–24 days post-infection, during hospitalization of mild or severe COVID-19 patients (Zhou et al., 2020a). During convalescence, in symptomatic and asymptomatic COVID-19 patients, Li et al. (2020a, b, c) carried out in China on a total of 18 SARS-CoV-2 positive patients. The study showed a long-term intermittent SARS-CoV-2 shedding in the respiratory tract in symptomatic and asymptomatic patients. The viral RNA and specific antibodies were detected during convalescence in 27.8% of the patients. The average length of virus shedding was 11.5 days in pre-symptomatic, 28 days in asymptomatic, and 31 days in mildly symptomatic COVID-19 patients. Besides, 38.9% of the patients maintained virus shedding after hospital discharge (Li et al., 2020b).

4.2.2. Transmission route

Previous studies reported the central role of respiratory and close contact in human-to-human SARS-CoV-2 transmission. Indeed, respiratory droplets and even in saliva generated from the human naso-oral route; coughing, sneezing, breathing, and even normal speaking (Anfinrud et al., 2020), may carry the viral particles leading to SARS-CoV-2 transmission by asymptomatic individuals (Wei et al., 2020). Also, the virus may be transmitted through contact of the facial T-zone with contaminated objects or fomites.

Airborne transmission of the SARS-CoV-2 is another route of infection. Despite being conflicted, previous studies showed the presence of SARS-CoV-2 particles in air sampling from closed environments, sustaining the airborne SARS-CoV-2 transmission (Zhang et al., 2020d).

Another viral transmission route may be nosocomial infections (Ong et al., 2020). For example, Luong-Nguyen et al. (2020) reported that in patients admitted to the digestive surgery department s from March 1 to April 5, 2020, 4.9% developed evident nosocomial infection with SARS-CoV-2 (Luong-Nguyen et al., 2020).

Also, intra-family transmission is documented showing that 16.3% of household transmissions were reported by household contact tracing of index COVID-19 cases (Rickman et al., 2021).

Other studies sustain the possible fecal-oral transmission of the virus. Indeed, SARS-CoV-2 viral RNA has been reported in infected patients' feces and toilet bowls in hospital environments (Chen et al., 2020b; Ong et al., 2020). Furthermore, support for such a hypothesis is provided by ACE2 in the human gut, facilitating the replication and survival of SARS-CoV-2 (Luo et al., 2020).

ACE2 in the placental villi and the uterus supports a possible vertical transmission of SARS-CoV-2 from mother to fetus. A previous study had examined samples from the pharynx of a newborn infant on the day of birth. The authors reported the presence of IgM and IgG antibodies against SARS-Cov-2, while PCR was negative for the newborn and the mother's vaginal discharge (Dong et al., 2020). Other reports pinpoint the presence of 3 SARS-CoV-2 positive newborns at day two post-natal among the 33 newborns of COVID-19 positive pregnant women (Zeng et al., 2020).

4.3. Genetic variants of SARS-CoV-2

From its emergence, several mutations are described for the SARS-COV-2 (Wang et al., 2020a), and hotspots of substitution/mutations are identified to be at positions 8750 and 28 112 (Zhang, Yang, Zhang and Lin, 2020c). The analysis of 95 SARS-CoV-2 genomes revealed the presence of 13 different mutations in the following regions: ORF1ab, S, 3a, M, ORF8, and N (Wang et al., 2020a). Studies on SARS-CoV-2 genomes from European countries reported the primary hotspots in positions 14 408, 23 403, 3036, whereas, in isolates from American and Canadian countries, only two positions appear to be hotspots for mutation in the SARS-CoV-2 genome (Pachetti et al., 2020).

4.3.1. The D614G variant

SARS-CoV-2 variant D614G have emerged in late January of 2020 (Korber et al., 2020). A glycine substitution characterizes this variant for the aspartic acid at position 614 of the spike glycoprotein (Korber et al., 2020; Morais et al., 2020). Patients infected with the D614G variant present higher viral loads in the upper respiratory tract (Korber et al., 2020). In addition, the D614G variant has increased infective capabilities (Korber et al., 2020). However, the D614G mutation does not impact SARS-CoV-2 pathogenesis (Hou et al., 2020), and patients infected with this variant did not show changes in disease severity (Korber et al., 2020).

4.3.2. The VOC 202012/01 variant

The Variant Of Concern (VOC) 202012/01 derived from the 20I/GR SARS-CoV-2 clade (also known as B.1.1.7 or 20I/501Y.V1) in southeast England, September 2020, and became prevalent in November/December 2020. The VOC 202012/01 has an estimated 40–70% increase in transmissibility compared to other variants (J. W. Tang, Tambyah and Hui, 2021). This variant has multiple mutations in the spike protein (deletion 69–70, deletion 144, substitutions N501Y, A570D, D614G, P681H, T716I, S982A, and D1118H) as well as mutations in other genomic regions (Fiorentini et al., 2021). Three mutations, namely N501Y, ΔH69/ΔV70, and P681H, are located in the S protein. The N501 residue of the S protein is one of the six critical amino acids interacting with the ACE2 receptor (Wan et al., 2020). The N501Y mutant demonstrated a significant increase in ACE2 binding affinity. The ΔH69/ΔV70 have been circulating for a long time (Kemp et al., 2021). Mutation ΔH69/ΔV70 is unlikely to increase the risk of viral escape from neutralizing antibodies, and the ΔH69/ΔV70 has either a similar sensitivity to neutralization by convalescent plasma as the wild type (Kemp et al., 2021) or increased sensitivity to neutralization by sera from mRNA-1273 (Moderna) vaccinated people (Shen et al., 2021). However, ΔH69/ΔV70 could lead to diagnostic failure by the Thermopath TaqPath test targeting the S gene (Wan et al., 2020). The P681H mutation locates near the furin cleavage site, which is essential for SARS-CoV-2 entry (Davies et al., 2021).

4.3.3. The 501Y.V2 variant

The 501Y.V2 (also called B.1.351 or 20H/501Y.V2) presents increase transmissibility. It emerged during the first outbreak in the Eastern Cape of South African in 2020 (Tegally et al., 2020). It became the predominant viral lineage in the Eastern and Western Cape by the end of November 2020 (Tegally et al., 2020). This variant was detected in 48 countries worldwide by March 2021. 501Y.V2 includes three substitutions in the receptor-binding domain (RBD) (K417N, E484K, and N501Y), five in the N-terminal domain (NTD) (L18F, D80A, D215G, R246I, and deletion at 242–244) and one in the S2 subunit (A701V). These confer partial or complete resistance to convalescent plasma and some monoclonal antibodies (mAbs), including class I/II mAbs directed against RBD and 4A8 that targets NTD (Wibmer et al., 2021).

4.3.4. The spike N453Y variant

It is also called cluster 5 variant or ΔFVI-spike and was first detected in North Jutland, Denmark, from August to September 2020. It is transmitted from mink to humans in mink farms. Five mutations in the S protein are characteristic of this mutant: Y453F, an H69/V70 deletion (ΔH69/ΔV70), I692V, S1147L, and M1229I. This variant may lead to decreased susceptibility to neutralizing antibodies which may cause a reduction in the duration of the immune protection conferred by vaccination or the natural course of infection (Focosi and Maggi, 2021).

4.3.5. The P.1 variant

The P.1 variant, derived from B.1.1.28 lineage, also shares similar close properties with N501Y.V2 (Moore and Offit, 2021). The first case of P.1 lineage, found first in Aracaju (Sergipe), Brazil, on 17 January 2021, emerged from multiple S protein mutations of known biological importance (K417T, E484K, and N501Y). Significantly, this has been associated with increased transmissibility (dos Santos et al., 2021).

4.4. Risk factors of COVID-19

Children and young adults are likely to have lower susceptibility and increased resistance than the elderly, adults, and newborns. Children and adolescents with no underlying conditions, like lung function impairment, immunosuppression… seem to present a lower vulnerability to SARS-CoV-2 infection, and they often develop a mild disease (Brodin, 2020). However, an impaired immune system response favors SARS-CoV-2 propagation and massive destruction of tissues (see the section “pathogenesis of COVID-19”), which may explain the severity of cases among elderly and infected patients with comorbidities. Increased exposure to the virus and increased viral load may also enhance the disease's severity. It is worth noting that Ellinghaus and colleagues (Ellinghaus et al., 2020) conducted a large genome-wide association study on more than 1900 patients with severe COVID-19 symptoms (with respiratory failure). They identified two genomic regions associated with severe COVID-19 disease. The first one is located on chromosome 3 (locus 3p21.31) and includes six genes. According to Zeberg et Pääbo, a genomic segment of about 50 kb, inherited from Neanderthals confers the risk (Zeberg and Pääbo, 2020). The second one is found on chromosome 9 (locus 9q34.2), corresponding to the ABO blood groups (higher risk in blood group A and protective effect in blood group O).

5. Life cycle and pathogenesis

5.1. SARS-CoV-2's life cycle

The life cycle of SARS-CoV-2 starts with binding the RBD of the surface spike glycoprotein (S protein) to ACE2 (Zhou et al., 2020b). The binding requires the transmembrane serine protease 2 (TMPRSS2) intervention, which triggers the S protein's proteolytic cleavage into subunits S1 and S2 for its activation (Hoffmann et al., 2020). This cleavage is indispensable for the interaction between SARS-CoV-2 and ACE2. The S1 segment allows the virus's attachment to ACE2, while the

S2 segment permits fusion of the cellular and SARS-CoV-2 membranes (T. Tang, Bidon, Jaimes, Whittaker and Daniel, 2020) (Figure 2).

The entry into the host cell relies on the endocytic autophagic pathway, a mechanism that has been widely investigated in other SARS-CoVs members. This process is controlled by several proteins, operating mainly in three consecutive stages. First, the ULK1/Atg 1 complex is engaged and localized to the pre-autophagosomal structure (PAS), regulating the initiation stage. Second, during the nucleation-elongation-maturation stages, ATG proteins and lipids are recruited to form phagophores which undergo an elongation by wrapping and engulfing the cytoplasm organelles. Once completed and maturated, the autophagosome is then transported. Third, autophagosomes and lysosomes underwent a fusion stage to form autophagolysosomes. Finally, degradation is the final stage wherein a breakdown of the cargos inside the autolysosome occurs (Figure 2). See (Li et al., 2020c) for review.

After encoding and releasing the (+) ssRNA, the replication complex's expression within the virion genomic RNA leads to encoding two open reading frames (ORFs), rep1a and rep1b, by a replicase. Two co-terminal polyproteins are produced, pp1a, and pp1ab, which encode the S, M, E, and N proteins vital for viral protein integrity (Fehr and Perlman, 2015). The ORF pp1ab also encodes essential non-structural proteins involved in producing the replicase machinery, Nsp 1-16. Meanwhile, the synthesized replicase is then cleaved by 3-chymotrypsin-like proteinase (3CLpro) and papain-like proteinase (PLpro) to produce functional and effective Nsp1-16, that is a replicase–transcriptase complex (RTC) deployed in viral replication and transcription (Hilgenfeld, 2014). The RTCis involved replicating and transcribing subgenomic RNAs(Fehr and Perlman, 2015). Nsps have additional enzyme domains and functions, such as Nsp 12, which encodes the RNA-dependent RNA polymerase (RdRp) domain (Astuti and Ysrafil, 2020). Thus, the replication of SARS-CoV-2's (+) ssRNA produces new viral proteins along a path that follows the general steps attached: the synthesis of RNA, proofreading of a template, and capping. In the host's endoplasmic reticulum and Golgi apparatus, the associated proteins and viral RNAs are assembled to form virions of SARS-CoV-2. Subsequently, the assembled virions travel in vesicles to the cell membrane, releasing them by exocytosis (Malik, 2020) (Figure 2).

5.2. Pathogenesis

The pathogenesis induced by SARS-CoV-2 relies on ACE2, which is a membrane protein that usually regulates the renin-angiotensin system (RAS), a mechanism in which the signaling of angiotensin II (Ang II) is central (Bahat, 2020). Indeed, the binding of SARS-CoV-2 to ACE2 and TMPRSS2 is followed by the fusion of the virus with the plasma membrane and endocytosis (Hoffmann et al., 2020; Zhou et al., 2020b). The association between viral spikes and ACE2 decreases the activity and expression of ACE2, therefore reducing its physiological function, which is detailed in the following section. The respiratory tract's epithelial cells express substantiallevels of ACE2, especially type II pneumocytes, where alveoli infection is the leading cause of COVID-19 morbidity (Zhao et al., 2020a; Zhou et al., 2020b). Because several other organs express this membrane-integrated protein, the infection can spread from there to many organs. Also, in some patients, an exacerbated immune response, including severe inflammation and cytokine activation, can lead to respiratory and multiple organ failure, resulting in death in some cases. The decreased activity and expression of ACE2 by SARS-CoV-2 promote pathological alteration underlying the most frequently observed COVID-19 symptoms. Thus, the RAS plays a crucial role in the disease's genesis following infection with SARS-CoV-2. Understanding the pathophysiology of COVID-19 provides a good understanding of the RAS implications and the physiological changes that follow the interaction of SARS-CoV-2 with ACE-2.

