RESOLUTION OF CORONAVIRUS DISEASE 2019 (COVID-19)

Keywords:

Novel coronavirus, SARS-CoV-2, COVID-19, severe acute respiratory syndrome coronavirus-2, diagnosis, epidemiology, pathology, treatment.

Abstract

Towards the end of 2019, an increasing number of viral pneumonia cases were reported in Wuhan Hubei Province, China. The causative agent was identified as a coronavirus, which has been named as the Severe Respiratory Syndrome Coronavirus 2 (SARS-COV-2). Since the initial outbreak, the virus has spread rapidly throughout China and other countries leading to significant human fatalities, resulting in a global pandemic. Attempts have been initiated to develop effective approaches that allow rapid detection of viral pathogens to prevent disease transmission, identify crises associated with health, and wellbeing, set up suitable treatment modalities, and monitor responses to treatment in order to control the current pandemic. Due to the high rate of transmission, changing nature of the viral symptoms, diagnosis and treatment modalities, an up to date comprehensive literature review is needed. This review provides a comprehensive overview on the current state of knowledge about the viral replication and pathogenicity, current diagnostic and therapeutic strategies and how they have been applied for the management of SARS-COV-2. This review will be of interest to scientists and clinicians and make a significant contribution towards the management of symptoms, development of vaccines and targeted therapies aiming to prevent and halt the outbreak.

1. INTRODUCTION

Coronaviruses (CoVs) are a positive-sense single-stranded RNA virus that cause diseases in humans and animals. The human coronaviruses (HCoVs) were first identified as causes of acute upper respiratory infection (URI) in 1962. Over the past few years, HCoVs have more often been found to be associated with severe upper and lower respiratory tract infection (RTI). They have been identified as a main cause of pneumonia in older adults and immunocompromised patients [1]. Over the last two decades, two highly pathogenic human coronaviruses were identified, including coronaviruses associated with severe acute respiratory syndrome (SARS-CoV-2) and the Middle East respiratory syndrome (MERS-CoV) which emerged in different regions of the world [2]. On 31st December, 2019, a new strain of coronavirus was isolated and named as severe acute respiratory syndrome coronavirus 2 (SARS-Cov-2) by the International Committee on Taxonomy of Viruses (ICTV) from patients with pneumonia of unknown aetiology in Wuhan city, China [3] . On 11th March, 2020, the World Health Organisation (WHO) announced that COVID-19 is a "public-health emergency of international concern" [4].

The CoVs belongs to the family Coronaviridae that consist of alpha, beta, delta, and gamma coronaviruses with large RNA genomes and a unique replication method; the new SARS-CoV-2 was identified as a beta-coronavirus [5]. A number of studies reported that the CoVs have the largest non-segmented genomes between all RNA viruses with a length of close to 30 kb [6]. This genome size increase enhances genomic plasticity, thus permitting alteration via mutations and recombination, resulting in higher genetic diversity and higher chances of cross-species transmission [7].

This review aims to provide a comprehensive overview of the current state of knowledge and research about the mode and mechanisms of transmission, epidemiology, pathogenicity, natural immunity, genetic basis, diagnostics and therapeutics for COVID-19 diseases.

2. EPIDEMIOLOGY, ORIGIN AND DISEASE TRANSMISSION

The study of evolving epidemiology and spread of COVID-19 pandemic is very important to acquire 'timely information to guide intervention policy' [8]. A recent study has attempted to depict the changing epidemiology and transmission dynamics of SARS-CoV-2 in mainland China (outside Hubei province) and reached a conclusion that initial steps taken to stop transmission of virus might have been effective in slowing down the outbreak [8]. The basic strategies for the control of ongoing pandemic are dependent on the control measure policies and human behaviour such as surveillance and isolation, contact tracing, movement restrictions, social distancing, hand washing and increased awareness in the community [8].

2.1. Ethnicity: The evidence suggests an overrepresentation of American blacks in the USA and black, Asian, and minority ethnic (BAME) communities in the UK among COVID-19 patients. For example, the first 11 doctors who died in the UK due to COVID-19 were all from BAME communities [9]. A study in the UK confirmed that a third of COVID-19 patients admitted to critical care units are from BAME groups. The death rates (per 100,000) in the New York City among Black/African American and Hispanic/Latino persons are 92.3 and 74.3, respectively, which are much higher in comparison with white (45.2) or Asian (34.5) groups. Living conditions, genetic predisposition, work circumstances, socio-economic inequalities, cultural, or lifestyle factors, and underlying health conditions may contribute this morbidity and mortality [10].

