Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.
Understanding novel COVID-19: Its impact on organ failure and risk assessment for diabetic and cancer patients

Begum Dariya\textsuperscript{a}, Ganji Purnachandra Nagaraju\textsuperscript{b,⁎}

\textsuperscript{a} Department of Bioscience and Biotechnology, Banasthali University, Vanasthali, Rajasthan, 304022, India
\textsuperscript{b} Department of Hematology and Medical Oncology, Winship Cancer Institute, Emory University, Atlanta, GA, 30322, USA

ARTICLE INFO

Keywords:
COVID-19
Clinical trials
Pandemic
SARS
SARS-CoV-2

ABSTRACT

The current pandemic outbreak of COVID-19 originated from Wuhan, China. It is caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) with significant mortality and morbidity rate. The severe risk factors are commonly detected in patients of older age and with medical comorbidities like cancer and diabetes. Scientists and doctors have scrambled to gain knowledge about the novel virus and its pathophysiology in order to discover possible therapeutic regimens and vaccines for COVID-19. The therapeutic strategies like targeting the viral genome emphasize the promising approach to target COVID-19. Additionally, blocking the receptor, ACE2 via the neutralizing antibodies for viral escape that prevents it from entering into the cells provides another therapeutic regimen. In this review article, we have presented the effect of SARS-CoV-2 infection in comorbid patients and discussed organ failure caused by this virus. Based on the data available from the scientific literature and ongoing clinical trials, we have focused on therapeutic strategies. We hope that we would fill the gaps that puzzled the researchers and clinicians with the best of our knowledge collected for the betterment of the patients for the coming future.

1. Introduction

The SARS-CoV-2 is the frightful pathogen responsible for the outbreak of COVID-19 \cite{1}. The disease emerged in Wuhan City, China, in late December 2019 \cite{2} and is highly contagious with rapid human-to-human transmission \cite{3}. The WHO declared the COVID-19 outbreak a global emergency \cite{1}. The confirmed cases rose to 2,101,164 with 140,773 deaths and approximately 532,830 recoveries in almost 210 countries (reported by CSSE). Organizations around the world debated potential therapeutic strategies for treating COVID-19 patients and public health strategies. This pandemic also threatened the economy of the entire world. The complete role and severity of SARS-CoV-2 remain undefined. In this review article, we have focused on determining the relationship between SARS-CoV-2 infection and organ failure. Additionally, we focused on the comorbid population that includes patients with diabetes, and/or cardiovascular disease, who are COVID-19.

It is well established that morphologically, a virus is composed of genetic material surrounded by a protein capsid, which in some animal viruses is then surrounded by a lipid bilayer \cite{4}. This small pathogen can cause a pandemic, raising global alarms. Looking back through history, many viruses have triggered pandemics similar to COVID-19, including smallpox, tuberculosis, plague, Spanish flu, HIV/AIDS, and H1N1 flu. Table 1 shows a list of viruses that have infected humans and had non-human host species.

SARS-CoV-2 belongs to the family \textit{Coronaviridae}, which includes viruses responsible for diseases from the cold to MERS and SARS \cite{1}. SARS coronavirus, MERS coronavirus, 229E, and OC43 primarily infect humans. SARS-CoV-2 shares many similarities with SARS: they both have a crown or halo-like appearance and a glycoprotein-studded envelope.

2. Structure

The SARS-CoV-2 virus varies structurally from other viruses that have transmembrane crown-like spiked glycoproteins \cite{5}. It has 4 structural proteins, including envelope, spike, nucleocapsid and...
membrane. They are comprised of the functional subunits $S_1$ and $S_2$, which are responsible for detecting ACE2 receptors present on the host cells. ACE2 receptors are utilized by the virus to enter the host cells [6–8]. ACE2 expression is detected on type I and type II alveolar epithelium, upper respiratory system, heart, kidney tubular epithelium, pancreas, endothelial cells and enterocytes. The external spike protein determines the infectious nature and host specificity of SARS-CoV-2. The host cells (ACE2) allow the entry of the virus through the process called endocytosis. Moreover, the transmembrane proximal serine protease 2 (TMPRSS2) is the host protein that facilitates the entry of the virus through the S protein [5,9]. Additionally, it is involved in priming the S protein and potentiates its cleavage (Fig. 1).

Later, in the cytoplasm, the endosome exposes single-stranded RNA, the virus’ genetic material. The genome of the virus encodes various non-structural proteins like papain-like protease (PLpro), RNA-dependent RNA polymerase (RdRp) and the coronavirus main protease, 3C-like protease (3CLpro) [10,11]. The virus then hijacks the machinery of the cell to synthesize the viral polypeptides that encode for the replicase transcriptase complex. The active virus produces RNA through RdRp. PLpro actively deubiquitinases certain immune regulator cells like IF3 and NF-κB to suppress the immune response [11,12]. It uses the endoplasmic reticulum to synthesize M and S proteins, which are essential for its outer capsule. The viral proteinases 3CLpro and PLpro more effectively cleave the viral polyproteins with the help of the host translation machinery [10,11]. They produce new spikes and glycoproteins that are assembled into numerous copies of the virus. After replication of the genetic material, the golgi bodies exocytose the viruses, which then attack other cells. The created stress on the endoplasmic reticulum by the virus also induces apoptosis of the healthy host cells after releasing millions of viral copies. The viruses continue to attack other cells or end up as droplets and enter the lungs [13]. As an immune response, a fever is generated as the host’s immune system fights to clear the virus out of the body. Pro-inflammatory chemokines are activated to produce inflammatory cells. CD4 + T helper cells develop immunity against SARS-CoV-2 by producing IFN-γ and IL-17 [14]. SARS-CoV-2 also targets these circulating immune cells and induces apoptosis of CD3, CD8 and CD4 cells, causing lymphocytopenia [15–18]. This results in the overproduction of cytokines, causing a cytokine storm as it is released from the inhibition of innate immunity. The cytokine storm results in hyper inflammation, ultimately causing failure of multiple organs [19–21]. For instance, under severe conditions, a patient’s immune system can attack the lung cells. This results in fluid filling the lungs and cell apoptosis, causing difficulty in breathing. In some cases, this leads to death.

### Table 1

Previous major outbreaks of viruses with cross-species transmission.

| Disease       | Year | Host                        | Country                           |
|---------------|------|-----------------------------|-----------------------------------|
| SWINE FLU/H1N1| 1919 | Pig                         | Uncertain                         |
| HIV/AIDS      | 1920 | Chimpanzee, Monkey          | Democratic Republic of the Congo  |
| EBOLA         | 1976 | Monkey                      | Sudan and Zaire* *Currently DRC   |
| BIRD FLU      | 1997 | Water fowl                  | Hong Kong                         |
| SARS          | 2002 | Civet cat                   | China                             |
| MERS          | 2012 | Camel                       | South Arabia (Multiple Countries) |
| SARS-CoV-2    | 2019 | ? (Rat: Primary host Intermediate host: Pangolin) | China                             |

![Fig. 1. Inhibition of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) entry, replication, and endocytosis.](image-url)
at this stage of vigorous spread, it is essential to determine the me-
cases, followed by North America and Europe. Italy and the US, how-
disease on March 11, 2020. Initially, China had the most confirmed
quickly, causing the WHO to announce COVID-19 a global pandemic

However, SARS-CoV-2 was transmitted rapidly, quickly crossing bor-
ners of various countries. Thus, the number of established cases climbed
during the incubation phase or when the patient exhibits symptoms [5].
However, sometimes, a person in the asymptomatic phase is also found
to be contagious. Such individuals are referred to as super-spreaders.
For these cases, the transmission route was skin to skin or touching
inanimate objects mediated via the nose, mouth or eyes [5]. Exhaled
respiratory aerosols droplets are airborne and can remain in the air for
long periods. Thus, direct inhalation of these aerosol droplets or
touching the surface of infected objects like latex, steel, aluminium, or
surgical gloves are possible modes of transmission [5]. Thus viruses like
SARS-CoV-2 virus remain active outside the host body [22]. Further-
more, faecal and sewage transmission are also possible modes of
transmission [22]. Similarly, the virus in sewage was found to be active
for a few days to a week [23].