5.2.1. Overview of RAS activity and role of ACEs

The SARS-CoV-2 accesses host cells because of the ACE-2 proteins. High levels of angiotensin II in the plasma of COVID-19 patients have been correlated with the severity of lung injury and viral load (Liu et al., 2020a), highlighting RAS's importance in pathogenesis. RAS plays an essential physiological role in systemic homeostasis. It is also involved in

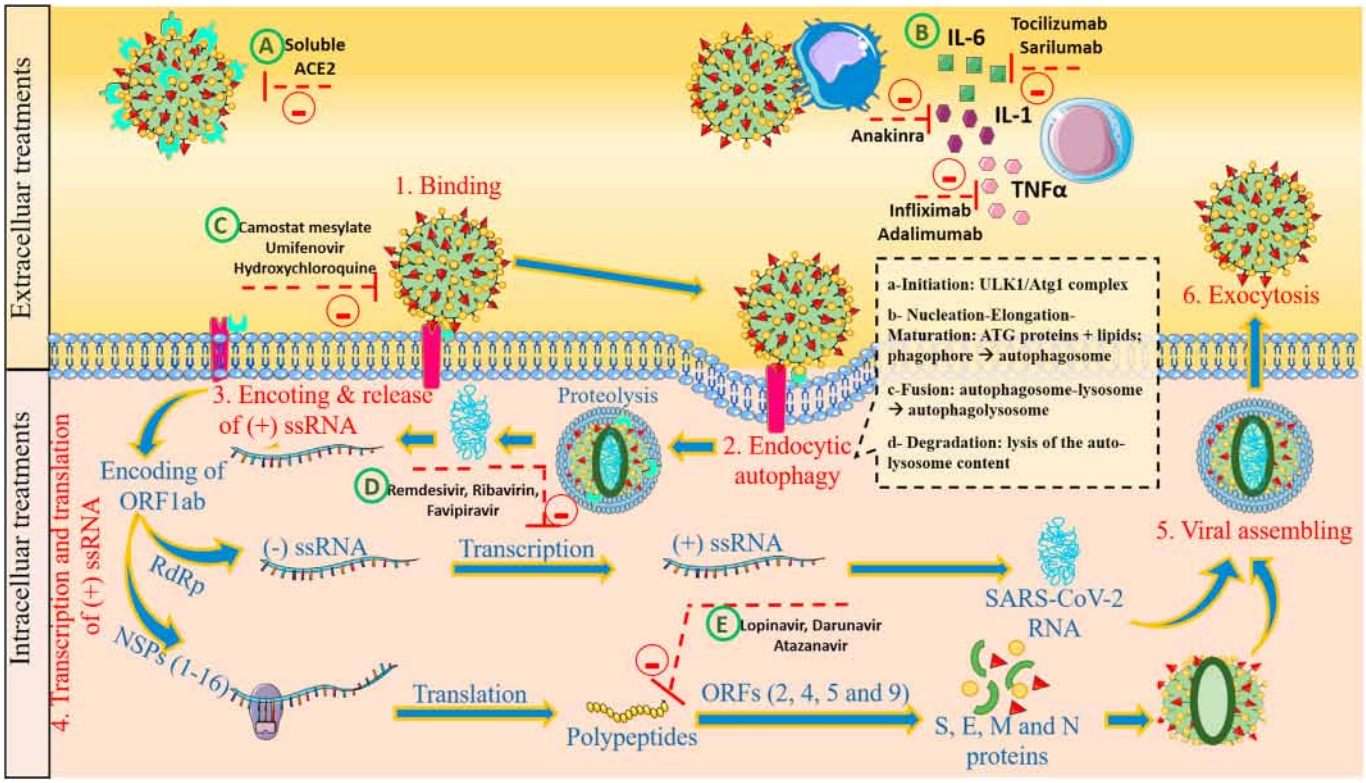

Figure 2. The renin-angiotensin system axis and the pathophysiology of COVID19 (modified according to Alexandre et al., 2020).

endocrine and autocrine regulatory effects on the lung, heart, liver, adrenal glands, kidneys, vascular endothelium, skeletal muscle, gonads, and brain (Goossens, 2012). Lastly, it is also involved in injury/repair function, cell growth and division, cytokine production, and inflammation (Varagic et al., 2014) (Figure 3). Two pathways with opposite effects, the classical and non-classical pathways, are described. The first one, the renin pathway, in the juxtaglomerular cells of kidneys, acts on the angiotensinogen, a substrate produced primarily in the liver, to yield angiotensin I (Ang I). Ang I is transformed into Ang II in the classical pathway, while it is transformed into Ang (1–7) in the nonclassical ones. The two pathways have antagonistic effects (Powers et al., 2018). Angiotensin-converting enzyme 1 (ACE1) and chymase promote Ang II production (Li et al., 2004). However, ACE2 produces Ang (1–7) by converting Ang II(Powers et al., 2018). Additional mechanisms are involved in RAS regulation but are not relevant in this review on SARS-CoV-2. The two peptides Ang II and Ang (1–7) achieve the regulatory functions of RAS through their binding with their receptors, Ang II type 1 and type 2 receptors (AT1 and AT2), and Ang (1–7) Mas1 receptor (Sriram and Insel, 2020). A hypothesis proposed that imbalance in the action of the ACE1-and ACE2-derived peptides may initiate the pathophysiology of COVID-19 (Sriram and Insel, 2020) (Figure 3).

5.2.2. *From RAS moderation to an altered immunity*

The SARS-CoV-2 promotes tissue injury and apoptosis in type II pneumocytes that express a high level of ACE2 (Zou et al., 2020). Consequently, this triggers an overactivation of the immune response and leads to the appearance of some of the COVID-19 symptoms, such as dry cough, asthenia, and multiorgan damage in severe cases. An increased level of chemokines and cytokines is observed in serum, especially interleukins, tumor necrosis factor (TNF-α), granulocyte colony-stimulating factor, essential fibroblast growth factor, granulocyte-macrophage colony-stimulating factor, and vascular endothelial growth factor (Huang et al., 2020). Various studies provide insight into the implication of immune cells such as macrophages, dendritic cells, T cells, and B cells in the defense against coronaviruses, especially SARS-CoV (Channappanavar et al., 2014). The course of COVID-19, such as lung injury and mild or severe illness, is linked to an imbalance between ACE1 and ACE2. This occurs because of an altered RAS activation and immune response (Sriram and Insel, 2020). In particular, Ang II accumulation has a pivotal implication in triggering inflammation. As SARS-CoV-2 binds to ACE2, Ang IIbinds to AT1R, it induces pro-inflammatory cytokines such as TNF-α and IL-6-soluble (s)IL-6R by the disintegrin and metalloprotease 17 (ADAM17) pathway. Consecutively, this activates the IL-6 amplifier (IL-6 AMP) and activates the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB). This mechanism leads to multiple inflammatory and autoimmune diseases (Murakami et al., 2019). On the other hand, SARS-CoV-2 triggers NF-κB expression (Figure 3), which is pivotal in regulating the immune response to infection (Luft et al., 2012). However, in SARS-CoV-2 infected cells, the activation of NF-κB stimulates IL-6 Amp and enhances the release of inflammatory cytokines and chemokines, including IL-6. This activation loop increasingly recruits leucocytes to the lesion, especially activated T cells and macrophages, that reinforce IL-6 Amp (Hirano and Murakami, 2020).

The inflammatory response implicates changes in a large number of cytokines, with increased expression of leukocytic pyrogen IL-1β, interleukin-1 receptor antagonist (IL1RA), IL7, IL8, IL9, IL10, fibroblast growth factor-β (FGF-β), colony-stimulating factor 3 of granulocytes, colony-stimulating factor 2, interferon-gamma, C-X-C motif chemokine ligand 10, platelet-derived growth factor, monocyte chemoattractant protein-1, macrophage inflammatory protein A (MIP1A), MIP1A B, and vascular permeability factor. Among COVID-19 cases, intensive care unit (ICU) patients revealed increased dosages of IL2, IL7, IL10, GCSF, IP10, MCP1, MIP1A, and TNF-α decreased concentrations of IL-6 compared with non-ICU patients (Huang et al., 2020). The overexpression of such a variety of chemokines and cytokines reportedly damages the lungs (He et al., 2020). In addition, it recruits various immune cells, such as macrophages, monocytes, and lymphocytes, especially in the alveoli, restricting gas exchanges. These modifications might also explain the large variety of symptoms and their declination in mild or severe COVID-19 disease.

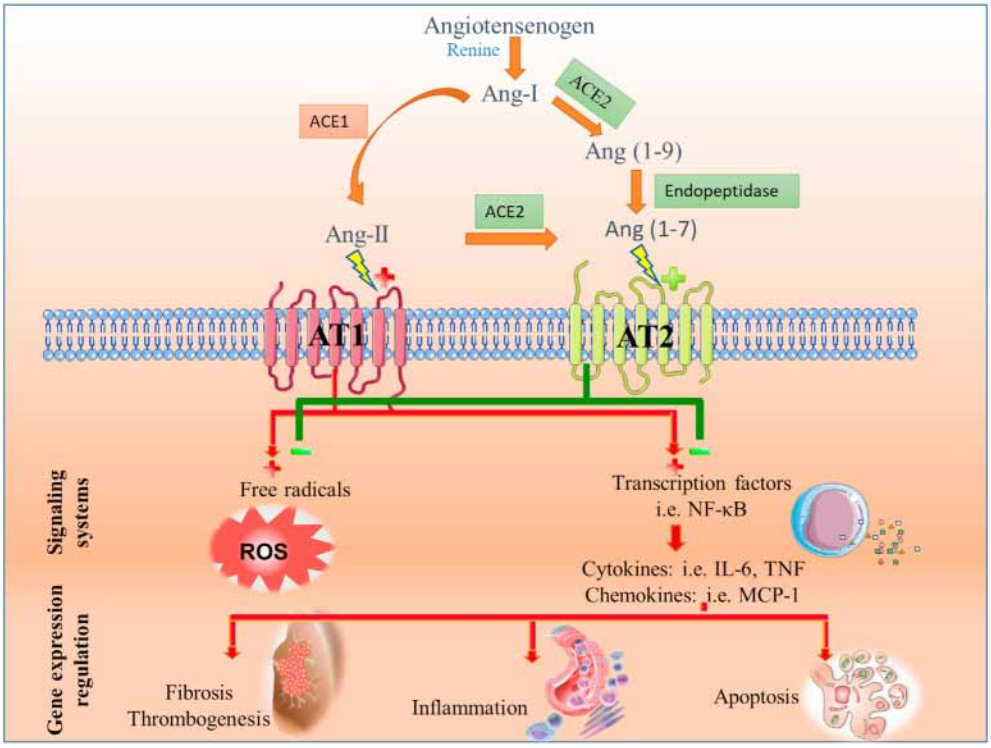

Figure 3. Summary of the SARS-CoV-2 life cycle with the possible therapeutic approaches. Steps of the life cycle: 1. the RBD of the viral spike bind to the ACE-2 with the intervention of TMPRSS2; 2. entry of the SARS-CoV-2 via endocytosis autophagy pathway where autolysosome integrate viral contents and cut it down; 3. Viral (+)ssRNA is encoded and released in the cytosol; 4. ORF1a and ORF1ab are the first genes encoded, expressing 16 non-structural proteins (NSPs) implicated in the transcription and translation processes. Among the NSPs, RdRp (RNA polymerase) copies the viral RNA. Genes of the ORFs 2, 4, 5, and 9 encode the spike, envelope, membrane successively, and nucleocapsid the structural proteins; 5. Assembling of the viral proteins and RNA in the host's endoplasmic reticulum and Golgi apparatus; 6. The assembled virions travel in vesicles to the cell membrane and are released by exocytosis. The possible therapeutic approaches: A. SARS-CoV-2 neutralization and scavenging through convalescent therapy and soluble ACE-2; B. Anti-inflammatory and immunomodulatory approaches using pharmacophores that impede the over-reaction of inflammatory response and cytokines storm; C. blockage of the viral fusion during penetration process; D. Inhibition of reverse transcription; E. The use of Protease inhibitors.