2.2. Transmission: The mode of transmission of COVID-19 seems to be similar to that of SARS-CoV [11]. For example, in 2002, the SARS-CoV emergence resulted from cross- species transmission from animal to human and spread further via human-to-human transmission. COVID-19 has now also followed the same pattern with superspreading events (SSEs) resulting to a pandemic [11].

With the progression of the outbreak, the primary mode of transmission from human to human has been identified to be through droplets of respiratory mucus secretion, and direct contact. Droplet transmission occurs when a person talks, sneezes or coughs and the virus is released from the respiratory secretions. Making direct contact with the mucous membrane of an infected patient, the droplets tends to transmit the virus. Droplets do not travel more than six feet and do not linger in the air. This raises uncertainty regarding the mechanism of transmission perhaps there are other possible ways by which a person can get infected, for example, by touching surface or objects that have the virus on it and then touching mouth, nose or eyes [12]. A study reported the presence of SARS-CoV-2 in faecal and blood swab, further indicating the possibility of multiply routes of transmission [13]. In the absence of an effective vaccine, the only way to control and halt this outbreak is to use isolation, frequent hand wash and social distancing as an effective preventive measure.

2.3. Herd immunity: Infected individuals may develop antibodies to the virus by 14 days following the onset of symptoms [14]. Preliminary evidence suggests that some of these antibodies are protective, but this remains to be established. However, it remains unknown whether all infected patients mount a protective immune response and how long this protective effect will last.

3. PATHOGENESIS AND REPLICATION

The coronaviruses have the largest genome among positive-stranded RNA viruses and possess the biggest known replicating RNA molecules. SARS-CoV-2 replication begins when the viral spike (S) glycoprotein on the surface of the virus binds to a complementary angiotensin-converting enzyme 2 (ACE2) receptor in the host cell [15]. The ACE2 receptor is expressed in epithelial cells within a range of organs including lung, kidney and blood vessels [16]. Analysis of the receptor binding domain (RBD) of the S protein reveals that majority of the amino acid residues important for receptor binding are conserved among SARS-CoV and SARS-CoV-2, implying that the SARS-CoV-2 strains use the same host receptor for cell entry [16]. The amino acid sequences of the ACE2 receptor responsible for binding in farm animals and cats has only a few exchanges compared with the human receptor, implying that the species barrier for SARS-CoV-2 transmission is limited [17]. However, after binding, there is a membrane fusion between the virus and the host cell and a protease of the host cell cleaves and activates the receptor-bounded spike protein allowing the virus to enter the host cell through endocytosis [18]. The viral genome then enters the cell cytoplasm. The SARS-CoV-2 RNA genome has a 5' methylated cap and a 3' polyadenylated tail, which allows the RNA to attach to the host cell's ribosome for translation. The viral genome is replicated with the help of a RNA-dependent RNA polymerase (RdRp) [19]. RdRp helps to meditate the synthesis of negative-sense genomic RNA from the positive-sense genomic RNA, which is followed by the replication of positive-sense genomic RNA from the negative -sense genomic RNA [19]. Additionally, the RdRp also mediates the transcription of the negative- sense sub-genomic mRNA to the corresponding sub-genomic positive mRNA. The positive genomic RNA becomes the progeny viruses. These RNAs are translated by the host ribosomes into membrane proteins and accessory proteins and this

translation process occurs in the endoplasmic reticulum (ER) [20]. The viral structural membrane proteins are Spike (S), Envelop (E), Membrane (M) and Nucleocapsis (N) proteins. SARS-CoV-2 uses the S-protein to bind on cell surface molecules. However, the S protein also regulates viral uptake and is regulated by the cell surface-associated transmembrane protease serine protease 2 (TMPRSS2), a key enzyme for S protein cleavage and priming [21]. The protein N binds the genomic RNA and the protein M is integrated into the membrane of the endoplasmic reticulum like the envelope protein S. The M proteins, which contain three putative transmembrane domains then direct protein-protein interactions required for an assemblage of viruses. Following its binding to the nucleocapsid, the final progeny viruses are transported by Golgi vesicles to the cell membrane and released into the extracellular space through exocytosis (Figure 1) [22].