As of now, there are 400 SARS-CoV-2 genomes available from the
NCBI database. The sequence analysis of these available genomes could
form the platform for vaccine development. Sardar et al. [24] compared
genomes of SARS-CoV-2 from diverse geographical origins including
Wuhan (China), Italy, India, the USA, and Nepal by performing an
integrated phylogenetic analysis using bioinformatics tools. Additionally,
they also predicted that unique antiviral host miRNAs may target SARS-
CoV-2 genes. They related past research studies about the inhibitory

cytokine and growth factor reviews 53 (2020) 43–52

Table 2
Organs and cells attacked by COVID-19 with the risk level for organ failure.

| Organ                         | Type of cell tested                  | Proportion of ACE2 | Risk for organ failure |
|-------------------------------|--------------------------------------|--------------------|------------------------|
| Respiratory Tract/ Lungs/ Alveolar cells | Respiratory epithelial cells/ AT2 cells | 2%                 | High                   |
| Nasal and Bronchi             | Nasal and bronchial samples          | No                 | Low                    |
| Heart                         | Myocardial cells                     | 7.5 %              | High                   |
| Pleum                         | Biliary epithelial cells             | ~39 %              | High                   |
| Oesophage                      | Oesophageal epithelial cells         | > 1%               | High                   |
| Stomach and liver             | < 1%                                 | Low                |                        |
| Kidney                        | Kidney proximal tube                 | 4%                 | High                   |
| Urinary bladder               | Bladder urothelial cells             | 2.4 %              | High                   |

3. Symptoms

The typical signs of COVID-19 infection are fatigue, cough, fever,
myalgia, and some patients have also developed dyspnoea. Respiratory
symptoms like cough, shortness of breath, acute respiratory syndrome
and organ injury are also detected as serious complications [2,13]. The
patients also experience lung alterations, reduced circulating lympho-
ocytes and platelet counts. Human-to-human transmission usually occurs
during the incubation phase or when the patient exhibits symptoms [5].
However, sometimes, a person in the asymptomatic phase is also found
to be contagious. Such individuals are referred to as super-spreaders.
For these cases, the transmission route was skin to skin or touching
inanimate objects mediated via the nose, mouth or eyes [5]. Exhaled
respiratory aerosols droplets are airborne and can remain in the air for
long periods. Thus, direct inhalation of these aerosol droplets or
touching the surface of infected objects like latex, steel, aluminium, or
surgical gloves are possible modes of transmission [5]. Thus viruses like
SARS-CoV-2 virus remain active outside the host body [22]. Further-
more, faecal and sewage transmission are also possible modes of
transmission [22]. Similarly, the virus in sewage was found to be active
for a few days to a week [23].

As of now, there are 400 SARS-CoV-2 genomes available from the
NCBI database. The sequence analysis of these available genomes could
form the platform for vaccine development. Sardar et al. [24] compared
genomes of SARS-CoV-2 from diverse geographical origins including
Wuhan (China), Italy, India, the USA, and Nepal by performing an
integrated phylogenetic analysis using bioinformatics tools. Additionally,
they also predicted that unique antiviral host miRNAs may target SARS-
CoV-2 genes. They related past research studies about the inhibitory

4. Epidemic to pandemic

The life-threatening pneumonia outbreak started as an epidemic
within Wuhan City, China. On December 31, 2019, the Wuhan Municipal Health Commission reported critically ill cases of viral
pneumonia. Later, the International Committee on Taxonomy of Viruses
(ICTV) identified the virus as SARS-CoV-2 [26]. The Chinese govern-
ment then mandated a quarantine to control the epidemic stage and
to determine the effectiveness of a quarantine against the virus [27].
However, SARS-CoV-2 was transmitted rapidly, quickly crossing bor-
ders of various countries. Thus, the number of established cases climbed
quickly, causing the WHO to announce COVID-19 a global pandemic
disease on March 11, 2020. Initially, China had the most confirmed
cases, followed by North America and Europe. Italy and the US, how-
ever, surpassed China in terms of the number of established cases. Thus,
at this stage of vigorous spread, it is essential to determine the me-

Table 2
Organs and cells attacked by COVID-19 with the risk level for organ failure.

| Organ                         | Type of cell tested                  | Proportion of ACE2 | Risk for organ failure |
|-------------------------------|--------------------------------------|--------------------|------------------------|
| Respiratory Tract/ Lungs/ Alveolar cells | Respiratory epithelial cells/ AT2 cells | 2%                 | High                   |
| Nasal and Bronchi             | Nasal and bronchial samples          | No                 | Low                    |
| Heart                         | Myocardial cells                     | 7.5 %              | High                   |
| Pleum                         | Biliary epithelial cells             | ~39 %              | High                   |
| Oesophage                      | Oesophageal epithelial cells         | > 1%               | High                   |
| Stomach and liver             | < 1%                                 | Low                |                        |
| Kidney                        | Kidney proximal tube                 | 4%                 | High                   |
| Urinary bladder               | Bladder urothelial cells             | 2.4 %              | High                   |

3. Symptoms

The typical signs of COVID-19 infection are fatigue, cough, fever,
myalgia, and some patients have also developed dyspnoea. Respiratory
symptoms like cough, shortness of breath, acute respiratory syndrome
and organ injury are also detected as serious complications [2,13]. The
patients also experience lung alterations, reduced circulating lympho-
ocytes and platelet counts. Human-to-human transmission usually occurs
during the incubation phase or when the patient exhibits symptoms [5].
However, sometimes, a person in the asymptomatic phase is also found
to be contagious. Such individuals are referred to as super-spreaders.
For these cases, the transmission route was skin to skin or touching
inanimate objects mediated via the nose, mouth or eyes [5]. Exhaled
respiratory aerosols droplets are airborne and can remain in the air for
long periods. Thus, direct inhalation of these aerosol droplets or
touching the surface of infected objects like latex, steel, aluminium, or
surgical gloves are possible modes of transmission [5]. Thus viruses like
SARS-CoV-2 virus remain active outside the host body [22]. Further-
more, faecal and sewage transmission are also possible modes of
transmission [22]. Similarly, the virus in sewage was found to be active
for a few days to a week [23].

As of now, there are 400 SARS-CoV-2 genomes available from the
NCBI database. The sequence analysis of these available genomes could
form the platform for vaccine development. Sardar et al. [24] compared
genomes of SARS-CoV-2 from diverse geographical origins including
Wuhan (China), Italy, India, the USA, and Nepal by performing an
integrated phylogenetic analysis using bioinformatics tools. Additionally,
they also predicted that unique antiviral host miRNAs may target SARS-
CoV-2 genes. They related past research studies about the inhibitory

was believed that bat, especially Rhinolophus affinis, was the natural
host of the virus [7]. It is still uncertain how this virus was transmitted
from bat to human, although some research has suggested that pangolin
(Manus javanica) could be the intermediate host [14,28,29]. The ag-
gressive intervention steps were taken by governments, such as iso-
lating and quarantining latent patients, have reduced the contact rate
and effectively decreased the peak for COVID-19 cases.