The blood count analysis of COVID-19 patients reported leucopenia in many cases, especially lymphopenia, a cardinal feature (He et al., 2020; Li et al., 2020a, b, c). Such a deficiency must represent a manifestation of the lymphocyte functional deficit, especially among CD4+ and CD8+ cells. This association betweenCOVID-19 severity and lymphocyte count is a good and reliable parameter for diagnostic purposes. Patients with more than 20% of lymphocytes bear moderate illness, those with 5–20% of lymphocytes present severe symptoms, and the most critical cases have less than 5% lymphocytes (Tan et al., 2020). Nevertheless, the mechanism leading to this decrease in lymphocytes is not entirely understood and should be linked to the aforementioned mechanisms involved in inflammatory cytokine disorders. It probably leads to lymphocyte apoptosis and immunosuppression following the hyper-production of TNF-α and IL-6 (Liao et al., 2002). A recent study proposes that the onset of lymphopenia is related to an increase in soluble IL-2 receptor (sIL-2R) levels, which was suggested to act as a negative regulatory factor of CD8+ T cells but not of CD4+ T cells, NK cells, or B cells (Zhang et al., 2020c). Previous studies point that increased plasma sIL-2R is a predictive indicator of a decreased cellular response to IL-2 because it reduces its bioavailability. However,sIL-2R also has a regulatory effect on T lymphocytes in various immunological disorders (Gooding et al., 1995). On the other hand, SARS-CoV-2 might cause lymphopenia through direct infection since lymphocytes express the ACE2 protein or via lymphatic organs attack by the virus (Liao et al., 2002).

5.2.3. From lung infection to multiple organ damage

The host lungs present a primary site of infection with SARS-CoV-2. Unsurprisingly, lung damage's pathophysiology evokes the RAS balance outlined so far. As in hypoxemic lung diseases, increased AngII concentration is critical, leading to respiratory distress. SARS-CoV-2 binds to the ACE2 protein to enter the cell and downregulates its activity. Besides, the virus itself down-regulates ACE2 expression. A compensatory inhibition of ACE1 in the lung, recorded after infection, may play a role in coughing. Following infection, a decreased concentration of Ang (1–7) and an increased concentration of AngII initiate an exaggerated activation of the AngII pathway (Bahat, 2020). Hence, lungs are subjected to significant damages due to enhanced chemokine and cytokine production, oxidative stress, increased fibrogenesis, and apoptosis (Fakhri et al., 2020). In addition to lung infection, injury to other organs has additionally been reported in several mild and severe cases of COVID-19. These are associated with the broad expression of ACE2 (Hamming et al., 2004)and TMPRSS2 in tissues and cells (Vaarala et al., 2001). Accordingly, muscles, nervous system, liver, kidneys, intestine are potential access points for SARS-CoV-2. Increased expression of alanine aminotransferase or aspartate aminotransferase and total bilirubin concentrations associated with abnormal liver function is documented. Most patients may have high levels of C-reactive protein that provide additional information on liver inflammation. In their stool and blood samples, approximately 2–10% of COVID-19 patients with diarrheapresentSARS-CoV-2RNA.

Indicators of tissue damage are detected in the blood of COVID-19 patients, like creatinine kinase and lactate dehydrogenase, both associated with an abnormal myocardial zymogram and indicative of muscle damage. In addition, in patients with severe cases and immunosuppression, about two-thirds present a high D-dimer level, indicative of potential nervous system injury (Hamming et al., 2004).

6. Management and therapeutic aspects of COVID-19

No vaccine is currently available for COVID-19, and no specific treatment is yet approved for COVID-19. The current therapy treats symptoms, especially respiratory symptoms, rather than the disease. The first step to treat COVID-19 is oxygen therapy (Chen et al., 2020a, b, c; Jin et al., 2020a, b) and appropriate isolation of patients to prevent transmission to other people and health care workers. Mild illness should be treated at home, with advice on danger signs. The usual principles are maintaining nutrition and hydration and controlling cough and fever. Also, patients with severe pneumonia require hospitalization and access to intensive care units, where mechanical ventilation is available (Chen et al., 2020a, b, c; Jin et al., 2020a, b). The Table 1 summarizes the therapeutic option to treat COVID-19.

6.1. Convalescent plasma (CP) therapy

Convalescent plasma from the serum of cured patients has been used for more than a century to treat and prevent various infectious diseases. In convalescent plasma, antibodies mediate curative effects by binding to a given contagious agent, counteracting its infective capacity, involving phagocytosis, activating complement, and inducing cellular cytotoxicity (Van Erp et al., 2019). Convalescent plasma therapy has been successfully used over the past two decades to manage MERS, SARS, and the H1N1 pandemic with proficient power and safety (Hung et al., 2011; Ko et al., 2018; Zhou et al., 2007). Clinical studies report good outcomes after convalescent plasma therapy. However, these studies presented some bias, such as a combination of non-randomized evaluations, confounding, predictor description, poor methodological conduct for participant selection, the dosage of convalescent plasma therapy, and treatment duration. Therefore, large multicentre clinical trials are necessary to establish a therapeutic protocol (Sarkar et al., 2020).

6.2. Anti-inflammatory agents and immunomodulators

SARS-CoV-2 infection is associated with an overactivation of inflammatory processes and the subsequent development of a “cytokine storm” in its severe form. Therefore, drugs with immunomodulatory properties, including natural and synthetic molecules able to modulate specific inflammatory pathways, are under evaluation (Figure 2).

6.2.1. IL-6

Among key cytokines, IL-6 has attracted significant attention, and monoclonal antibodies that interfere with the IL-6 receptor are now in Phase 2/3 clinical trials for possible therapy for COVID-19 (Zhang et al., 2020a). As tocilizumab (Figure 2) (IL-6 antagonist) can prevent hyperactivation of the inflammatory pathways, it can be used at an early stage of COVID-19 (Zhang et al., 2020b). This drug is one of the first used in China to treat pulmonary complications in patients with severe SARS-CoV-2 infection (Xu et al., 2020a). Trials with siltuximab and sarilumab (Figure 2), other IL-6 receptor antagonists similar to tocilizumab, are underway combined with conventional care or alone in patients with severe COVID-19 (Mihai et al., 2020).

6.2.2. IFN-γ

Another promising strategy is to target interferon-gamma (IFN-γ). Baricitinib, an approved drug for rheumatoid arthritis management, has been tested to manage COVID-19 severity (Stebbing et al., 2020). The drug is a reversible and selective inhibitor of Janus kinases 1 and 2 (JAK1 and JAK2) (Richardson et al., 2020). They are cytoplasmic enzymes with tyrosine kinase activity that facilitate the transmission of signals from the cell surface (IFN-γ, IL-6), activating transcription factors (STAT). Subsequently, STATs are translocated to the nucleus and regulate gene coding expression for growth factors and cytokines involved in inflammation and immune function. This pathway, called the JAK-STAT signaling pathway, promotes the “cytokine storm”. Besides, inhibition of Janus kinases 1 and 2 perturbs the function of AAK1 and blocks virus entry and the intracellular viral assembly (Lu et al., 2020a, b). Thus, Baricitinib can be used to inhibit both viral access and the inflammatory response associated with SARS-CoV-2 infection (Richardson et al., 2020). Thus, it may represent an additional therapeutic alternative for the treatment of COVID-19 (Richardson et al., 2020). A nonrandomized Phase II clinical trial has begun to evaluate the safety and efficacy of Baricitinib, Hydroxychloroquine, Lopinavir/Ritonavir, and Sarilumab in the treatment of 1,000 patients with COVID-19. In addition, Ruxolitinib, Sunitinib, and Fedratinib, selective inhibitors of JAK, could be effective against

Table 1. Current therapeutic options.

Name	Type	Mode of action	Reported effects	References
CP therapy	Transfusion	Binding of antibodies to SARS-CoV-2 particles counteracting its infective capacity	Improvement in clinical symptoms and decrease in viral loads within days following transfusion	Sarkar et al. (2020)
Tocilizumab, siltuximab, sarilumab	Anti-inflammatory	IL-6 antagonist, preventing hyperactivation of the pro-inflammatory pathway	Phase II and III clinical trials	Mihai et al. (2020)
Baricitinib	Anti-inflammatory (management of rheumatoid arthritis)	Inhibition of JAK1 and JAK2 enzymatic activity, blocking the entry of the virus and its intracellular assembly	An open-label study conducted in Italy (NCT04358614) confirms the use of baricitinib combined with lopinavir/ritonavir in patients with mild COVID-19 pneumonia.	Richardson et al. (2020)
Ruxolitinib, sunitinib and fedratinib	Anti-inflammatory	Inhibition of JAK, reduction in cytokine levels, including IL-6, IFN-γ, and reduction in viral endocytosis	A non-randomized Phase II clinical trial is ongoing.	Stebbing et al. (2020)
Hydroxychloroquine	Antimicrobial agent (Antimalarial)	Inhibition of viral enzymes activity, of ACE2 cellular receptors expression, and immunomodulation via modulation of cytokine release	Inhibition of SARS-CoV-2 entry and replication	D'Alessandro et al., 20
Infliximab, adalimumab	Anti-TNF antibodies	Modulation of the inflammatory level	Considered as a valid therapeutic option	Feldmann et al. (2020)
Ciclesonide	Anti-inflammatory (Corticosteroid)	Anti-inflammatory and antiviral activity	Inhaled ciclesonide relieves local inflammation in the lungs of patients with pneumonia	Iwabuchi et al. (2020)
hrsACE2	An antiviral agent with lure and scavenger activity	Reducing viral multiplication and infection in cell culture by acting as a lure for SARS-CoV-2	Currently, no known published data regarding efficacy or safety in the treatment of COVID-19	Monteil et al. (2020)
Camostatmesylate	Protease inhibitor	They are blocking TMPRSS2cellular protease activity and fusion.	Clinical trials are ongoing	Shang et al. (2020)
Umifenovir	Nucleoside analog with antiviral activity	Blocking membrane-viral envelope fusion	Monotherapy with umifenovir in patients with COVID-19 resulted in a negative viral conversion	Zhou et al., 2020a, b
Lopinavir/Ritonavir	Protease inhibitor	Inhibition of the major SARS-CoV-2 protease	Reduces viral load and improves clinical symptoms of COVID-19	Zhou et al., 2020a, b
Darunavir	Protease inhibitor	Blockade of SARS-CoV-2 replication	Clinical trials ongoing in China	Lythgoe & Middleton, 2020
Atazanavir	Protease inhibitor	Binding to the active site of the SARS CoV-2 MPro and inhibiting SARS-CoV-2 virus replication	Option for COVID-19 therapy	Fintelman-Rodrigues et al. (2020)
Remdesivir	Reverse transcription inhibitor	Inhibiting the RNA-dependent RNA polymerase (RdRp)	Shows a superior effect to placebo	Scavone et al. (2020)
Favipiravir	Reverse transcription inhibitor	inhibiting the RNA-dependent RNA polymerase (RdRp) and then the viral RNA synthesis	Reduces viral load and decreases adverse events	Frediansyah et al. (2020)
Eidd-2801	Nucleoside analog	inhibiting the RNA-dependent RNA polymerase (RdRp) and then the viral RNA synthesis	Experimental therapeutics tested *in vivo*	Toots et al. (2019)
Ribavirin	Nucleoside analog	Interacting with polymerases function, preventing viral RNA capping and replication	Clinical trials point out that ribavirin stops the viral spread	Khalili et al. (2020)

SARS-CoV-2 by reducing cytokine levels and inflammation, including IL-6, IFN-γ, and viral endocytosis (Stebbing et al., 2020).

6.2.3. TNFα

It is another crucial cytokine involved in inflammatory diseases. In COVID-19 patients, an elevated level of TNFα is recorded in tissues and blood. The role of anti-TNF treatment was recently considered for decreasing inflammation in COVID-19 (Feldmann et al., 2020; Gong et al., 2020). Anti-TNF antibodies, such as infliximab or adalimumab (Figure 2), are thought to modulate the patient's inflammatory response level. Recent clinical studies demonstrate that the blockade of TNF's enhanced inflammatory activity results in a rapid reduction in IL-1 and IL-6 concentrations (Feldmann and Maini, 2001). Thus, a single infusion of anti-TNF antibodies at the early stage of infection may help treat patients with COVID-19 (Feldmann et al., 2020).

6.2.4. IL-1

The family of interleukin-1, which has pro-inflammatory roles, has been considered in patients with COVID-19 because of their essential role in the symptoms recorded during the "cytokine storm" syndrome, including edema, fever, organ dysfunction. A high IL-1 level is observed in patients with COVID-19 (Huang et al., 2020). Anakinra (recombinant interleukin-1 receptor antagonist) (Figure 2) is a therapeutic option with IL-1-blocking properties (Monteagudo et al., 2020). A group of U.S. researchers proposed that intravenous infusion of anakinra's could have survival benefits, as it may reverse patients' "cytokine storm" (Monteagudo et al., 2020).