4. THE GENDERED IMPACT OF SARS-COV-2

Interestingly, gender-dependent susceptibility patterns have been observed in SARS-CoV-2 infections, with males shown to be more affected than females. One study of 140 patients diagnosed with SARS-CoV-2 in China, found that a higher percentage of males were critically ill (67%) in comparison to females [23]. Additionally, a recent report found that out of 1099 patients, 58% of these were men [24]. Similar patterns have also observed previously for both the SARS-CoV and MERS-CoV infections. Males and females differ in their immunological response to infectious pathogens, with males often exhibiting a much weaker immune response in comparison to females [25]. Animal models have previously been utilised to investigate the difference in susceptibility of each gender to the SARS-CoV virus. A study involving induction SARS-CoV among mice of different ages found that male mice display enhanced susceptibility to the SARS-CoV compared with age-matched female mice [26]. Male mice have exhibited higher titres of the virus, alveolar oedema, increased vascular leakage and prolonged

inflammatory response which was indicated by elevated levels in pro-inflammatory cytokines and chemokines [26]. Male mice also have presented with increased levels of inflammatory monocyte macrophages (IMM) and neutrophils within their lungs, and a reduction in these inflammatory monocyte macrophages partially protected these mice from SARS [26] . A reason for this protective effect is due to the fact that IMMs are a predominant source of both chemokines and pro-inflammatory cytokines. Studies have found that elevated levels of cytokines and chemokines found in mice models, correlated with an increase in the number of IMMs [27]. Examples of such chemokines and pro-inflammatory cytokines include IL2, IL7, IL10, CCL2, IP10, MCP1, MIP1α, and TNFα, all of which have shown to contribute to the lethality of both SARS-CoV and COVID-19 by inducing cytokine storm [28].

Many factors can lead to sex-specific differences in disease outcomes. For example, females sex hormone oestrogens have been shown to lead to the downregulation of MCP-1 expression during inflammation and thus inhibit TLR4 mediated NFκβ activation in macrophages, ultimately resulting in suppression in monocyte-macrophage recruitment. To further support this, researchers have found that treating female mice with an oestrogen receptor antagonist or ovariectomy (removal of ovaries) have led to increased mortality for SARS-CoV overall. On the other hand, treating gonadectomised mice with oestrogen has led to a reduction in chemokines TNF and CCL2 and showed a protective effect against the influenza virus [29]. Additionally, when male mice have been treated with a non- steroidal anti-androgen such as flutamide or when complete removal of testes is performed (gonadectomy), no difference is observed in overall mortality and morbidity following treatment with SARS-CoV virus. The SARS-CoV virus however, causes a reduction in serum testosterone levels. This sex-dependent susceptibility has also been observed in humans and thus identifies the protective effects of oestrogen receptor

signalling in females as well as suggesting that androgens may not play a role in the pathogenesis of SARS-CoV [26] . A recent study has also found similar gender-based distribution patterns for SARS-CoV-2. Jin et al. (2020) have compared the mortality and severity of COVID-19 between males and females [30]. After observing patient survival and deceased data, the study has concluded that despite gender distribution being symmetrical in the survival group, there have been a higher percentage of males in the deceased group and thus concluded that despite both genders having the same susceptibility, males tend to have higher severity and increased mortality, an effect that is independent of age and susceptibility [30]. Taken together, the data indicate that there may be a sex-dependent predisposition that makes males more susceptible to infectious pathogens (Figure 2) [25,26]. This implies that male gender is a possible risk factor that can lead to poor outcomes for patients with viral infections such as SARS-CoV-2.

5. CLINICAL AND PATHOLOGICAL CHARACTERISTICS OF COVID-19

The clinical features of COVID-19 are varied and non-specific; disease presentation can range from asymptomatic to severe pneumonia and death [31]. Yuki et al. provided a classification of COVID-19 patients based on clinical features/lab investigation which are shown in Table 1 [32].