5. COVID effect on organ failure

In addition to the symptoms discussed previously, there are other
clinical manifestations observed with COVID-19 infection, including
the failure of multiple organs. SARS-CoV and 2019-nCoV / SARS-CoV-2
were found to share a common progenitor with HKU9−1, the bat
coronavirus. The similarity in the spike structure proteins of SARS-CoV-
2 showed a higher affinity with ACE2 as discussed earlier [5]. ACE2
receptors are present on the target cells, making the cells highly sus-
ceptible to the entry of SARS-CoV-2 and subsequent pathogenesis. For
instance, type II alveolar cells (AT2) of the lungs are believed to have
higher ACE2 expression and are the primary targets for SARS-CoV-2
[7]. In this study, also examined different cell types from different or-
gans that showed ACE2 expression using single-cell-RNA seq (ScRNA-
seq) data to determine the effect of COVID-19 for the first time. We
tabulated their results for different organs showing the type of cells
tested, the proportion of cells expressing ACE2, and the risk of organ
failure in Table 2. The expression levels of ACE2 mRNA and protein
in different organs were specified with the presence of gene transcription.
They further strengthened their work by analysing ACE2 expression
levels in various human organs and comparing the results with the
Human Protein Atlas, databases like Uniprot and a few works in the
literature. Their analysis of various published data demonstrated that
ACE2 proteins are expressed in the epithelial cells of lung alveolar cells,
myocardial cells, gastrointestinal cells and renal tubules [6,30–33].
Additionally, myocardial infarctions increase ACE2 expression, in-
creasing the likelihood of cardiac injury [34]. This contributes to the
understanding of the effect of COVID-19 on various organs.

Cardiac injury was the most common complication that related
to an elevated risk of disease severity in COVID-19 patients. About 23% of
COVID-19 ill patients had cardiac injury [17], and 13% showed an
elevation in creatinine kinase [35]. The mRNA and protein ACE2 ex-
pression levels are higher in these patients with cardiac disease,
creating an increased risk for severe COVID-19 complications, including
heart failure. Moreover, it was also suggested by Liang Chen et al. that
the human heart infected with SARS-CoV-2 attacks pericytes, resulting
in microvascular disorders [36]. This microvascular disorder causes
dysfunction in capillary endothelial cells, low microvascular reactivity
and high vascular permeability. The modelling and docking results also
showed that SARS-CoV-2 has a receptor-binding domain that fits well
with human ACE2 receptors. Moreover, the amino acid residues in-
cluding 491Tyr, 441Leu, 479Gln, 487Asn, 472Phe and 480Ser of the
SARS-CoV-2 mature spike protein are involved in binding with the
ACE2 receptor [36]. Thus, these amino acid residues in the binding
domain are important to consider in the design of potential drug
treatments. Taken together, these findings show that COVID-19 in patients with cardiovascular disease often results in a critical condition and death.

The organ failure common in COVID-19 patients results in alveolar and acute respiratory failure [3]. Because there is a substantial comparison between the pathogenesis of SARS-CoV-2 and SARS, researchers and clinicians should explore the infection mechanisms of SARS-CoV-2 based on the effect of SARS. Earlier research showed that about 6.7% of SARS patients possessed acute kidney injury (AKI), leading to a mortality of almost 91.7% [37]. Thus, physicians need to consider the effect of SARS-CoV-2 on the kidney. Cheng et al. [38] explored the occurrence of AKI in COVID-19 patients to determine their association. They reported that 14.4% of the COVID-19 patients in the study showed elevated levels of serum creatinine upon admission. Most of these patients were male, older, or had other illnesses. Additionally, 13.1% had elevated blood urea nitrogen (BUN). After hospitalization (10 days), the serum creatinine peak elevated to 91 ± 67 μmol/L, and about 43.9% of the patients showed proteinuria. These patients also showed a higher incidence of AKI (11.9%) after hospitalization; only 5.1% had AKI during admission. The in-hospital mortality recorded was 16.1%; however, those with raised baseline serum creatinine had a mortality rate of 33.7%. Furthermore, the Univariate Cox regression analysis also showed that COVID-19 patients who were male and/or older than 65 were highly prone to in-hospital death. Therefore, clinicians must be aware of kidney diseases in COVID-19 patients after hospitalization as early diagnosis and effective treatment would reduce the death rate in patients.

6. COVID-19 effect on cancer patients

Recent clinical data has shown that cancer patients receiving anti-neoplastic treatment are highly vulnerable to the effects of COVID-19, similar to immune-suppressed and older (> 60 years) patients [39]. Patients with hematological malignancy, neutropenia or lymphopenia as well as those receiving multiple doses of chemotherapy are at higher risk for hospitalization (4 times) higher and death (10 times) higher compared with the healthy population of COVID-19 patients [40]. Moreover, cancer patients diagnosed with COVID-19 who received antitumor therapy within 14 days before diagnosis are at elevated risk for severe complications. Zhang et al. [41] also concluded that malignant patients with COVID-19 had poor prognosis. They suggested that vital COVID-19 screening should be carried out for the cancer patients receiving antitumor therapy, and cancer patients with COVID-19 should avoid using immunosuppression drugs or use a decreased dose.

The demographic data from Italy showed that among 3000 reported COVID-19 cases, 20 % of the patients who died had a medical history of malignancy in the previous 5 years [42]. Among 1524 patients joined to the Zhongnan Hospital of Wuhan University, 12 patients had COVID-19 [39]. This same study showed that the patients with NSCLC (7 patients) who were > 60 years of age had the highest incidence rate for COVID-19 disease [39], followed by oesophageal (4 patients) and breast cancer (3 patients) [41]. The report also showed that these patients were more likely to suffer life-threatening complications and require ICU admission or mechanical ventilation [39]. These deaths were due to acute myocardial infarction, acute respiratory syndrome, septic shock and pulmonary embolism [41].

For these 28 cancer patients in Wuhan who also had COVID-19, the lab findings at the time of admission included low blood count (anemic), leucopenia and lymphopenia [41]. Additionally, low levels of serum albumin, high levels of serum globulin and high lactate dehydrogenase with sensitive C-reactive protein in higher levels and erythrocyte sedimentation rate were also detected [41]. The radiological findings included ground-glass opacity, patchy consolidation [43], interlobular septal thickening, reticular appearances and fibrous strips. The patients with patchy consolidations were at greater risk for developing severe problems than those without [43]. Moreover, lung cancer patients were reported with decreased lung volume along with pneumonia [41]. It was also shown that among these malignant patients with COVID-19, 70% of the patients had stage IV cancer and are with severe complications [41]. The research and clinical data available now contribute to the proper understanding of the risk of COVID-19 occurrence in malignant patients. Thus, this helps oncologists tailor the COVID-19 clinical management for the benefit of such patients. Additionally, establishing essential guidelines and recommendations for the care of cancer patients based on a patient’s age, affected organ and stage of cancer during the COVID-19 outbreak is very crucial [44].