6.3. Corticosteroids

It is alleged that corticosteroid treatment is not supported for viral pneumonia. Studies have revealed that the use of corticosteroids for patients with SARS-CoV and MERS-CoV correlates with a significantly higher mortality rate than conventional therapy. A similar observation is reported in influenza-associated pneumonia (Ni et al., 2019). There are currently only few clinical trials on methylprednisolone's therapeutic benefit in COVID-19 patients (Belhadi et al., 2020). A study concludes with better results and reduced mortality (Wu et al., 2020). A recent case study in Japan demonstrated that inhaled ciclesonide, which possesses anti-inflammatory and antiviral activity *invitro,* relieves local inflammation in the lungs of patients with COVID-19 pneumonia and suppresses viral spread (Iwabuchi et al., 2020).

6.4. Antiviral agents

The life cycle stages of viruses constitute potential targets for pharmacotherapy. Promising drug targets include non-structural proteins (3-chymotrypsin-like protease, papain-like protease, RNA-dependent RNA polymerase) and immune regulatory pathways (Figure 2).

6.4.1. Soluble ACE2 as a virus scavenger and neutralizer

An alternative therapeutic approach is soluble ACE2 as a neutralizer and a virus trap. The soluble ACE2 produced by proteolytic cleavage of the membrane anchor is generally recovered in plasma; however, the concentration of soluble ACE2 is low. Increasing the availability of soluble ACE2 at the tissue level would compete with the membrane-bound ACE2, resulting in the suppression of virus entry into cells (Monteil et al., 2020). Strikingly, a recombinant form of ACE2reduces viral growth and infection in cell culture, acting as a lure for SARS-CoV-2 (Monteil et al., 2020).

6.4.2. Fusion inhibitors

Fusion inhibitors are antivirals that block the fusion process during viral penetration into the host cell. Several drugs are available, such as camostatmesylate and umifenovir, demonstrating antiviral activity against SARS-CoV-2 (Gasmi et al., 2020; Richardson et al., 2020) (Figure 2).

- ✓ **Camostat mesylate, E64, and nafamostat mesylate.** The attachment of the virus to the cell receptor requires the S protein's priming with cellular proteases. The virus engages the cellular protease TMPRSS2 to prime the S protein to enter and spread within the infected host (Shulla et al., 2011). Blocking this pathway could reduce the viral titer of SARS-CoV-2. The serine protease inhibitor (camostat mesylate) that acts on TMPRSS2 activity significantly reduces the entry of MERS-CoV andSARS-CoV and two into lung cells (Hoffmann et al., 2020).
  Additionally, camostat mesylate and E-64d (a cysteine protease inhibitor) could successfully inhibit the attachment of SARS-CoV-2 to TMPRSS2(Shang et al., 2020). A second serine protease inhibitor, called nafamostat mesylate, is fifteen times more effective in inhibiting the entry of the SARS-CoV-2 virus than the inhibitors mentioned above. Due to its favorable safety profile and potent antiviral activity, nafamostat mesylate is an alternative to camostat mesylate (Balakumar et al., 2017). Nafamostat mesylate is also used to treat disseminated intravascular coagulation and be of interest for COVID-19 management (Yang et al., 2020a, b).
- ✓ **Umifenovir**, also known as Arbidol, is a nucleoside antiviral drug targeting the haemagglutinin glycoprotein. Its mechanism of action includes targeting the S/ACE2 protein interaction and blocking the fusion between the viral envelope and the host cell membrane (Kadam and Wilson, 2017). Monotherapy with umifenovir resulted in a negative viral conversion, as the virus was not detected within 14 days (Zhu et al., 2020b). In addition, Arbidol and Arbidol mesylate compounds demonstrate *in vitro* inhibitory effects on SARS virus replication (Khamitov et al., 2008). Randomized clinical trials in China are underway to evaluate the efficacy and therapeutic potential of umifenovir in treating SARS-CoV-2 pneumonia (Zhu et al., 2020b).
- ✓ **Hydroxychloroquine (HCQ) and chloroquine (CQ)** are approved molecules for treating rheumatoid arthritis, lupus, erythematosus, and malaria. Both have antiviral activity against HIV, hepatitis B, Zika, and H1N1 virus (D'Alessandro et al., 2020). CQ and HCQ prevent virus entry by interfering with the glycosylation and proteolytic maturation of proteins and the terminal glycosylation of ACE2. They also inhibit endocytosis by increasing the pH of endosomes, Golgi vesicles, and lysosomes. Also, they inhibit cytokine production by altering membrane stability, transcriptional activity, and signaling pathways (Schrezenmeier and Dörner, 2020). The FDA issued an emergency use authorization for HCQ and CQ on March 28 to treat patients with the SARS-CoV-2 virus. In addition, a combination of HCQ and azithromycin is proposed as an effective treatment for reducing viral load in patients with COVID- 19 (Gautret et al., 2020).

6.4.3. Protease inhibitors

When entering host cells, the viral genome is released in single-stranded RNA (positive). The genome is then translated by a ribosomal framework shift mechanism that creates two polyproteins, pp1 a and pp1 ab. Two proteases,papain-like proteinase and 3-chymotrypsin-like proteinase (MPro), are involved in the cleavage of the polyproteins translated from the viral RNA into functional proteins for virus packaging and replication. Therefore, blocking the activity of these enzymes would inhibit viral replication (Hilgenfeld, 2014) (Figure 2).

- ✓ **Lopinavir/Ritonavir.** Lopinavir is used in combination with ritonavir to treat and prevent HIV infection. This combination inhibits the protease of the virus. A specific combination of lopinavir/ritonavir (Kaletra®) demonstrates antiviral effects against SARS-CoV (Chu, 2004). The ritonavir-lopinavir combination could reduce viral load and improve the clinical symptoms of COVID-19 (Zhu et al., 2020b). The combination of ritonavir/lopinavir and umifenovir also significantly inhibits the lung damage progression during SARS-CoV-2 infection (Deng et al., 2020). Additional clinical trials are underway to evaluate the efficacy of lopinavir/ritonavir for COVID-19 in Spain, China, France, Thailand, Canada, Hong Kong, and the United States (Khalili et al., 2020).
- ✓ **Darunavir,** an anti-HIV drug, is approved for COVID-19 treatment in Italy (Nicastri et al., 2020). The drug is used in a combination regimen with cobicistat or ritonavir, and *in vitro* studies demonstrate a replication blocking effect against SARS-CoV-2 (Harrison, 2020). Clinical trials of a combination of darunavir and cobicistat, known as PREZCOBIX®, are ongoing in China (Lythgoe and Middleton, 2020).
- ✓ **Atazanavir,** *In silico* study, highlights a higher binding efficiency of atazanavir to the active site of the SARS CoV-2 MPro, than lopinavir and an efficient *in vitro* inhibition of SARS-CoV-2 virus replication (Fintelman-Rodrigues et al., 2020). Furthermore, in HIV- patients, a combination of atazanavir and ritonavir improved lipid parameters and glucose absorption, decreasing glucose fasting more effectively than the lopinavir-ritonavir combination (Noor et al., 2006).
- ✓ **Saquinavir and other protease inhibitors**, such as nelfinavir, amprenavir, and indinavir, also show effects against COVID-19 because of their high structural similarity level. In silico study demonstrates that indinavir and saquinavir are candidates to inhibit 3CLPro activity (Hall and Ji, 2020). They also potently inhibit SARS-CoV-2 virus replication *in vitro*, nelfinavir being the best candidate (Norio et al., 2020). Saquinavir is used for the treatment of patients with COVID-19 in Singapore. Two other candidates

identified *in silico*, paritaprevir, and raltegravir, demonstrate potent inhibition of 3CLPro activity (Khan et al., 2020).

6.4.4. Reverse transcription inhibitors

Another strategy to combat SARS-CoV-2 infection involves targeting the reverse transcription step by blocking RdRp and preventing viral replication. It is the primary target of many existing nucleotide drugs, such as remdesivir, ribavirin, favipiravir, EIDD-2801, and galidesivir (Figure 2).

- ✓ **Remdesivir** is a nucleotide analog with antiviral properties against most single-stranded RNA viruses in cultured cells and non-human animal models. It targets the RdRpessential for viral replication and demonstrates antiviral activity against single-stranded RNA viruses (MERS and SARS) (Agostini et al., 2019). Currently, remdesivir's safety and efficacy have been evaluated in a Phase 3 trial involving 1, 600 patients (Scavone et al., 2020). In addition, analysis of Italian clinical practice data revealed that this drug was first used in the Spallanzani Hospital in Rome in COVID-19 patients and administered in 12 Italian clinical centers (Scavone et al., 2020).
- ✓ **Favipiravir,** a purine (guanine) analog, is a derivative of the pyrazine carboxamides, a RoRp inhibitor (Frediansyah et al., 2020). Initially developed for the treatment of influenza, the drug attracted attention for the treatment of COVID-19 because of its broad antiviral spectrum. A recent clinical trial highlighted its efficacy in patients with COVID-19 (Cai et al., 2020). Patients receiving favipiravir present better chest recovery, faster viral load reduction, and fewer adverse events than the control group. Today, favipiravir is used to treat COVID-19 in Indonesia and Japan, following several randomized clinical trials (Frediansyah et al., 2020). Favipiravir is a potential drug candidate for COVID-19, but drug interaction may alter its plasma concentration and pharmacokinetics (Agostini et al., 2019).
- ✓ **Eidd-2801,** The β-D-N4-hydroxycytidine or Eidd-2801 is a ribonucleoside analog, orally bioavailable, with a broad antiviral spectrum against RNA viruses. The mechanism of action is similar to that of remdesivir (Toots et al., 2019). Recent reports indicated that EIDD-2801 inhibits viral replication in mouse and human cells infected with SARS-COV (Toots et al., 2019). This drug mimics ribonucleoside's function by stopping the spread of the virus through the replication process. EIDD-2801 can reduce severe lung damage and viral load within 48 h of mice's infection (Toots et al., 2019).
- ✓ **Ribavirin** is a guanine analog prescribed to treat coronavirus infection, specifically MERS and SARS (Wang et al., 2020a, b, c). Ribavirin interacts with polymerase function, preventing viral RNA capping and stopping replication. Simultaneously, it also inhibits the inosine monophosphate dehydrogenase, promoting the degradation of viral RNA by inhibiting guanosine production. Besides, ribavirin's presence increases the RNA mutation rate, resulting in viral progeny loss of virulence (Khalili et al., 2020).

6.4.5. Artificial liver blood purification system (ALPS)

Clinical trials revealed the ALPS′ efficacy in reducing the serum levels of cytokines known as the leading cause of inflammation in COVID-19 patients. Indeed, the ALPS showed beneficial and promising results in patients with severe H7N9 influenza and cytokine storm (X. Liu et al., 2015). While in COVID-19, the technique was beneficial for reducing the cytokine storm in Chinese patients (Xu et al., 2020a, b).

6.4.6. Vaccination

In the absence of a practical therapeutic approach for curing Covid-19 patients, vaccination remains the path to global immunization. The race for Covid-19 vaccine development had started around the world (Figure 4) (Callaway, 2020). At the same time, the pressure created by the pandemic spread elicited the development of the SARS-CoV-2 vaccine that had been carried at financial risks by avoiding the traditional vaccine development procedure (Lurie et al., 2020).

More than 270 COVID-19 vaccine candidates were developed, with more than 90 clinical trials (Le et al., 2020). These comprise nucleic acid (RNA and DNA) (Mulligan et al., 2020) based vaccines, replication-deficient and replication-competent human and simian adenoviral vector vaccines (Zhu et al., 2020a), inactivated whole-cell viruses subunit protein vaccines, 16 and virus-like particles (Gao et al.,

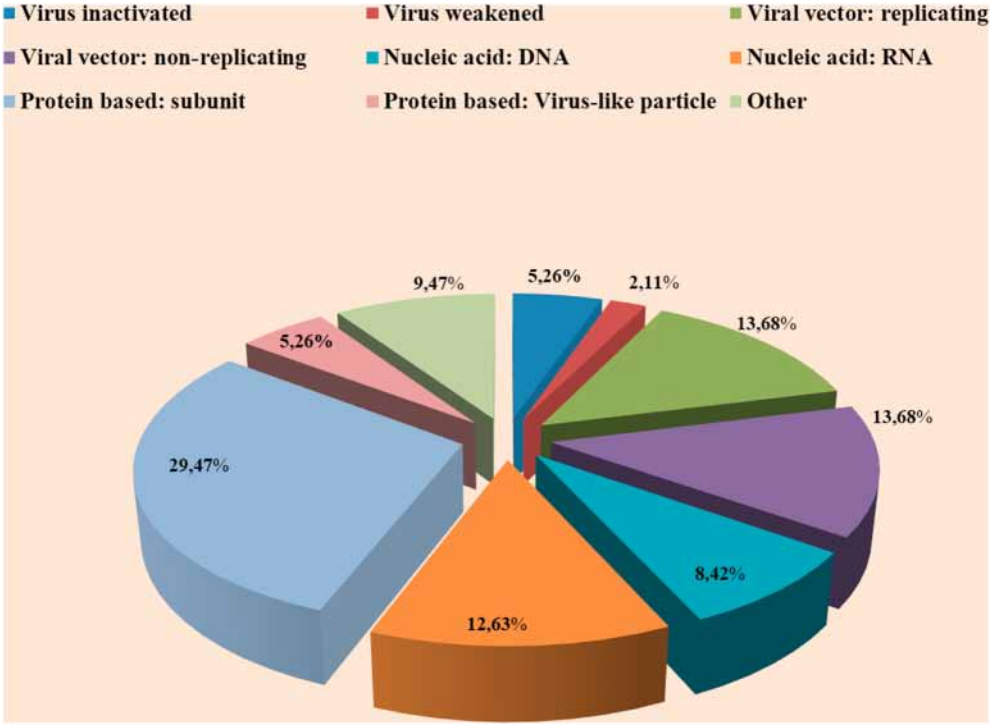

Figure 4. Graphical representation of the different vaccines developed against SARS-Cov-2 based on the technology adopted (classical and non-classical approaches). *: Trials assessing the efficacy of already existing vaccines against (poliovirus, tuberculosis) against SARS-Cov-2. (modified according to Callaway, 2020).