The symptoms have been reported to appear after an incubation period between 2-14 days [18]. The period from the onset of SARS-CoV-2 symptoms to death ranged from 6 to 41 days which is dependent on the age and the status of the patient's immune system [18]. The age range affected was mostly middle-aged patients with a mean age range of 40-59 years and older (> 60 years) [22,33]. Additionally, studies reported that SARS-CoV-2 disease progressed faster among the elderly compared with those under the age of 60 years [33]. A research study analysing 1099 laboratory-confirmed patients in Wuhan, has found common clinical features characterised as mild and moderate symptoms which includes fever (88.7%), cough (67.8%), fatigue (38.1%),

sputum production (33.4%), dyspnoea (18.7%), sore throat (13.9%), and headache (13.6%) [33]. However, some of the patients display gastrointestinal symptoms, with diarrhoea (3.8%) and vomiting (5.0%). Fever and cough are the most dominant symptoms associated with SAR-CoV-2 and the temperature range is within 39-degree Celsius. About 80% of confirmed SARS-CoV-2 cases have suffered from only mild to moderate forms of the disease, with approximately 12% of patients being elderly. Asymptomatic carriers of SARS-CoV-2, who presented with a history of underlying health conditions such as hypertension, chronic obstructive pulmonary disease, diabetes, cardiovascular disease, have later developed critical illnesses, which manifested as respiratory failure, septic shock, multiple organ failure and eventually death [18,28].

A comprehensive study reported that SARS-CoV-2 affected children within the age group of <14, these Paediatric patients < 16 years of age with COVID-19 had much milder of fever , cough, diarrhoea, and moderate case symptoms [34]. Compared to children with SARS, younger COVID-19 patients also showed less upper respiratory symptoms (e.g. cough and pharyngeal congestion), but pneumonia was more common (53%) and very similar to the prevalence with SARS (65%) [35].

However, a study reported that the presence of leukopenia, lymphopenia, and elevated myocardial enzymes in children with COVID-19 was relative to those of adults [34]. The Study reported that the abnormal results in paediatric patients were elevated serum creatine kinase MB (31%), reduced lymphocytes (31%), leukopenia (19%) and enhanced procalcitonin (17%). Some characteristics differed significantly between the mild and moderate clinical form of COVID-19 as seen in adult patients, including reduced lymphocyte, increased body temperature, high levels of procalcitonin, D-dimer and creatine kinase MB [35].

Patients who met the criteria by exhibiting the symptoms discussed above have undergone laboratory examinations to test for SARS-CoV-2 and respiratory pathogens. The samples have been collected as early as symptom onset to obtain higher virus concentration. The laboratory examination includes a complete blood count, coagulation profile, biochemical test (including renal and liver function, creatine kinase, lactate dehydrogenase, and electrolytes), collection of respiratory specimens such as; nasal and pharyngeal swabs, bronchoalveolar lavage fluid, sputum, or bronchial aspirates, inflammatory markers such as; serum procalcitonin, and C-reactive protein (CRP) [33].

6. DIAGNOSTIC TESTING OF SARS-COV-2

Clinical diagnostic testing plays an essential role in the clinical care of patients with infectious diseases. This includes the detection of specific pathogens and monitoring of patient conditions, decisive therapy, measuring prognosis, management and disease surveillance. Various laboratory techniques have been used to confirm the presence or absence of the virus as well as determining its severity (Table 2). These techniques include molecular testing methods that detect the viral RNAs such as real-time polymerase chain reaction (RT-PCR) and serological testing methods to detect antibodies of the SARS-CoV-2 such as immunofluorescent assay (IFA) [37].

RT-PCR, a molecular diagnostic technique is used as a rapid and sensitive method for the detection of the viral RNAs. This technique has currently been favoured for the detection of SARS-CoV-2 as it is able to detect viral RNAs at extremely low concentrations in human plasma. While this technique may detect SARS-CoV-2, it may generate false-positive results. A rapid reverse transcriptase loop-mediated isothermal amplification (RT-LAMP) assay has been used, which extends the capacity of laboratories to process 2.5 time more clinical specimens

249 comparative with standard qRT-PCR and hence may provide an opportunity for high-throughput
250 screening of SARS-CoV-2 [38].