7. Risk of COVID-19 in patients with diabetes mellitus

Patients with diabetes mellitus (DM), obesity and/or hypertension and COVID-19 have increased mortality and morbidity rates [17,18,35,42,45–47]. However, the association of DM with hypertension and cardiovascular diseases as risk factors for COVID-19 is still unknown and not clear. In one study that included 52 ICU-admitted COVID-19 patients, about 22% of the patients were diabetic. Of the 52 admitted patients, 32 did not survive [17,44]. This suggests that DM is the predominant comorbidity with COVID-19. A few mechanisms have been suggested by researchers to explain the high susceptible of DM patients to COVID-19 pathogenesis. These include having an efficient cellular binding and easy entry of the virus, low chance for viral clearance, weakened T-cell function, highly prone to cytokine storm and hyperinflammation. Additionally, ACE2 expression weakens with the administration of insulin [48,49], whereas ACE2 expression is up-regulated by hypoglycaemic agents like thiazolidinediones, glucagon-like peptides-1, ACE inhibitors, angiotensin-receptor blockers, anti-hypertensives and statins [50–54]. The rodent DM model showed higher expression ACE2 in heart, lung, kidney and pancreas compared with normal controls [48,49]. Furthermore, Rao et al. [55] from their Mendelian randomization study determined from the diseases and traits that the lungs of DM patient showed increased expression of ACE2. The protein levels of proteases like furin that facilitate the cleaving of the spike protein for virus entry were also found to be overexpressed in DM patients [56]. In order to understand the association between ACE2 expression in DM patients and COVID-19 infection, we must understand the mechanism of ACE2 action. ACE2 catalyses the conversion of angiotensin II to angiotensin 1-9, and angiotensin 1-9, (Fig. 2). These act as antioxidants and anti-inflammatory enzymes and are found to be protective against lung Acute respiratory distress syndrome (ARDS) [57]. After SARS-CoV-2 binds with ACE2, the virus degrades it, and thus the free angiotensin II induces acute lung injury [58]. Additionally, increased loss of potassium levels through urine and increased secretion of aldosterone also result after the intrusion of the virus [35]. Thus, ACE2 is unable to protect against lung injury after the entry of SARS-CoV-2 because ACE2 is degraded by the virus. The aetiology is still confusing, but it is clear that DM patients are at higher risk for severe complications with COVID-19. Thus, we have an urgent need for research studies focused on determining how hyperinsulinaemia and hyperglycaemic conditions affect SARS-CoV-2 infection and how DM might affect vaccine efficacy.

8. Therapeutic strategies for novel COVID-19

Unfortunately, therapeutic treatments are not yet available for this COVID-19 outbreak as it takes years for a drug to come into the market. However, at present, the clinical trials and sympathetic use are being expedited. Thus currently, social distancing, patient isolation and supportive medical care and monitoring are the only available approaches. The potential pharmaceutical approaches to blocking the ACE2 receptor or a viral protein to mediate the inhibition of COVID-19 are tabulated in Table 3. These include the following potential options:
Angiotensin I potentiates the cleavage of ACE2 in RAS with the formation of angiotensin (1-9)

Fig. 2. Angiotensin converting enzyme (ACE) catalyzes the conversion of angiotensin I to angiotensin II. ACE2 catalyses the formation of angiotensin (1-9) and angiotensin (1-7) from angiotensin I and angiotensin II respectively.

8.1. Developing a vaccine

Developing safe and efficient vaccines during the COVID-19 pandemic stage is very crucial. The antibodies developed against viral spike proteins by the host immune system are utilized in developing vaccines. The process includes purifying the plasma that contains antibodies from a recovered COVID-19 patient. The next step is targeting these antibodies to the spike protein of the virus to neutralize it and likely to develop passive immunity against disease [58]. Moreover, structural and sequence homology of SARS-CoV-2 with the other lethal CoV viruses such as SARS and MERS would help determine the best epitope to use in the design of an anti-SARS-CoV-2 vaccine. This would essentially neutralize the viral S protein, although creating a vaccine is a slow process. The SARS-CoV and SARS-CoV-2 spike proteins are 76.5 % homologous at the amino acid level [5]. Recently, Wan et al. [69] also determined that SARS-CoV with residue 479 (lysine) and SARS-CoV-2 with glutamine 394 residue recognize and bind to lysine 31 of the ACE2 receptor in humans [70]. An alternate approach is to inject neutralizing antibodies into COVID-19-infected animals to obtain purified polyclonal antibodies from these animals [71]. This process can be expedited, but the outcome is not guaranteed as the animals might not produce the expected neutralizing antisera [72].

8.2. Inhibiting the priming activity of TMPRSS2

TMPRSS2 is a proximal serine protease present in the host that plays a crucial role in proteolytic processing called priming. It is actively involved in priming of the S protein of SARS-CoV-2 after its binding with the ACE2 receptor [73]. Thus, it is crucial for the entry and spread of SARS-CoV-2. A couple of reports recently showed that SARS-CoV-2 also enters through this mechanism, and thus the entry of SARS-CoV-2 into cells may be blocked by using inhibitors of TMPRSS2, such as camostat mesylate (Fig. 1) [7,67].

8.3. ACE2 receptor blockers

ACE2 is a mono-carboxy peptidase that hydrolyses angiotensin II. As discussed earlier, ACE2 binds with high affinity to SARS-CoV-2, thereby allowing the virus to enter the host cells. Thus, targeting the binding site of the ACE2 receptor and SARS-CoV-2 with antibodies or therapeutic drugs might provide a successful treatment strategy. Moreover, ACE2 shows similar homology with ACE, which hydrolyses angiotensin I to angiotensin II [74]. This led to a lot of confusion between ACE inhibitors and ACE2 inhibitors. Increased ACE activity and reduced ACE2 activity promote lung injury. Furthermore, there have been several reports that ACE inhibitors (ACEI) inhibit the expression of ACE2 in kidney and heart [50]. As determined histologically, ACE2 is primarily membrane-bound but is also present as a soluble form in body fluids at a very low level [75,76]. The cleavage in the membrane ADAM17 anchor by a disintegrin and metalloprotease 17 present at the membrane-bound ACE2 receptor increases the occurrence of more soluble ACE2 in the body fluids (Fig. 1). Thus, the membrane-bound ACE2 is no longer available for SARS-CoV-2 to bind with it (Fig. 1). Angiotensin II via its type 1 receptor (AT1R) induces the upregulation of ADAM17, which potentiates the cleavage and increases the soluble ACE2 concentration in the body fluids. Thus, AT1R upregulates ADAM17 and increases soluble ACE2 [77], whereas the administration of AT1R blockers (ARB) prevents the process and maintains the membrane-bound ACE2 receptors (Fig. 1). Additionally, ARB is also found to consistently alter the expression of ACE2 at the protein and mRNA levels. ACE2 expression is upregulated in the renal vasculature and cardiac tissue [78–80]. Therefore, using ARB to treat for pathological conditions like lung injury without any complaint of COVID-19 infection is beneficial, but it may be critical during COVID-19 infection [81,82]. Lung injury without SARS-CoV-2 infection is caused by downregulated alveolar ACE2 levels and decreased angiotensin II metabolism [83,84]. However, several researchers have proposed the use of ARB to protect against lung injury during COVID-19 infection.