Table 2. Human COVID-19 vaccines.

Vaccine (developer)	Efficacy against symptomatic infection (phase III trials)	Effectiveness (post-implementation)
Whole-cell inactivated virus		
CoronaVac (Sinovac Biotech)	50–84% after 2 doses	-
BBIBP-CorV (Sinopharm)	86% after 2 doses	-
WIBP-CorV (Sinopharm)	73% after 2 doses	-
mRNA		
BNT162b2 mRNA (BioNTech/Pfizer)	95% after 2 doses; 52% after 1 dose	Symptomatic infection: 94–96% (2 doses) and 46–80% (1 dose) Any infection: 86–92% (2 doses) and 46–72% (1 dose) Hospitalization: 87% (2 doses) and 71–85% (1 dose) Asymptomatic infection: 79% (1 dose) and 90% (2 doses)
mRNA-1273 (Moderna)	95% after 2 doses; 92% after 1 dose	Symptomatic infection: 90% (2 doses) and 80% (1 dose)
Viral vector		
ChAdOx1 nCoV-19 (Oxford/Astra-Zeneca)	62–67% after 2 doses,76% after 1 dose	Hospitalization: 80–94% after 1 dose
Gam-COVID-Vac (Gamaleya Research Institute)	91% after 2 doses; 74% after 1 dose	-
Ad26.COV2.S (Janssen)	67% after 1 dose	-
Ad5-nCoV (CanSino Biologics)	66% after 1 dose	-
Protein subunit		
NVX-CoV2373 (Novavax)	90% by 7 days after second dose	-

2020). As of April 2021, 28 of these vaccines have entered phase III clinical trials (Table 2). Five have reported efficacy in the literature and/or in publicly available detailed reports submitted to regulatory authorities, resulting in emergency approvals for use in a large number of countries. These include the BNT162b2 (Pfizer/BioNTech) and mRNA-1273 (Moderna) mRNA vaccines and the three adenoviral vector vaccines ChAdOx1 nCoV-19 (University of Oxford/AstraZeneca), Gam-COVID-Vac (Gamaleya Research Institute), and Ad26.COV2.S (Janssen). A protein subunit vaccine (NVX-CoV2372; Novavax) and an inactivated whole-cell viral vaccine (BBV152; Bharat Biotech) showed positive effectiveness results in the companies' official press releases (Table 2), and BBV152 has received emergency approval in several countries. Four other vaccines have suggested positive efficacy through media reports-the Ad5-nCoV adenoviral vector vaccine (CanSino Biologics), and the CoronaVac whole-cell inactivated vaccines (Sinovac Biotech), BBIBP-CorV (Sinopharm), and WIBP-CorV (Sinopharm) (Table 2).

7. Conclusion

In conclusion, SARS-CoV-2 is an emerging highly transmissible Coronavirus that causes a high mortality rate in the aging population. A better understanding of the physiopathology of SARS-CoV-2 will open opportunities to develop (i) tools to identify people at risk and (ii) drugs to treat them.

Declarations

Author contribution statement

All authors listed have significantly contributed to the development and the writing of this article.

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Data availability statement

Data included in article/supplementary material/referenced in article.

Declaration of interests statement

The authors declare no conflict of interest.

Additional information

No additional information is available for this paper.

References

Agostini, M.L., Pruijssers, A.J., Chappell, J.D., Gribble, J., Lu, X., Andres, E.L., Denison, M.R., 2019. Small-molecule antiviral β-D- N 4 -hydroxycytidine inhibits a proofreading-intact coronavirus with a high genetic barrier to resistance. J. Virol. 93 (24).

Alexandre, J., Cracowski, J.-L., Richard, V., Bouhanick, B., 2020. Renin-angiotensin-aldosterone system and COVID-19 infection. In: Dans Annales D'endocrinologie, 81. Elsevier, pp. 63–67.

Almeida, J.D., Tyrrell, D.A., 1967. The morphology of three previously uncharacterized human respiratory viruses that grow in organ culture. J. Gen. Virol. 1 (2), 175–178.

Andersen, K.G., Rambaut, A., Lipkin, W.I., Holmes, E.C., Garry, R.F., 2020. The proximal origin of SARS-CoV-2. Nat. Med. 26 (4), 450–452.

Anfinrud, P., Bax, C.E., Stadnytskyi, V., Bax, A., 2020. Could SARS-CoV-2 be transmitted via speech droplets? medRxiv.

Assiri, A., McGeer, A., Perl, T.M., Price, C.S., Al Rabeeah, A.A., Cummings, D.A.T., Memish, Z.A., 2013. Hospital outbreak of Middle East respiratory syndrome coronavirus. N. Engl. J. Med. 369 (5), 407–416.

Astuti, I., Ysrafil, 2020. Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2): an overview of viral structure and host response. Diab. Metabol. Synd.: Clin. Res. Rev. 14 (4), 407–412.

Bahat, G., 2020. COVID-19 and the renin angiotensin system: implications for the older adults. J. Nutr. Health Aging 13.

Balakumar, P., Anand-Srivastava, M.B., Jagadeesh, G., 2017. Renin-angiotensin-aldosterone: an inclusive, an invigorative, an interactive and an interminable system. Pharmacol. Res. 125, 1–3.

Belhadi, D., Peiffer-Smadja, N., Lescure, F.-X., Yazdanpanah, Y., Mentré, F., Laouénan, C., 2020. A Brief Review of Antiviral Drugs Evaluated in Registered Clinical Trials for COVID-19. medRxiv.

Bogoch, I.I., Watts, A., Thomas-Bachli, A., Huber, C., Kraemer, M.U.G., Khan, K., 2020. Pneumonia of unknown aetiology in Wuhan, China: potential for international spread via commercial air travel. J. Trav. Med. 27 (2).

Bradburne, A.F., Bynoe, M.L., Tyrrell, D.A.J., 1967. Effects of a "new" human respiratory virus in volunteers. Br. Med. J. 3 (5568), 767–769.

Brian, D.A., Baric, R.S., 2005. Coronavirus Genome Structure and Replication, pp. 1–30 (S.l.) : (s.n.).

Brodin, P., 2020. Why is COVID-19 so mild in children? Acta Paediatr. 109 (6), 1082–1083.

Cai, Q., Yang, M., Liu, D., Chen, J., Shu, D., Xia, J., Liu, L., 2020. Experimental Treatment with Favipiravir for COVID-19: an Open-Label Control Study. Engineering.

Callaway, E., 2020. The race for coronavirus vaccines: a graphical guide. Nature 580 (7805), 576.

Cascella, M., Rajnik, M., Cuomo, A., Dulebohn, S.C., Di Napoli, R., 2020. Features, evaluation and treatment coronavirus (COVID-19). StatPearls (S.l.) : (s.n.). Repéré à. http://www.ncbi.nlm.nih.gov/pubmed/32150360.