251 Serological detection of SARS-CoV-2 detects antibodies that are present in the serum samples as
252 part of the immune response against the virus. Four serological tests including neutralization test,
253 enzyme-linked immunosorbent assay (ELISA), immunofluorescent assay (IFA), and
254 immunochromatographic test (ICT) have been used for detecting antibodies to SARS-CoV-2
255 [39]. The IFA technique analyses the presence of serum IgM and IgG antibodies against SARS-
256 CoV-2 [40]. The IFA serological method produces negative results from samples collected at the
257 incubation period of the disease but positive results have been observed in samples collected at a
258 later phase of the disease [40]. The RT-PCR technique has been shown to detect only active
259 infections and is the most sensitive method of detecting viral RNAs. However, during the
260 recuperating phase of the disease, detecting antibodies in serum specimens has shown to be more
261 important than detecting viral RNAs in the case of acute patients and asymptomatic carriers. This
262 suggests that serological tests can be used as a confirmatory test of the infection. The progress of
263 developing antibodies in response to an infection is both time and host-dependent. Recent studies
264 have shown that most patients infected with SARS-CoV-2 seroconvert from 7 to 11 days of post-
265 exposure, while some patients may develop antibodies sooner. Because of this natural delay,
266 antibody testing may not always be accurate in cases of acute condition [41]. Detection and
267 isolation of HCoVs in cell culture is not routinely carried out for diagnostic purposes. This is
268 mainly due to a lack of permissive cell lines and a lack of viable antisera for culture validation
269 [42]. However, isolation of the virus in cell cultures is an essential part to provide isolates for
270 characterization and to developing vaccines and therapeutics for SARS-CoV-2 [43]. These
271 serological assays have shown to be valuable for the detection of HCoV in different populations

of patients, including immunocompromised patients with pneumonia, and frail elderly persons with symptoms of respiratory tract infections (RTI) [44]. Although RT-PCR remains the most frequent assays to make a conclusive diagnosis of SARS-CoV-2 infection [45], the limited availability of RT-PCR assay facilities in the early phase of the outbreak has restricted efficient diagnosis of infected patients with SARS-CoV-2 [46].

Chest CT findings have been recommended as major evidence for clinical diagnosis of SARS-CoV-2 infection diseases [47], and it has been found to be an essential clinical finding to detect the diseases at an early stage [48]. Moreover, because of the likelihood of a false negative RT-PCR result, the National Health Commission of the People's Republic of China has encouraged diagnosis to rely on chest CT alone [49]. Some cases of asymptomatic infection have been discovered based on abnormal lung findings on CT imaging, which implies that chest CT imaging should be applied in asymptomatic high-risk individuals with a history of exposure to patients with SARS-CoV-2 pneumonia to simplify initial identification of the disease [50]. Researchers have also proposed that CT imaging can be applied as the primary screening tool for SARS-CoV-2. Moreover, the CT scans play a key role in distinguishing SARS-CoV-2 pneumonia from other respiratory diseases displaying similar clinical signs and symptoms [51], and hence can be applied as the primary screening tool for SARS-CoV-2.

7. CURRENT AND PROSPECTIVE TREATMENT MODALITIES OF SARS-COV-2

The management and treatment of SARS-CoV-2 is extremely challenging due to asymptomatic presentations and high infectivity of virus, and lack of effective drugs and vaccines. The Current and prospective treatment modalities for the treatment of SARS-CoV-2 are summarized in Table 3 and highlighted in the following sections:

7.1 Life support: The prime approaches are the management of symptoms, signs, care to maintain essential requirements of life support like oxygen saturation and blood pressure and treating secondary diseases like other microbial infections and organs failure [52].

7.2. Palliative care: Palliative care management and bereavement supports are essential to manage COVID-19 patients, caregivers and healthcare workers [53]. Therefore, supports are needed for complex symptom management, psychological and bereavement support, and spiritual care [54]. It has been widely suggested to use of opioids as a safe and effective palliative care intervention for patients with breathlessness and pain [55].