To summarize, comorbidities including cardiovascular, hypertension diseases and diabetes 2, are generally treated with blockers such as RAS blockers, ARBs, ACE inhibitors and AR blockers. The current clinical trials performed to determine the efficacy of drugs against COVID-19 are tabulated in Table 4. Moreover, in the most recent studies, Liu et al. [85] determined that the serum levels of angiotensin II are increased in COVID-19 patients who had pneumonia and lung injury. This indicates that SARS-CoV-2 disrupts the balance of the ratio of ACE/ACE2, resulting in increased levels of angiotensin II. This further induces inflammation, pulmonary vasoconstriction and oxidative organ damage, causing acute lung injury. Thus, the modulation of RAS by ARBs or recombinant ACE2 increases the amount of ACE2 receptors and controls the levels of angiotensin II [86]. Moreover, this also increases the level of soluble ACE2 that competitively binds with SARS-CoV-2,
The role of vital proteins of host and virus during infection and the possible efficacy of the drugs against SARS-CoV-2.

| Table 3                                                                 | Refs          |
|-------------------------------------------------------------------------|---------------|
| **Proteins to target**                                                  | **Hypothesis to act against SARS-CoV-2** | **Already tested against SARS-CoV-2** | **Possible adverse side effects** |
| Ebola, Hepatitis C, RSV                                                  |               |                               | Nausea, vomiting, gastrointestinal disturbances, cardiac abnormalities, allergic reactions and gastrointestinal disorders. |
| Elevated levels of transaminases and renal injury.                    | [60, 62]      |                               | Nausea, vomiting, gastrointestinal disturbances, cardiac abnormalities, allergic reactions and gastrointestinal disorders. |
| Adverse side effects                                                     |               |                               |                                                                 |
| **Proteins**                                                             | **Drugs**     | **References**                |
| **Viral Genome proteins**                                               | **Hypothetical to act against SARS-CoV-2** | **Already tested against SARS-CoV-2** | **Possible adverse side effects** |
| S protein Spike protein helps in holding virus to the host              | Arbidol       |                               | Prevents binding of S protein to the host-cell membrane and blocks its entry. |
| PLpro Papain-like protease- proteolysis viral polyprotein               | Lopinavir     |                               | Prevents binding of viral S protein to the host-cell membrane and blocks its entry. |
| 3CLpro Coronavirus protease- proteolysis viral polyprotein              | Remdesivir    |                               | Prevents binding of S protein to the ACE2 receptor and blocks its entry. |
| ACE2 Protein receptor binds with viral S protein allowing virus to enter the host cell | Camostat mesylate | – | Camostat mesylate prevents binding of viral S protein to the ACE2 receptor. |

**Additional approaches**

Additionally, rapid sequencing of the SARS-CoV-2 genome has enabled epidemiological tracking, diagnosis and promotes the development of therapeutic strategies for infection prevention. The SARS-CoV-2 genome sequence has been published recently (the GenBank accession number is MN908947.3), allowing researchers to synthesize the gene and consider S protein expression as the immunogen. Understanding other viruses like MERS-CoV and SARS-CoV from the past offers novel insights into potential therapies for combating COVID-19. Researchers are now targeting different parts of the viral mechanism for infection.

One approach is to prevent the reproduction of SARS-CoV-2 by targeting the viral RNA polymerase, which is used to synthesize the viral RNA genome and is not produced naturally in the host body [88]. If the viral polymerase could be selectively targeted or blocked, the virus could no longer produce RNA copies and the viral infection could be stopped. For instance, remdesivir is a drug developed against the Ebola virus specifically, but it showed promising results when used to treat MERS-CoV infection [63]. Remdesivir, conceals the viral RNA polymerase and prevents the proofreading to occur via the viral exo-nucleases. This way it decreases the viral RNA production in the host cells (Fig. 1). Remdesivir was also suggested to give positive results when used against SARS-CoV-2, and a clinical trial sponsored by the NIH began in February 2020. However, the clinical impact of this drug against COVID-19 is still unclear and researchers are waiting for the outcome of the patient’s ongoing clinical trials.

Targeting viral processing is another possible treatment strategy, which takes advantage of the fact that viral proteases have a specific site where protein cutting occurs [89]. Therefore, drugs that fit into this specific site can block the functionality of a viral protease, thereby inhibiting viral protein production. Viral proteases are promising therapeutic targets since they are available in limited numbers in the host and have a specific site for catalytic activity [89]. This type of therapy has been successfully used against HIV, and now researchers are seeking to use protease inhibitors against SARS-CoV-2.

Targeted disruption of the packaging of a virus is another possible approach since, after packaging, the virus leaves the host cell through exocytosis and attacks other cells [90]. However, in coronaviruses there are no proteins specifically designed for packaging; all of the viral proteins are actively involved in viral packaging. Thus, this type of approach does not seem promising for the treatment of COVID-19.

Other potential treatments target the virulent shell. The fully matured virus particles have a shell made up of spike and membrane proteins. The membrane proteins are buried within the membrane, but the spike proteins are external. Thus, a virus can be targeted exteriorly by attacking the spike proteins with drugs. Since it is on the exterior, the spike protein is also the main target of antibodies produced by the host’s immune system [91]. This led to the development of vaccines against SARS-CoV-2, which we have already discussed earlier in this article.

**Use of chloroquine and hydroxychloroquine**

Chloroquine and its derivative hydroxychloroquine have long been used for the prevention and treatment of malaria and chronic inflammatory diseases like rheumatoid arthritis [92]. Both of these drugs are found to be very effective in treating dysregulations caused by a coronavirus in China [63]. It was notably reported that chloroquine inhibits the replication of HCoV-229E and SARS-CoV-1. It was also found to prevent the entry of virus by inhibiting the glycosylation of ACE2 receptors, block proteases and regulate acidification in the endosome (Fig. 1). Chloroquine and hydroxychloroquine also promote an
### Table 4

List of current clinical trials performing to determine the efficacy of drugs.

| Source | Title of the study | Intervention | NCT number | Phase | Posted on Date | Sponsor |
|--------|-------------------|--------------|-------------|-------|----------------|---------|
| -      |  |  | NCT04324996 | Phase I/II | March 27, 2020 | Chongqing Public Health Medical Center |
| -      |  |  | NCT04302766 | Phase II | March 10, 2020 | U.S. Army Medical Research and Development |
| -      |  |  | NCT04330300 | Phase IV | April 13, 2020 | National University of Ireland, Galway, Ireland |
| -      |  |  | NCT04321096 | Phase I | April 6, 2020 | University of Aarhus |
| -      |  |  | NCT04335786 | Phase IV | April 8, 2020 | Radboud University |
| -      |  |  | NCT04328012 | Phase II | April 8, 2020 | Bassett Healthcare |
| -      |  |  | NCT04340544 | Phase III | April 9, 2020 | University Hospital Tuebingen |
| -      |  |  | NCT04342221 | Phase III | April 9, 2020 | University Hospital Tuebingen |
| -      |  |  | NCT04313127 | Phase II | April 14, 2020 | Instituto Nacional de Rehabilitacion |
| -      |  |  | NCT04341389 | Phase II | April 15, 2020 | Institute of Biotechnology, Academy of Military Medical Sciences, PLA of China |
| -      |  |  | NCT04343989 | Phase II | April 15, 2020 | Instituto Nacional de Medicina y Infectología del Ejército, El Salvador |
| -      |  |  | NCT04345341 | Phase II | April 16, 2020 | Instituto Nacional de Medicina y Infectología del Ejército, El Salvador |
| -      |  |  | NCT04343989 | Phase II | April 16, 2020 | Instituto Nacional de Medicina y Infectología del Ejército, El Salvador |
| -      |  |  | NCT04343989 | Phase II | April 16, 2020 | Instituto Nacional de Medicina y Infectología del Ejército, El Salvador |
immunomodulatory effect via the production of cytokines and suppress autophagy and lysosomal functionality in host cells [90,93]. Chloroquine was identified to suppress SARS-CoV-2 growth in vitro, showing more than a half-maximal effective concentration (EC50) with a low micromolar range [94]. There are no adverse side effects known for the proposed usage of chloroquine against COVID-19 [95]. There was a sharp increase in the prescription of these drugs for COVID-19 patients with the reference of USA President Mr Donald Trump in late March in the US (https://www.bbc.com/news/51980731). Furthermore, it was also granted by the Food and Drugs Administration (FDA) for the use of hydroxychloroquine and chloroquine drug as an emergency as authorized for COVID-19 therapy. There are more than 20 clinical trials carried in the US, UK, China and Spain on these drugs. The later reports from the clinical trials also suggested that chloroquine drug would minimise the disease duration [95]. But, later on, April 24, the FDA also licenced the usage of the drug issued under the warning regarding the dangerous threat for the serious heart rhythm adverse side effects in COVID-19 patients when used. However, to get a complete clearance of virus, chloroquine is combined with other drugs. For instance, hydroxychloroquine combined with azithromycin resulted in greater clearance of virus than hydroxychloroquine alone [96].