Channappanavar, R., Zhao, J., Perlman, S., 2014. T cell-mediated immune response to respiratory coronaviruses. Immunol. Res. 59 (1-3), 118–128.
Chen, N., Zhou, M., Dong, X., Qu, J., Gong, F., Han, Y., Zhang, L., 2020a. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet 395 (10223), 507–513.
Chen, Y., Chen, L., Deng, Q., Zhang, G., Wu, K., Ni, L., Wei, C., 2020b. The presence of SARS-CoV-2 RNA in the feces of COVID-19 patients. J. Med. Virol. 92 (7), 833–840.
Chen, Z.-M., Fu, J.-F., Shu, Q., Chen, Y.-H., Hua, C.-Z., Li, F.-B., Wang, W., 2020c. Diagnosis and treatment recommendations for pediatric respiratory infection caused by the 2019 novel coronavirus. World J. Pediatr. 1–7.
Chu, C.M., 2004. Role of lopinavir/ritonavir in the treatment of SARS: initial virological and clinical findings. Thorax 59 (3), 252–256.
Cleri, D.J., Ricketti, A.J., Vernaleo, J.R., 2010. Severe acute respiratory syndrome (SARS). Infect. Dis. Clin. 24 (1), 175–202.
Corman, V.M., Muth, D., Niemeyer, D., Drosten, C., 2018. Hosts and sources of endemic human coronaviruses. Adv. Virus Res. 100, 163–188.
Cortellis, T.M., 2020. Disease briefing: coronaviruses. Clar. Anal. Solut. 3, 51 (2020).
D'Alessandro, S., Scaccabarozzi, D., Signorini, L., Perego, F., Ilboudo, D.P., Ferrante, P., Delbue, S., 2020. The use of antimalarial drugs against viral infection. Microorganisms 8 (1), 85.
Davies, N.G., Abbott, S., Barnard, R.C., Jarvis, C.I., Kucharski, A.J., Munday, J.D., Washburne, A.D., 2021. COVID-19 genomics UK (COG-UK) consortium. In: Diaz-Ordaz, Keogh, R., Eggo, R.M., Funk, S., Jit, M., Atkins, K.E., Edmunds, W.J. (Eds.), Estimated Transmissibility and Impact of SARS-CoV-2 Lineage B, 1 (7).
De Groot, R.J., Baker, S.C., Baric, R., Enjuanes, L., Gorbalenya, A.E., Holmes, K.V., Talbot, P.J., 2012. Family Coronaviridae, P 806–820. Virus Taxonomy: Classification and Nomenclature of Viruses. Ninth Report of the International Committee On Taxonomy Of Viruses. Academic Press, London, United Kingdom.
Deng, L., Li, C., Zeng, Q., Liu, X., Li, X., Zhang, H., Xia, J., 2020. Arbidol combined with LPV/r versus LPV/r alone against Corona Virus Disease 2019: a retrospective cohort study. J. Infect. 81 (1), e1–e5.
Dong, L., Tian, J., He, S., Zhu, C., Wang, J., Liu, C., Yang, J., 2020. Possible vertical transmission of SARS-CoV-2 from an infected mother to her newborn. JAMA 323 (18), 1846–1848.
dos Santos, C.A., Bezerra, G.V.B., de Azevedo Marinho, A.R.R.A., Alves, J.C., Tanajura, D.M., Martins-Filho, P.R., 2021. SARS-CoV-2 genomic surveillance in Northeast Brazil: timing of emergence of the Brazilian variant of concern P1. J. Trav. Med. 28 (7), 1–3.
Fakhri, S., Nouri, Z., Moradi, S.Z., Farzaei, M.H., 2020. Astaxanthin, COVID-19 and immune response: focus on oxidative stress, apoptosis and autophagy. Phytother Res. 9 (June), 2017–2019.
Falsey, A.R., Walsh, E.E., Hayden, F.G., 2002. Rhinovirus and coronavirus infection–associated hospitalizations among older adults. J. Infect. Dis. 185 (9), 1338–1341.
Fehr, A.R., Perlman, S., 2015. Coronaviruses: an overview of their replication and pathogenesis. In: Maier, Dans H.J., Bickerton, E., Britton, P. (Eds.), Coronaviruses: Methods and Protocols, 1282. Springer New York, New York, NY, pp. 1–23.
Feldmann, M., Maini, R.N., 2001. Anti-TNFα therapy of rheumatoid arthritis: what have we learned? Annu. Rev. Immunol. 19 (1), 163–196.
Feldmann, M., Maini, R.N., Woody, J.N., Holgate, S.T., Winter, G., Rowland, M., Hussell, T., 2020. Trials of anti-tumour necrosis factor therapy for COVID-19 are urgently needed. Lancet 395 (10234), 1407–1409.
Fintelman-Rodrigues, N., Sacramento, C., Lima, C.R., da Silva, F.S., Ferreira, A., Mattos, M., Souza, T.M., 2020. Atazanavir Inhibits SARS-CoV-2 Replication and Pro-inflammatory Cytokine Production.
Fiorentini, S., Messali, S., Zani, A., Caccuri, F., Giovanetti, M., Ciccozzi, M., Caruso, A., 2021. First detection of SARS-CoV-2 spike protein N501 mutation in Italy in August, 2020. Lancet Infect. Dis.
Focosi, D., Maggi, F., 2021. Neutralising antibody escape of SARS-CoV-2 spike protein: risk assessment for antibody-based Covid-19 therapeutics and vaccines. Rev. Med. Virol.
Fouchier, R.A.M., Hartwig, N.G., Bestebroer, T.M., Niemeyer, B., De Jong, J.C., Simon, J.H., Osterhaus, A.D.M.E., 2004. A previously undescribed coronavirus associated with respiratory disease in humans. Proc. Nat. Acad. Sci. U.S.A. 101 (16), 6212–6216.
Frediansyah, A., Tiwari, R., Sharun, K., Dhama, K., Harapan, H., 2020. Antivirals for COVID-19: A Critical review. Clinical Epidemiology and Global Health.
Fung, S.-Y., Yuen, K.-S., Ye, Z.-W., Chan, C.-P., Jin, D.-Y., 2020. A tug-of-war between severe acute respiratory syndrome coronavirus 2 and host antiviral defence: lessons from other pathogenic viruses. Emerg. Microb. Infect. 9 (1), 558–570.
Gao, Q., Bao, L., Mao, H., Wang, L., Xu, K., Yang, M., Lv, Z., 2020. Development of an inactivated vaccine candidate for SARS-CoV-2. Science 369 (6499), 77–81.
Gasmi, A., Noor, S., Tippairote, T., Dadar, M., Menzel, A., Bjørklund, G., 2020. Individual risk management strategy and potential therapeutic options for the COVID-19 pandemic. Clin. Immunol. 215, 108409.
Gautret, P., Lagier, J.-C., Parola, P., Hoang, V.T., Meddeb, L., Mailhe, M., Raoult, D., 2020. Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial. Int. J. Antimicrob. Agents 56 (1), 105949.
Gerna, G., Campanini, G., Rovida, F., Percivalle, E., Sarasini, A., Marchi, A., Baldanti, F., 2006. Genetic variability of human coronavirus OC43-, 229E-, and NL63-like strains and their association with lower respiratory tract infections of hospitalized infants and immunocompromised patients. J. Med. Virol. 78 (7), 938–949.
Gong, J., Dong, H., Xia, S.Q., Huang, Y.Z., Wang, D., Zhao, Y., Wang, Q., 2020. Correlation Analysis between Disease Severity and Inflammation-Related Parameters in Patients with COVID-19 Pneumonia. medRxiv.
Gooding, R., Riches, P., Dadian, G., Moore, J., Gore, M., 1995. Increased soluble interleukin-2 receptor concentration in plasma predicts a decreased cellular response to IL-2. Br. J. Cancer 72 (2), 452–455.
Goossens, G.H., 2012. The renin-angiotensin system in the pathophysiology of type 2 diabetes. Obes. Facts 5 (4), 611–624.
Gorbalenya, A.E., Snijder, E.J., Spaan, W.J.M., 2004. Severe acute respiratory syndrome coronavirus phylogeny: toward consensus. J. Virol. 78 (15), 7863–7866.
Guan, W., Ni, Z., Hu, Y., Liang, W., Ou, C., He, J., Zhong, N., 2020. Clinical characteristics of coronavirus disease 2019 in China. N. Engl. J. Med. 382 (18), 1708–1720.
Hall, D.C., Ji, H.-F., 2020. A search for medications to treat COVID-19 via in silico molecular docking models of the SARS-CoV-2 spike glycoprotein and 3CL protease. Trav. Med. Infect. Dis. 35, 101646.
Hamming, I., Timens, W., Bulthuis, M.L.C., Lely, A.T., Navis, G.J., van Goor, H., 2004. Tissue distribution of ACE2 protein, the functional receptor for SARS coronavirus. A first step in understanding SARS pathogenesis. J. Pathol. 203 (2), 631–637.
Harrison, C., 2020. Coronavirus puts drug repurposing on the fast track. Nat. Biotechnol. 38 (4), 379–381.
He, F., Deng, Y., Li, W., 2020. Coronavirus Disease 2019 : what We Know ?, pp. 719–725 (March).
Henry, R., 2020. Etymologia: coronavirus. Emerg. Infect. Dis. 26 (5), 1027, 1027.
Hilgenfeld, R., 2014. From SARS to MERS: crystallographic studies on coronaviral proteases enable antiviral drug design. FEBS J. 281 (18), 4085–4096.
Hirano, T., Murakami, M., 2020. COVID-19: a new virus, but a familiar receptor and cytokine release syndrome. Immunity 52 (5), 731–733.
Hoffmann, M., Kleine-Weber, H., Schroeder, S., Krüger, N., Herrler, T., Erichsen, S., Pöhlmann, S., 2020. SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. Cell 181 (2), 271–280 e8.
Hou, Y.J., Chiba, S., Halfmann, P., Ehre, C., Kuroda, M., Dinnon, K.H., Takahashi, K., 2020. SARS-CoV-2 D614G variant exhibits efficient replication ex vivo and transmission in vivo. Science 370 (6523), 1464–1468.
Huang, C., Wang, Y., Li, X., Ren, L., Zhao, J., Hu, Y., Cao, B., 2020. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 395 (10223), 497–506.
Hung, I.F.N., To, K.K.W., Lee, C.-K., Lee, K.-L., Chan, K., Yan, W.-W., Lai, K.-Y., 2011. Convalescent plasma treatment reduced mortality in patients with severe pandemic influenza A (H1N1) 2009 virus infection. Clin. Infect. Dis. 52 (4), 447–456.
Iwabuchi, K., Yoshie, K., Kurakami, Y., Takahashi, K., Kato, Y., Morishima, T., 2020. Therapeutic potential of ciclesonide inhalation for COVID-19 pneumonia: report of three cases. J. Infect. Chemother.
Jin, Y.-H., Cai, L., Cheng, Z.-S., Cheng, H., Deng, T., Fan, Y.-P., Huang, Q., 2020a. A rapid advice guideline for the diagnosis and treatment of 2019 novel coronavirus (2019-nCoV) infected pneumonia (standard version). Milit. Med. Res. 7 (1), 4.
Jin, Y., Yang, H., Ji, W., Wu, W., Chen, S., Zhang, W., Duan, G., 2020b. Virology, epidemiology, pathogenesis, and control of COVID-19. Viruses 12 (4), 372.
Kadam, R.U., Wilson, I.A., 2017 Jan 10. Structural basis of influenza virus fusion inhibition by the antiviral drug Arbidol. Proc. Natl. Acad. Sci. U. S. A. 114 (2), 206–214.
Kaur, N., Singh, R., Dar, Z., Bijarnia, R.K., Dhingra, N., Kaur, T., 2020. Genetic comparison among various coronavirus strains for the identification of potential vaccine targets of SARS-CoV2. Infect. Genet. Evol. 104490.
Kemp, S.A., Meng, B., Ferriera, I., Datir, R., Harvey, W.T., Papa, G., Gallo, G., 2021. The COVID-19 Genomics UK (COG-UK) Consortium. In: Carabelli, A.M., Kenyon, J.C., Lever, A.M., De Marco, A., Saliba, C., Culap, K., Cameroni, E., Piccoli, L., Corti, D., James, L.C., Bailey, D., Robertson, D.L., Gupta, R.K. (Eds.), Recurrent Emergence and Transmission of a SARS-CoV-2 Spike Deletion H, p. 69.
Khalili, J.S., Zhu, H., Mak, N.S.A., Yan, Y., Zhu, Y., 2020. Novel coronavirus treatment with ribavirin: groundwork for an evaluation concerning COVID-19. J. Med. Virol. 92 (7), 740–746.
Khamitov, R.A., Loginova, S.I., Shchukina, V.N., Borisevich, S.V., Maksimov, V.A., Shuster, A.M., 2008. [Antiviral activity of arbidol and its derivatives against the pathogen of severe acute respiratory syndrome in the cell cultures]. Vopr. Virusol. 53 (4), 9–13. Repéré à. http://www.ncbi.nlm.nih.gov/pubmed/18756809.
Khan, R.J., Jha, R.K., Amera, G.M., Jain, M., Singh, E., Pathak, A., Singh, A.K., 2020. Targeting SARS-CoV-2: a systematic drug repurposing approach to identify promising inhibitors against 3C-like proteinase and 2'-O-ribose methyltransferase. J. Biomol. Struct. Dynam. 1–14.
Kissler, S.M., Tedijanto, C., Goldstein, E., Grad, Y.H., Lipsitch, M., 2020. Projecting the transmission dynamics of SARS-CoV-2 through the postpandemic period. Science 368 (6493), 860–868.
Ko, J.-H., Seok, H., Cho, S.Y., Ha, Y.E., Baek, J.Y., Kim, S.H., Kang, E.-S., 2018. Challenges of convalescent plasma infusion therapy in Middle East respiratory coronavirus infection: a single centre experience. Antivir. Ther. 23 (7), 617–622.
Korber, B., Fischer, W.M., Gnanakaran, S., Yoon, H., Theiler, J., Abfalterer, W., Foley, B., 2020. Tracking changes in SARS-CoV-2 spike: evidence that D614G increases infectivity of the COVID-19 virus. Cell 182 (4), 812–827.
Lam, T.T.-Y., Shum, M.H.-H., Zhu, H.-C., Tong, Y.-G., Ni, X.-B., Liao, Y.-S., Guan, Y., 2020. Identification of 2019-nCoV Related Coronaviruses in Malayan Pangolins in Southern China bioRxiv.
Lauer, S.A., Grantz, K.H., Bi, Q., Jones, F.K., Zheng, Q., Meredith, H.R., Lessler, J., 2020. The incubation period of coronavirus disease 2019 (COVID-19) from publicly reported confirmed cases: estimation and application. Ann. Intern. Med. 172 (9), 577–582.
Le, T.T., Cramer, J.P., Chen, R., Mayhew, S., 2020. Evolution of the COVID-19 vaccine development landscape. Nat. Rev. Drug Discov. 19 (10), 667–668.

Letko, M., Marzi, A., Munster, V., 2020. Functional assessment of cell entry and receptor usage for SARS-CoV-2 and other lineage B betacoronaviruses. Nat. Microbiol. 5 (4), 562–569.
Li, F., 2013. Receptor recognition and cross-species infections of SARS coronavirus. Antivir. Res. 100 (1), 246–254.
Li, M., Liu, K., Michalicek, J., Angus, J.A., Hunt, J.E., Dell'Italia, L.J., Husain, A., 2004. Involvement of chymase-mediated angiotensin II generation in blood pressure regulation. J. Clin. Invest. 114 (1), 112–120.
Li, Q., Guan, X., Wu, P., Wang, X., Zhou, L., Tong, Y., Feng, Z., 2020a. Early transmission dynamics in Wuhan, China, of novel coronavirus–infected pneumonia. N. Engl. J. Med. 382 (13), 1199–1207.
Li, W., Su, Y.-Y., Zhi, S.-S., Huang, J., Zhuang, C.-L., Bai, W.-Z., Zhou, Y.-B., 2020b. Virus shedding dynamics in asymptomatic and mildly symptomatic patients infected with SARS-CoV-2. Clin. Microbiol. Infect. 26 (11), 1556 e1.
Li, X., He, S., Ma, B., 2020c. Autophagy and autophagy-related proteins in cancer. Mol. Cancer 19 (1), 12.
Liao, Y.-C., Liang, W.-G., Chen, F.-W., Hsu, J.-H., Yang, J.-J., Chang, M.-S., 2002. IL-19 induces production of IL-6 and TNF-α and results in cell apoptosis through TNF-α. J. Immunol. 169 (8), 4288–4297.
Lin, C.-M., Saif, L.J., Marthaler, D., Wang, Q., 2016. Evolution, antigenicity and pathogenicity of global porcine epidemic diarrhea virus strains. Virus Res. 226, 20–39.
Liu, X., Zhang, Y., Xu, X., Du, W., Su, K., Zhu, C., Jiang, J., 2015. Evaluation of plasma exchange and continuous veno-venous hemofiltration for the treatment of severe avian influenza a (H7N9): a cohort study. Ther. Apher. Dial. 19 (2), 178–184.
Liu, Yang, Yan, L.M., Wan, L., Xiang, T.X., Le, A., Liu, J.M., Zhang, W., 2020a. Viral dynamics in mild and severe cases of COVID-19. Lancet Infect. Dis. 2019 (20), 2019–2020.
Liu, Yingxia, Yang, Y., Zhang, C., Huang, F., Wang, F., Yuan, J., Liu, L., 2020b. Clinical and biochemical indexes from 2019-nCoV infected patients linked to viral loads and lung injury. Sci. China Life Sci. 63 (3), 364–374.
Lu, H., 2020. Drug treatment options for the 2019-new coronavirus (2019-nCoV). BioSci. Trend 14 (1), 69–71.
Lu, H., Stratton, C.W., Tang, Y., 2020a. Outbreak of pneumonia of unknown etiology in Wuhan, China: the mystery and the miracle. J. Med. Virol. 92 (4), 401–402.
Lu, R., Zhao, X., Li, J., Niu, P., Yang, B., Wu, H., Tan, W., 2020b. Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding. Lancet 395 (10224), 565–574.
Luft, F.C., Dechend, R., Ller, D.N.M.Ü., 2012. Immune Mechanisms in Angiotensin II-Induced Target-Organ Damage, 44.
Luo, S., Zhang, X., Xu, H., 2020. Don't overlook digestive symptoms in patients with 2019 novel coronavirus disease (COVID-19). Clin. Gastroenterol. Hepatol. 18 (7), 1636–1637.
Luong-Nguyen, M., Hermand, H., Abdalla, S., Cabrit, N., Hobeika, C., Brouquet, A., Sauvanet, A., 2020. Nosocomial infection with SARS-Cov-2 within departments of digestive surgery. J. Visc. Surg. 157 (3), S13–S18.
Lurie, N., Saville, M., Hatchett, R., Halton, J., 2020. Developing Covid-19 vaccines at pandemic speed. N. Engl. J. Med. 382 (21), 1969–1973.
Lythgoe, M.P., Middleton, P., 2020. Ongoing clinical trials for the management of the COVID-19 pandemic. Trends Pharmacol. Sci. 41 (6), 363–382.
Malik, Y.A., 2020. Properties of coronavirus and SARS-CoV-2. Malays. J. Pathol. 42 (1), 3–11.
McIntosh, K., Dees, J.H., Becker, W.B., Kapikian, A.Z., Chanock, R.M., 1967. Recovery in tracheal organ cultures of novel viruses from patients with respiratory disease. Proc. Natl. Acad. Sci. Unit. States Am. 57 (4), 933–940.
Medicine, P., 1962. Dorothy Hamre, pp. 190–193 (30734).
Mihai, C., Dobrota, R., Schröder, M., Garaiman, A., Jordan, S., Becker, M.O., Distler, O., 2020. COVID-19 in a patient with systemic sclerosis treated with tocilizumab for SSc-ILD. Ann. Rheum. Dis. 79 (5), 668–669.
Monteagudo, L.A., Boothby, A., Gertner, E., 2020. Continuous intravenous anakinra infusion to calm the cytokine storm in macrophage activation syndrome. ACR Open Rheumatol. 2 (5), 276–282.
Monteil, V., Kwon, H., Prado, P., Hagelkrüys, A., Wimmer, R.A., Stahl, M., Penninger, J.M., 2020. Inhibition of SARS-CoV-2 infections in engineered human tissues using clinical-grade soluble human ACE2. Cell 181 (4), 905–913 e7.
Moore, J.P., Offit, P.A., 2021. SARS-CoV-2 vaccines and the growing threat of viral variants. JAMA, J. Am. Med. Assoc. 325 (9), 821–822.
Morais, I.J., Polveiro, R.C., Souza, G.M., Bortolin, D.I., Sassaki, F.T., Lima, A.T.M., 2020. The global population of SARS-CoV-2 is composed of six major subtypes. Sci. Rep. 10 (1), 1–9.
Moratto, D., Chiarini, M., Giustini, V., Serana, F., Magro, P., Roccaro, A.M., Quiros-Roldan, E., 2020. Flow cytometry identifies risk factors and dynamic changes in patients with COVID-19. J. Clin. Immunol.
Mulligan, M.J., Lyke, K.E., Kitchin, N., Absalon, J., Gurtman, A., Lockhart, S., Swanson, K.A., 2020. Phase I/II study of COVID-19 RNA vaccine BNT162b1 in adults. Nature 586 (7830), 589–593.
Murakami, M., Kamimura, D., Hirano, T., 2019. Pleiotropy and specificity: insights from the interleukin 6 family of cytokines. Immunity 50 (4), 812–831.
National Health Commission of People's Republic of China, 2020. An Update of Novel Coronavirus Pneumonia Outbreak as of 22:00 on February 12. Available online: http://www.nhc.gov.cn/xcs/yqtb/202002/26fb16805f024382bff1de80c918368f.shtml. (Accessed 15 June 2020).
Ni, Y.-N., Chen, G., Sun, J., Liang, B.-M., Liang, Z.-A., 2019. The effect of corticosteroids on mortality of patients with influenza pneumonia: a systematic review and meta-analysis. Crit. Care 23 (1), 99.
Nicastri, E., D'Abramo, A., Faggioni, G., De Santis, R., Mariano, A., Lepore, L., Molinari, F., Petralito, G., Fillo, S., Munzi, D., Corpolongo, A., Bordi, L., Carletti, F., Castiletti, C., Colavita, F., Lalle, E., Bevilacqua, N., Giancola, M.L., Scorzolini, L., Lanini, S., Palazzolo, C., De Domenico, A., Spinelli, M.A., Scognamiglio, P., Piredda, P., Iacomino, R., Mone, A., Puro, V., Petrosillo, N., Battistini, A., Vairo, F., Lista, F., Ippolito, G., 2020 Mar. On Behalf of Inmi and the Italian Army Covid-Study Groups. Coronavirus disease (COVID-19) in a paucisymptomatic patient: epidemiological and clinical challenge in settings with limited community transmission, Italy, February 2020. Euro. Surveill. 25 (11), 2000230.
Noor, M.A., Flint, O.P., Maa, J.-F., Parker, R.A., 2006. Effects of atazanavir/ritonavir and lopinavir/ritonavir on glucose uptake and insulin sensitivity: demonstrable differences in vitro and clinically. AIDS 20 (14), 1813–1821.
Norio, Y., Shutoku, M., Tyuji, H., Naoki, Y., 2020. Nelfinavir Inhibits Replication of Severe Acute Respiratory Syndrome Coronavirus 2 in Vitro, 1–5. bioRxiv preprint.
Ogando, N.S., Ferron, F., Decroly, E., Canard, B., Posthuma, C.C., Snijder, E.J., 2019. The curious case of the nidovirus exoribonuclease: its role in RNA synthesis and replication fidelity. Front. Microbiol. 10 (August), 1–17.
Ong, S.W.X., Tan, Y.K., Chia, P.Y., Lee, T.H., Ng, O.T., Wong, M.S.Y., Marimuthu, K., 2020. Air, surface environmental, and personal protective equipment contamination by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) from a symptomatic patient. JAMA 323 (16), 1610–1612.
Ou, X., Liu, Y., Lei, X., Li, P., Mi, D., Ren, L., Qian, Z., 2020. Characterization of spike glycoprotein of SARS-CoV-2 on virus entry and its immune cross-reactivity with SARS-CoV. Nat. Commun. 11 (1), 1620.
Pachetti, M., Marini, B., Benedetti, F., Giudici, F., Mauro, E., Storici, P., Gallo, R.C., 2020. Emerging SARS-CoV-2 mutation hot spots include a novel RNA-dependent-RNA polymerase variant. J. Transl. Med. 18, 1–9.
Pan, L., Mu, M., Yang, P., Sun, Y., Wang, R., Yan, J., Tu, L., 2020. Clinical characteristics of COVID-19 patients with digestive symptoms in Hubei, China: a descriptive, cross-sectional, multicenter study. Am. J. Gastroenterol. 115 (5), 766–773.
Powers, S.K., Morton, A.B., Hyatt, H., Hinkley, M.J., 2018. The renin-angiotensin system and skeletal muscle. Exerc. Sport Sci. Rev. 46 (4), 205–214.
Ren, L.-L., Wang, Y.-M., Wu, Z.-Q., Xiang, Z.-C., Guo, L., Xu, T., Wang, J.-W., 2020. Identification of a novel coronavirus causing severe pneumonia in human. Chinese Med J 133 (9), 1015–1024.
Richardson, P., Griffin, I., Tucker, C., Smith, D., Oechsle, O., Phelan, A., Stebbing, J., 2020. Baricitinib as potential treatment for 2019-nCoV acute respiratory disease. Lancet (London, England) 395 (10223), e30.
Rickman, H.M., Rampling, T., Shaw, K., Martinez-Garcia, G., Hail, L., Coen, P., Houlihan, C.F., 2021. Nosocomial transmission of coronavirus disease 2019: a retrospective study of 66 hospital-acquired cases in a London teaching hospital. Clin. Infect. Dis. 72 (4), 690–693.
Rothan, H.A., Byrareddy, S.N., 2020. The epidemiology and pathogenesis of coronavirus disease (COVID-19) outbreak. J. Autoimmun. 109 (February), 102433.
Sarkar, S., Soni, K.D., Khanna, P., 2020. Convalescent plasma a clutch at straws in COVID-19 management! A systematic review and meta-analysis. J. Med. Virol.
Scavone, C., Brusco, S., Bertini, M., Sportiello, L., Rafaniello, C., Zoccoli, A., Capuano, A., 2020. Current pharmacological treatments for COVID-19: what's next? Br. J. Pharmacol. bph.15072.
Schrezenmeier, E., Dörner, T., 2020. Mechanisms of action of hydroxychloroquine and chloroquine: implications for rheumatology. Nat. Rev. Rheumatol. 16 (3), 155–166.
Severe Covid-19 GWAS Group, Ellinghaus, D., Degenhardt, F., Bujanda, L., Buti, M., Albillos, A., Invernizzi, P., Fernández, J., Prati, D., Baselli, G., Asselta, R., Grimsrud, M.M., Milani, C., Aziz, F., Kässens, J., May, S., Wendorff, M., Wienbrandt, L., Uellendahl - Werth, F., Zheng, T., Yi, X., de Pablo, R., Chercoles, A.G., Palom, A., Garcia-Fernandez, A.E., Rodriguez-Frias, F., Zanella, A., Bandera, A., Protti, A., Aghemo, A., Lleo, A., Biondi, A., Caballero-Garralda, A., Gori, A., Tanck, A., Carreras Nolla, A., Latiano, A., Fracanzani, A.L., Peschuck, A., Julià, A., Pesenti, A., Voza, A., Jiménez, D., Mateos, B., Nafria Jimenez, B., Quereda, C., Paccapelo, C., Gassner, C., Angelini C, Cea C, Solier, A., Pestaña, D., Muñiz-Diaz, E., Sandoval, E., Paraboschi, E.M., Navas, E., García Sánchez, F., Ceriotti, F., Martinelli-Boneschi, F., Peyvandi, F., Blasi, F., Téllez, L., Blanco-Grau, A., Hemmrich- Stanisak, G., Grasselli, G., Costantino, G., Cardamone, G., Foti, G., Aneli, S., Kurihara, H., ElAbd, H., My, I., Galván-Femenia, I., Martín, J., Erdmann, J., Ferrusquía-Acosta, J., Garcia-Etxebarria, K., Izquierdo-Sanchez, L., Bettini, L.R., Sumoy, L., Terranova, L., Moreira, L., Santoro, L., Scudeller, L., Mesonero, F., Roade, L., Rühlemann, M.C., Schaefer, M., Carrabba, M., Riveiro-Barciela, M., Figuera Basso, M.E., Valsecchi, M.G., Hernandez - Tejero, M., Acosta-Herrera, M., D'Angiò, M., Baldini, M., Cazzaniga, M., Schulzky, M., Cecconi, M., Wittig, M., Ciccarelli, M., Rodríguez-Gandía, M., Bocciolone, M., Miozzo, M., Montano, N., Braun NvSacchi, N., Martínez, N., Özer, O., Palmieri, O., Faverio, P., Preatoni, P., Bonfanti, P., Omodei, P., Tentorio, P., Castro, P., Rodrigues, P.M., Blandino Ortiz, A., de Cid, R., Ferrer, R., Gualtierotti, R., Nieto, R., Goerg, S., Badalamenti, S., Marsal, S., Matullo, G., Pelusi, S., Juzenas, S., Aliberti, S., Monzani, V., Moreno, V., Wesse, T., Lenz, T.L., Pumarola, T., Rimoldi, V., Bosari, S., Albrecht, W., Peter, W., Romero-Gómez, M., D'Amato, M., Duga, S., Banales, J.M., Hov, J.R., Folseraas, T., Valenti, L., Franke, A., Karlsen, T.H., 2020 Oct 15. Genomewide association study of severe Covid-19 with respiratory failure. N. Engl. J. Med. 383 (16), 1522–1534.
Shang, J., Ye, G., Shi, K., Wan, Y., Luo, C., Aihara, H., Li, F., 2020. Structural basis of receptor recognition by SARS-CoV-2. Nature 581 (7807), 221–224.
Shen, X., Tang, H., McDanal, C., Wagh, K., Fischer, W., Theiler, J., Sanders, K.O., 2021. SARS-CoV-2 variant B. 1.1. 7 is susceptible to neutralizing antibodies elicited by ancestral spike vaccines. Cell Host Microbe 29 (4), 529–539.
Shereen, M.A., Khan, S., Kazmi, A., Bashir, N., Siddique, R., 2020. COVID-19 infection: emergence, transmission, and characteristics of human coronaviruses. J. Adv. Res. 24, 91–98.