9. Conclusions

The outbreak of SARS-CoV-2 is an ongoing global public health crisis. The expedition of clinical trials for various potential therapeutic drugs is essential to evaluate their efficacy at this midpoint of the pandemic. The pressure on researchers to develop promising therapeutic drugs for COVID-19 is very high. These drugs include cytokines, bioengineered and vector-based antibodies to block the gene expression of the virus and to develop a vaccine. However, there are currently no therapeutic drugs available to treat COVID-19. Clinical symptoms caused by SARS-CoV-2 infection should be closely monitored to determine whether the virus has infected internal organs so that appropriate therapy can be performed. A patient’s demographic data and past medical history are crucial to forming a good therapeutic plan. Moreover, together, antiviral research and clinical trials will improve the effectiveness of therapy and facilitate the production of a drug or vaccine in record time. In this article we focused on the effect of COVID-19 with other diseases (comorbidities) and associated organ injury to provide researchers with a better understanding of the clinical implications of COVID-19. We also focused on the ongoing research and clinical trials conducted for the benefit of COVID-19 patients to determine the efficacy of drugs for treatment.

Contributors

GPN involved in literature search, figures, and study design, BD involved in literature search, and figures. BD and GPN drafted and finalized the paper. Both authors read, and approved this review.

Declaration of Competing Interest

None to declared.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.cytogfr.2020.05.001.

References

[1] C.P.E.R.E. Novel, The epidemiological characteristics of an outbreak of 2019 novel coronavirus diseases (COVID-19) in China, Zhonghua liuxingbingxue za zhi = Zhonghua liuxingbingxue zazhi 41 (2) (2020) 145.
[2] N. Zhu, D. Zhang, W. Wang, X. Li, B. Yang, J. Song, X. Zhao, B. Huang, W. Shi, B. Lu, A novel coronavirus from patients with pneumonia in China, 2019, N. Engl. J. Med. 382 (8) (2020) 727–733.
[3] C. Huang, Y. Wang, X. Li, L. Ren, J. Zhao, Y. Hu, L. Zhang, G. Fan, J. Xu, X. Gu, Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China, Lancet 395 (10223) (2020) 497–506.
[4] D.P. NAYAK, Virus morphology, replication, and assembly, Viral Ecology (2000) 63.
[5] X. Xu, P. Chen, J. Wang, J. Feng, H. Zhou, X. Li, W. Zhang, P. Hao, Evolution of the novel coronavirus from the ongoing Wuhan outbreak and modeling of its spike protein for risk of human transmission, Sci. China Life Sci. 63 (3) (2020) 457–460.
[6] D. Harmer, M. Gilbert, R. Borman, K.L. Clark, Quantitative mRNA expression profiling of ACE2 2, a novel human angiotensin converting enzyme, FEBS Lett. 552 (1–2) (2002) 107–110.
[7] P. Zhou, X.-L. Yang, X.-G. Wang, B. Hu, L. Zhang, W. Zhang, H.-R. Si, Y. Zhu, B. Li, C.-L. Huang, A pneumonia outbreak associated with a new coronavirus of probable bat origin, Nature 579 (7798) (2020) 270–273.
[8] M.C. Letko, A. Marzi, V. Munster, Functional assessment of cell entry and receptor usage for SARS-CoV-2 and other lineages B betacoronaviruses, Nat. Microbiol. 5 (4) (2020) 562–569.
[9] A.C. Walls, Y.-J. Park, A.M. Tortorici, A. Wall, A.T. McGeoir, D. Veesler, Structure, function, and antigenicity of the SARS-CoV-2 spike glycoprotein, Cell 181 (2) (2020) 281–292.
[10] J. Ziebuhr, E.J. Snijder, A.E. Gorbalenya, Virus-encoded proteinases and proteolytic processing in the Nidovirales, J. Gen. Virol. 81 (4) (2000) 853–879.
[11] Y.M. Báez-Santos, S.E.S. John, A.D. Mesecar, The SARS-coronavirus papain-like protease: structure, function and inhibition by designed antiviral compounds, Antiviral Res. 115 (2015) 21–38.
[12] T. Lee, M.M. Cherney, C. Huitjema, J. Liu, K.E. James, P.C. Powers, L.D. Elts, M.N. James, Crystal structures of the main peptidase from the SARS coronavirus inhibited by a substrate-like aza-peptide epoxide, J. Mol. Biol. 353 (5) (2005) 1137–1151.
[13] Y.G. Li, W.Z. Bai, T. Hashikawa, The neuroinvasive potential of SARS-CoV2 may be at least partially responsible for the respiratory failure of COVID-19 patients, J. Med. Virol. (2020) 1–3.
[14] L. Wahlba, N. Jain, A.Z. Fire, M.J. Shoura, K.L. Artiles, M.J. McCoy, D.E. Jeong, Identification of a pangolin niche for a 2019-nCoV-like coronavirus through an extensive meta-genomagenic search, bioRxiv (2020).
[15] L.-J. Chen, T. Xu, H.-Y. Yu, Q.-C. Zhong, J.-C. Zhong, The ACE2/aepin signaling, microRNAs, and hypertension, Int. J. Hypertens. 2015 (2015) 496861.
[16] C. Wu, X. Chen, Y. Cai, X. Zhang, X. Zhou, X. Hu, H. Huang, L. Zhang, X. Zhou, C. Du, Y. Zhang, Risk factors associated with acute respiratory distress syndrome and death in patients with coronavirus disease 2019 pneumonia in Wuhan, China, JAMA Intern. Med. (2020).
[17] X. Yang, Y. Yu, J. Xu, H. Shi, H. Liu, Y. Wu, L. Zhang, Y. Zu, M. Fang, T. Yu, 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. 52213:2600 (2020) 30079–30085.
[18] J.-J. Zhang, X. Dong, Y.-Y. Cao, Y.-d. Yuan, Y.-b. Yang, Y.-q. Yan, C.A. Akdis, Y.-d. Gao, Clinical characteristics of 140 patients infected with SARS-CoV-2 in Wuhan, China, Allergy (2020).
[19] Y. Gao, T. Li, M. Han, X. Li, J. Li, W. Xu, Y. Yu, Y. Zhu, Y. Liu, X. Wang, L. Wang, Diagnostic Utility of Clinical Laboratory Data Determinations for Patients with the Severe Covid-19, J. Med. Virol. (2020).
[20] P. Mehta, D.F. McAuley, M. Brown, E. Sanchez, R.S. Tattersall, J.J. Manson, COVID-19: consider cytokine storm syndromes and immunosuppression, Lancet 395 (10229) (2020) 1033–1034.
[21] S. Wan, Q. Yi, S. Fan, J. Yu, X. Zhang, L. Guo, C. Lang, Q. Xiao, K. Xiao, Z. Yi, Characteristics of lymphocyte subsets and cytokins in peripheral blood of 123 hospitalized patients with 2019 novel coronavirus pneumonia (NCP), Medrxiv (2020).
[22] D.J. Weber, W.A. Rutala, W.A. Fischer, H. Kanamori, E.E. Sickbert-Bennett, Emerging infectious diseases: Focus on infection control issues for novel coronavirus (Severe Acute Respiratory Syndrome-Cov and Middle East Respiratory Syndrome-Cov), hemorhagic fever viruses (Lassa and Ebola), and highly pathogenic avian influenza viruses, A (H5N1) and A (H7N9), Am. J. Infect. Control 44 (5) (2016) 531–532.
[23] L.-J. Chen, R. Xu, H.-Y. Yu, Q.-C. Zhong, J.-C. Zhong, The ACE2/aepin signaling, microRNAs, and hypertension, Int. J. Hypertens. 2015 (2015) 496861.
[24] C. Hou, J. Chen, Y. Zhou, L. Hua, J. Yuan, S. He, Y. Guo, S. Zhang, Q. Jia, C. Zhao, The effectiveness of the quarantine of Wuhan city against the Corona Virus Disease 2019 (COVID-19): well-validated SEIR model analysis, J. Med. Virol. (2020).
[25] T.Y-Y. Lam, M.H.-H. Shum, H.-C. Zhu, Y.-G. Tong, X.-B. Ni, Y.-S. Liao, W. Wei, Y.-W. M. Cheung, W.-J. Li, L.-F. Li, Identification of 2019-nCoV related coronaviruses in Malayan pangolins in southern China, BioRxiv (2020).
[26] K. Xiao, J. Zhai, Y. Feng, N. Zhou, X. Zhang, J.-J. Zou, N. Li, Y. Guo, X. Li, X. Shen, 50
Isolation and characterization of 2019-nCoV-like coronavirus from Malanese pangolins, BioRxiv (2020).