Shulla, A., Heald-Sargent, T., Subramanya, G., Zhao, J., Perlman, S., Gallagher, T., 2011. A transmembrane serine protease is linked to the severe acute respiratory syndrome coronavirus receptor and activates virus entry. J. Virol. 85 (2), 873–882.
Sriram, K., Insel, P.A., 2020. A hypothesis for pathobiology and treatment of COVID-19: the centrality of ACE1/ACE2 imbalance. Br. J. Pharmacol. (April), 1–20.
Stebbing, J., Phelan, A., Griffin, I., Tucker, C., Oechsle, O., Smith, D., Richardson, P., 2020. COVID-19: combining antiviral and anti-inflammatory treatments. Lancet Infect. Dis. 20 (4), 400–402.
Tan, L., Wang, Q., Zhang, D., Ding, J., Huang, Q., Tang, Y.Q., Miao, H., 2020. Lymphopenia predicts disease severity of COVID-19: a descriptive and predictive study. Signal Transd. Target. Ther. 5 (1), 16–18.
Tang, J.W., Tambyah, P.A., Hui, D.S.C., 2021. Emergence of a new SARS-CoV-2 variant in the UK. J. Infect. 82 (4), e27-e28.
Tang, T., Bidon, M., Jaimes, J.A., Whittaker, G.R., Daniel, S., 2020. Coronavirus membrane fusion mechanism offers a potential target for antiviral development. Antivir. Res. 178, 104792.
Tegally, H., Wilkinson, E., Giovanetti, M., Iranzadeh, A., Fonseca, V., Giandhari, J., Msomi, N., 2020. Emergence and Rapid Spread of a New Severe Acute Respiratory Syndrome-Related Coronavirus 2 (SARS-CoV-2) Lineage with Multiple Spike Mutations in South Africa. MedRxiv.
Toots, M., Yoon, J.-J., Cox, R.M., Hart, M., Sticher, Z.M., Makhsous, N., Plemper, R.K., 2019. Characterization of orally efficacious influenza drug with high resistance barrier in ferrets and human airway epithelia. Sci. Transl. Med. 11 (515), eaax5866.
Tse, L.V., Hamilton, A.M., Friling, T., Whittaker, G.R., 2014. A novel activation mechanism of avian influenza virus H9N2 by furin. J. Virol. 88 (3), 1673–1683.
Vaarala, M.H., Porvari, K.S., Kellokumpu, S., Kyllönen, A.P., Vihko, P.T., 2001. Expression of transmembrane serine protease TMPRSS2 in mouse and human tissues. J. Pathol. 193 (1), 134–140.
Van Der Hoek, L., Pyrc, K., Jebbink, M.F., Vermeulen-Oost, W., Berkhout, R.J.M., Wolthers, K.C., Berkhout, B., 2004. Identification of a new human coronavirus. Nat. Med. 10 (4), 368–373.
Van Erp, E.A., Luytjes, W., Ferwerda, G., Van Kasteren, P.B., 2019. Fc-mediated antibody effector functions during respiratory syncytial virus infection and disease. Front. Immunol. 10, 548.
Varagic, J., Ahmad, S., Nagata, S., Ferrario, C.M., 2014. ACE2: angiotensin II/angiotensin-(1-7) balance in cardiac and renal injury. Curr. Hypertens. Rep. 16 (3), 1–9.
Vijgen, L., Keyaerts, E., Moës, E., Thoelen, I., Wollants, E., Lemey, P., Van Ranst, M., 2005. Complete genomic sequence of human coronavirus OC43: molecular clock analysis suggests a relatively recent zoonotic coronavirus transmission event. J. Virol. 79 (3), 1595–1604.
Walls, A.C., Park, Y.-J., Tortorici, M.A., Wall, A., McGuire, A.T., Veesler, D., 2020. Structure, function, and antigenicity of the SARS-CoV-2 spike glycoprotein. Cell 181 (2), 281–292 e6.
Wan, Y., Shang, J., Graham, R., Baric, R.S., Li, F., 2020. Receptor recognition by the novel coronavirus from Wuhan: an analysis based on decade-long structural studies of SARS coronavirus. J. Virol. 94 (7).
Wang, C., Liu, Z., Chen, Z., Huang, X., Xu, M., He, T., Zhang, Z., 2020a. The establishment of reference sequence for SARS-CoV-2 and variation analysis. J. Med. Virol. 92 (6), 667–674.
Wang, D., Hu, B., Hu, C., Zhu, F., Liu, X., Zhang, J., Peng, Z., 2020b. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in wuhan, China. JAMA, J. Am. Med. Assoc. 323 (11), 1061–1069.
Wang, M., Cao, R., Zhang, L., Yang, X., Liu, J., Xu, M., Xiao, G., 2020c. Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro. Cell Res. 30 (3), 269–271.
Wei, W.E., Li, Z., Chiew, C.J., Yong, S.E., Toh, M.P., Lee, V.J., 2020. Presymptomatic transmission of SARS-CoV-2—Singapore, january 23–march 16, 2020. MMWR (Morb. Mortal. Wkly. Rep.) 69 (14), 411.
Wibmer, C.K., Ayres, F., Hermanus, T., Madzivhandila, M., Kgagudi, P., Oosthuysen, B., Van der Berg, K., 2021. SARS-CoV-2 501Y. V2 escapes neutralization by South African COVID-19 donor plasma. Nat. Med. 27 (4), 622–625.
Woo, P.C.Y., Huang, Y., Lau, S.K.P., Yuen, K.-Y., 2010. Coronavirus genomics and bioinformatics analysis. Viruses 2 (8), 1804–1820.
Woo, P.C.Y., Lau, S.K.P., Chu, C., Chan, K., Tsoi, H., Huang, Y., Yuen, K., 2005. Characterization and complete genome sequence of a novel coronavirus, coronavirus HKU1, from patients with pneumonia. J. Virol. 79 (2), 884–895.
Woo, P.C.Y., Lau, S.K.P., Lam, C.S.F., Lai, K.K.Y., Huang, Y., Lee, P., Yuen, K.-Y., 2009. Comparative analysis of complete genome sequences of three avian coronaviruses reveals a novel group 3c coronavirus. J. Virol. 83 (2), 908–917.
Woo, P.C.Y., Wang, M., Lau, S.K.P., Xu, H., Poon, R.W.S., Guo, R., Yuen, K., 2007. Comparative analysis of twelve genomes of three novel group 2c and group 2d coronaviruses reveals unique group and subgroup features. J. Virol. 81 (4), 1574–1585.
Wu, C., Chen, X., Cai, Y., Zhou, X., Xu, S., Huang, H., Zhang, Y., 2020. Risk factors associated with acute respiratory distress syndrome and death in patients with coronavirus disease 2019 pneumonia in Wuhan, China. JAMA Intern. Med.
Xu, K., Cai, H., Shen, Y., Ni, Q., Chen, Y., Hu, S., Huang, H., 2020a. Management of corona virus disease-19 (COVID-19): the Zhejiang experience. J. Zhejiang Univ. 49 (1), 0.
Xu, X., Han, M., Li, T., Sun, W., Wang, D., Fu, B., Li, X., 2020b. Effective treatment of severe COVID-19 patients with tocilizumab. Proc. Natl. Acad. Sci. Unit. States Am. 117 (20), 10970–10975.
Yang, G., Tan, Z., Zhou, L., Yang, M., Peng, L., Liu, J., He, S., 2020a. Effects of angiotensin II receptor blockers and ACE (Angiotensin-Converting enzyme) inhibitors on virus infection, inflammatory status, and clinical outcomes in patients with COVID-19 and hypertension. Hypertension 76 (1), 51–58.
Yang, X., Yu, Y., Xu, J., Shu, H., Xia, J., Liu, H., Shang, Y., 2020b. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. Lancet Respir. Med. 8 (5), 475–481.
Zeberg, H., Pääbo, S., 2020 Nov. The major genetic risk factor for severe COVID-19 is inherited from Neanderthals. Nature 587 (7835), 610–612.
Zeng, L., Xia, S., Yuan, W., Yan, K., Xiao, F., Shao, J., Zhou, W., 2020. Neonatal early-onset infection with SARS-CoV-2 in 33 neonates born to mothers with COVID-19 in Wuhan, China. JAMA Pediatr. 174 (7), 722–725.
Zhang, Che, Gu, J., Chen, Q., Deng, N., Li, J., Huang, L., Zhou, X., 2020a. Clinical and epidemiological characteristics of pediatric SARS-CoV-2 infections in China: a multicenter case series. PLoS Med. 17 (6), e1003130.
Zhang, Chi, Wu, Z., Li, J.-W., Zhao, H., Wang, G.-Q., 2020b. The cytokine release syndrome (CRS) of severe COVID-19 and interleukin-6 receptor (IL-6R) antagonist tocilizumab may be the key to reduce the mortality. Int. J. Antimicrob. Agents.
Zhang, L., Yang, J.-R., Zhang, Z., Lin, Z., 2020c. Genomic Variations of SARS-CoV-2 Suggest Multiple Outbreak Sources of Transmission. Medrxiv.
Zhang, R., Li, Y., Zhang, A.L., Wang, Y., Molina, M.J., 2020d. Identifying airborne transmission as the dominant route for the spread of COVID-19. Proc. Natl. Acad. Sci. Unit. States Am. 117 (26), 14857–14863.
Zhao, S., Lin, Q., Ran, J., Musa, S.S., Yang, G., Wang, W., Wang, M.H., 2020. Preliminary estimation of the basic reproduction number of novel coronavirus (2019-nCoV) in China, from 2019 to 2020: a data-driven analysis in the early phase of the outbreak. Int. J. Infect. Dis. 92, 214–217.
Zhong, N., Zheng, B., Li, Y., Poon, L., Xie, Z., Chan, K., Guan, Y., 2003. Epidemiology and cause of severe acute respiratory syndrome (SARS) in Guangdong, People's Republic of China, in February, 2003. Lancet 362 (9393), 1353–1358.
Zhou, B., Zhong, N., Guan, Y., 2007. Treatment with convalescent plasma for influenza A (H5N1) infection. N. Engl. J. Med. 357 (14), 1450–1451.
Zhou, F., Yu, T., Du, R., Fan, G., Liu, Y., Liu, Z., Cao, B., 2020a. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet 395 (10229), 1054–1062.
Zhou, P., Fan, H., Lan, T., Yang, X.-L., Shi, W.-F., Zhang, W., Ma, J.-Y., 2018. Fatal swine acute diarrhoea syndrome caused by an HKU2-related coronavirus of bat origin. Nature 556 (7700), 255–258.
Zhou, P., Yang, X., Lou, Wang, X.G., Hu, B., Zhang, L., Zhang, W., Shi, Z.L., 2020b. A pneumonia outbreak associated with a new coronavirus of probable bat origin. Nature 579 (7798), 270–273.
Zhu, F.-C., Li, Y.-H., Guan, X.-H., Hou, L.-H., Wang, W.-J., Li, J.-X., Wang, L., 2020a. Safety, tolerability, and immunogenicity of a recombinant adenovirus type-5 vectored COVID-19 vaccine: a dose-escalation, open-label, non-randomised, first-in-human trial. Lancet 395 (10240), 1845–1854.
Zhu, Z., Lu, Z., Xu, T., Chen, C., Yang, G., Zha, T., Xue, Y., 2020b. Arbidol monotherapy is superior to lopinavir/ritonavir in treating COVID-19. J. Infect. 81 (1), e21-e23.
Zou, X., Chen, K., Zou, J., Han, P., Hao, J., Han, Z., 2020. Single-cell RNA-seq data analysis on the receptor ACE2 expression reveals the potential risk of different human organs vulnerable to 2019-nCoV infection. Front. Med. 14 (2), 185–192.