I. Hamming, W. Timens, M. Bulthuis, A. Lely, G. Navis, H. van Goor, Tissue distribution of ACE2 protein, the functional receptor for SARS coronavirus. A first step in understanding SARS pathogenesis, The Journal of Pathology: A Journal of the Pathological Society of Great Britain and Ireland 203 (2) (2004) 631–637.

M.A. Crackower, R. Sarao, G.Y. Oudit, C. Yagil, I. Kozieradzki, S.E. Scanga, Tissue specific up regulation of ACE2 in rabbit model of atherosclerosis by atorvastatin: role of epigenetic histone modifications, Biochem. Pharmacol. 93 (3) (2017) 438–441.

S. Kowalczyk, A. Broer, N. Tietze, J.M. Vanlambrouck, J.E. Rasko, S. Broer, A protein complex in the brush-border membrane explains a Hartnup disorder allele, FASEB J. 22 (8) (2008) 2880–2887.

M. Dongouh, F. Hsieh, E. Baronas, K. Godbout, M. Gosselin, N. Stagliano, B.D. Dariyand G. P. Nagaraju, Angiotensin converting enzyme 2 is an essential regulator of heart function, Nature 417 (6891) (2002) 822–828.

L. Chen, X. Li, M. Chen, Y. Feng, C. Xiong, The ACE2 expression in human heart indicates a new potential mechanism of heart injury among patients infected with SARS-CoV-2, Cardiovasc. Res. 116 (6) (2020) 1097–1100.

K.H. Chu, W.K. Tsang, C.S. Tang, M.F. Lam, F.M. Lai, K.F. To, K.S. Fung, H.L. Tang, W.W. Yan, H.W. Chiu, Acute renal impairment in coronavirus-associated severe acute respiratory syndrome, Kidney Int. 67 (2) (2005) 698–705.

Y. Cheng, R. Luo, K. Wang, M. Zhang, Z. Wang, L. Dong, J. Li, Y. Yao, S. Ge, G. Xu, Kidney disease is associated with in-hospital death of patients with COVID-19, Kidney Int. 94 (1) (2018) 105–113.

P. Sidaway, COVID-19 and cancer: what we know so far, Nat. Oncol. (2020) 1–11.

A. Rittmaner, N. Elaikam-Raz, I. Vinograd, I. Hamming, W. Timens, M. Bulthuis, A. Lely, G. Navis, H. van Goor, Tissue distribution of ACE2 protein, the functional receptor for SARS coronavirus. A first step in understanding SARS pathogenesis, The Journal of Pathology: A Journal of the Pathological Society of Great Britain and Ireland 203 (2) (2004) 631–637.

L. Zhang, F. Zhu, L. Xie, C. Wang, J. Wang, R. Chen, P. Jia, H. Guan, L. Peng, Y. Chen, Clinical characteristics of COVID-19-infected cancer patients: a retrospective case study in three hospitals within Wuhan, China, Ann. Oncol. 30(2) 7534 (2020) 36383–36993.

G. Onder, G. Rezza, S. Brusaforo, Case-fatality rate and characteristics of patients dying in relation to COVID-19 in Italy, JAMA 323(16) (2020) 1622–1623.

H. Shi, X. Han, N. Jiang, Y. Cao, O. Alwood, J. Gu, Y. Fan, C. Zhang, Radiological findings from 81 patients with COVID-19 pneumonia in Wuhan, China: a descriptive study, Lancet Infect. Dis. 20 (4) (2020) 425–434.

N. Bittar, J. Kattan, H.R. Kourie, D. Mukherji, N.E. Saghir, The Lebanese Society of Medical Oncology (LSMO) statement on the care of patients with cancer during the COVID-19 pandemic, Future Medicine (2020) 615–617.

C.F.D. Control, Prevention, National Diabetes Statistics Report, 2020, Centers for Disease Control, Atlanta, GA (2020). pp. 1–12.

J. Yang, Y. Zhang, X. Guo, K. Pu, Z. Chen, Q. Guo, R. Ji, H. Wang, Y. Wang, Y. Zhou, Prevalence of comorbidities in the novel Wuhan coronavirus (COVID-19) infection: a systematic review and meta-analysis, Int. J. Infect. Dis. 94 (2020) 91–95.

P. Zhou, T. Yu, R. Wang, D. Wang, X. Li, Y. Zhong, Z. Xiao, S. Liu, Y. Yang, R. Guo, Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective study, Lancet Infect. Dis. 20 (4) (2020) 425–434.

H. Roca-Ho, M. Riera, V. Palau, J. Pascual, M.J. Soler, Characterization of ACE2 and ACE2 expression within different organs of the NOD mouse, Int. J. Mol. Sci. 18 (3) (2017) 563.

J. Yu, W. Deng, A crucial role of angiotensin converting enzyme 2 (ACE2) in SARS coronavirus infection, Med. Sci. Monit. 26 (2020) II-181 (2020) 1-1.

C.M. Farrar, J. Jessup, M.C. Chappell, D.B. Avellini, K.B. Brossmann, E.A. Tallant, D.I. Diz, P.E. Gallagher, Effect of angiotensin-converting enzyme inhibition and angiotensin II receptor blockers on cardiac angiotensin-converting enzyme-2, Circulation 111 (20) (2005) 2605–2610.

M. Romani-Pérez, V. Outeiriño-Iglesias, C.M. Moya, P. Sanz-Tebar, L.C. González-Matías, E. Vigo, F. Mallos, Activation of the GLP-1 receptor by ligulatuzumab increases ACE2 expression, rescues right ventricular hypertrophy, and improving the production of SP-A and SP-B in the lungs of type 1 diabetes rats, Endocrinology 156 (10) (2015) 3559–3569.

K. Tóth, G. Patel, S. Kumar, P.A. Karpe, M. Sanghavi, V. Outeiriño-Iglesias, Tissue specific up-regulation of ACE2 in rabbit model of atherosclerosis by atorvastatin: role of epigenetic histone modifications, Biochem. Pharmacol. 93 (3) (2015) 343–351.

B.D. Van-Asperen, L. De Bats, R. Lutter, J.R. Vliegenthart, P.A. Schep, GNY. Moll, M.J. Van den Hoof, J. Kaminke, A.C. Vanaken, L. Van Overhoven, I. Verheyden, M. Paul, W.-j. Guan, Z.-y. Ni, Y. Hu, W.-h. Liang, C.-q. Ou, J.-x. He, L. Liu, H. Shan, C.-l. Lei, L.M. Burrell, J. Risvanis, E. Kubota, R.G. Dean, P.S. MacDonald, S. Lu, C. Tikellis, S. Kowalczuk, A. Broer, N. Tietze, J.M. Vanslambrouck, J.E. Rasko, S. Broer, A.I. Hamming, W. Timens, M. Bulthuis, A. Lely, G. Navis, H. van Goor, Tissue distribution of ACE2 protein, the functional receptor for SARS coronavirus. A first step in understanding SARS pathogenesis, The Journal of Pathology: A Journal of the Pathological Society of Great Britain and Ireland 203 (2) (2004) 631–637.

M. Romaní-Pérez, R. Lutter, P.A. Specht, G.N. Moll, J.B. van Woensel, C.M. van der Loos, H. van Goor, J. Kamilke, S. Florquin, A.P. Bo, Acute respiratory distress syndrome leads to reduced ratio of ACE/ACE2 activities and is prevented by angiotensin-(1–7) or an angiotensin II receptor antagonist, J. Pathol. 225 (4) (2011) 518–525.

W. Zhang, Y.-Z. Xu, B. Liu, R. Wu, Y.-Y. Yang, Q.-Q. Xie, X. Zhang, P. Santisteban, L.C. González-Fuentes, Angiotensin converting enzyme inhibitor increases ACE2 expression in insulin-sensitive tissues with high-fat diet-induced nonalcoholic steatohepatitis, Sci. World J. 2014 (2010) 604309.
F398–F405.

[81] J. Wysocki, A. Goodling, M. Burgaya, K. Whitlock, J. Ruzinski, D. Batlle, M. Afkarian, Urine RAS components in mice and people with type 1 diabetes and chronic kidney disease, Am. J. Physiol. Renal Physiol. 313 (2) (2017) F487–F494.

[82] L. Bitker, L.M. Burrell, Classic and nonclassic renin-angiotensin systems in the critically ill, Crit. Care Clin. 35 (2) (2019) 213–227.

[83] D. Gurwitz, Angiotensin receptor blockers as tentative SARS‐CoV‐2 therapeutics, Drug Dev. Res. (2020).

[84] Y. Imai, K. Kuba, S. Rao, Y. Huan, F. Guo, B. Guan, P. Yang, R. Sarao, T. Wada, H. Leong-Poi, Angiotensin-converting enzyme 2 protects from severe acute lung failure, Nature 436 (7047) (2005) 112–116.

[85] Y. Liu, Y. Yang, C. Zhang, F. Huang, F. Wang, J. Yuan, Z. Wang, J. Li, J. Li, C. Feng, Clinical and biochemical indexes from 2019-nCoV infected patients linked to viral loads and lung injury, Sci. China Life Sci. 63 (3) (2020) 364–374.

[86] B. Shanmugaraj, K. Siriwattananon, K. Wangkanont, W. Phoolcharoen, Perspectives on monoclonal antibody therapy as potential therapeutic intervention for Coronavirus disease-19 (COVID-19), Asian Pac. J. Allergy Immunol. 38 (1) (2020) 10–18.

[87] A. Savarino, J.R. Boelaert, A. Cassone, G. Majori, R. Cauda, Effects of chloroquine on viral infections: an old drug against today’s diseases, Lancet Infect. Dis. 3 (11) (2003) 722–727.

[88] D. Zhou, S.-M. Dai, Q. Tong, COVID-19: a recommendation to examine the effect of hydroxychloroquine in preventing infection and progression, J. Antimicrob. Chemother. (2020).

[89] Y. Liu, Y. Yang, C. Zhang, F. Huang, F. Wang, J. Yuan, Z. Wang, J. Li, J. Li, C. Feng, Clinical and biochemical indexes from 2019-nCoV infected patients linked to viral loads and lung injury, Sci. China Life Sci. 63 (3) (2020) 364–374.

[90] C. A. Devaux, J.-M. Rolain, P. Colson, D. Raoult, New insights on the antiviral effects of chloroquine against coronavirus: what to expect for COVID-19? Int. J. Antimicrob. Agents (2020) 105938.

[91] J. Lung, Y.S. Lin, Y.H. Yang, Y.L. Chou, L.H. Shu, Y.C. Cheng, H.T. Liu, C.Y. Wu, The potential chemical structure of anti-SARS-CoV-2 RNA-dependent RNA polymerase, J. Med. Virol. (2020).

[92] A. Savarino, J.R. Boelaert, A. Cassone, G. Majori, R. Cauda, Effects of chloroquine on viral infections: an old drug against today’s diseases, Lancet Infect. Dis. 3 (11) (2003) 722–727.

[93] D. Zhou, S.-M. Dai, Q. Tong, COVID-19: a recommendation to examine the effect of hydroxychloroquine in preventing infection and progression, J. Antimicrob. Chemother. (2020).

[94] X. Yao, F. Ye, M. Zhang, C. Cui, B. Huang, P. Niu, X. Liu, L. Zhao, F. Dong, C. Song, In vitro antiviral activity and projection of optimized dosing design of hydroxychloroquine for the treatment of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), Clin. Infect. Dis. (2020).

[95] J. Gao, Z. Tian, X. Yang, Breakthrough: Chloroquine phosphate has shown apparent efficacy in treatment of COVID-19 associated pneumonia in clinical studies, Biosci. Trends 14 (1) (2020) 72–73.

[96] P. Gautret, J.-C. Lagier, P. Parola, L. Meddeb, M. Mailhe, B. Doudier, J. Courjon, V. Giordanengo, V.E. Vieira, H.T. Dupont, Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial, Int. J. Antimicrob. Agents (2020) 105949.