7.3. Drug development and the use of antiviral drugs: Attempts to develop vaccines against human corona virus infections, including SARS-CoV and MERS-CoV have been initiated but due to viral sequence multiplicity the success has been limited [56]. There have been more than 400 clinical trials registered in both the International and Chinese Clinical Trials Registry Platform to appraise the risk and benefit researched drug for the management of SARS-CoV-2. These trials aim at either to develop new agents or repurpose established drugs including Remdesivir, Oseltamivir, ASC09F (HIV protease inhibitor), Lopinavir, Ritonavir, Darunavir, and Cobicistat, which are in phase I-III trials [57]. Drugs developed for SARS-CoV and MERS-CoV have also been tested specifically for SARS-CoV-2 [58] . Multiple studies have reported that Remdesivir (Code No.: GS-5734), a broad-spectrum antiviral agent, which have been found to be highly effective for the treatment of severe SARS-CoV-2 [59]. Remdesivir in combination with chloroquine has also been found to be beneficial for the treatment of SARS-CoV-2 [60]. The protease inhibitor drugs including Ritonavir, Darunavir and Cobicistat, which were designed to block HIV viral replication, have been tested. The safety and efficacy of these drugs for the treatment of SARS-CoV-2 infection are not strong [61] .

7.4. Anti-coagulants: As increased thromboembolic events have been observed among hospitalized patients, association between administration of in-hospital anti-coagulants and survival in a large cohort (n=2773) of hospitalized patients with COVID-19 has been investigated. Treatment with anticoagulants has been found to be associated with improved hospital survival among COVID-19 patients [62]. Therefore, prospective randomized trials are required to determine whether systemic anti-coagulants offer a survival benefit in hospitalized patients with COVID-19 [63].

7.5. Anti-malarial drugs: In early 2020, the chief administrative body of the People's Republic of China has reported that chloroquine phosphate, an age-old medicine for the treatment of malaria, are effective in treating SARS-CoV-2 correlated pneumonia in multicentre clinical studies [64]. Recently, the FDA has issued an Emergency Use Authorization (EUA) to allow drugs such as hydroxychloroquine sulphatesulphate and chloroquine phosphate products to be tested for certain hospitalized patients with SARS-CoV-2 [65]. The efficacy and safety profile of chloroquine and hydroxychloroquine have been evaluated over ten hospitals in Wuhan, Jingzhou, Guangzhou, Beijing, Shanghai, Chongqing, and Ningbo and it has been reported that chloroquine elicits antiviral potential in the management of the SARS-CoV-2 induced pneumonia-related complications [66]. Chloroquine has been utilized for over 70 years, and its safety issues are well documented as safe medicine. During the current deadly pandemic of COVID-19, chloroquine phosphate has been recommended for treatment SARS-CoV-2 induced severe respiratory syndrome, if there is no pre-existing contraindication [66]. Chloroquine and hydroxychloroquine may exert their antiviral activities in part by increasing the pH in host cell lysosomes which in turn inhibits hydrolytic activity of protease enzymes that are required for processing of viral glycoprotein during infection [67].

7.6. Monoclonal antibodies: Additional approaches have been undertaken either to develop a vaccine that contains antigen derived from the spike protein which can boost recognition of the virus by immune cells or to develop monoclonal antibodies that bind to the coronavirus spike protein and block the interaction with the human cells [68] . For example, a recent study has reported that the CR3022, a SARS-CoV-specific human monoclonal antibody, is capable of binding to the RBD of SARS-CoV-2 [69]. The RBD of SARS-CoV-2 has been considered as a target for developing neutralizing antibodies against both SARS-CoV and MERS-CoV [70]. Pan-coronavirus fusion inhibitors such as EK1 and EK1C4 have been generated, which are capable of blocking the infection of both SARS-CoV and MERS-CoV. These antibodies and peptides have the potential for either prophylactic or therapeutic usages [69,71].

7.7. Convalescent plasma therapy: Recently, convalescent plasma therapy has been recommended to treat COVID-19 patients [72]. The plasma collected from individuals who have recovered from COVID-19 contains antibodies to SARS-CoV-2. Although convalescent plasma has been tested during 2003 SARS-CoV-1, 2009-2010 H1N1 influenza virus, and 2012 MERS-CoV epidemics, its safety and efficacy in COVID-19 patients require further clinical investigation.

7.8 Type 1 interferons (IFNs): Type I IFNs are antiviral cytokines have a broad antiviral activity that induce a large range of proteins and can impair viral replication in targeted cells. Interferon treatments are currently evaluated in clinical trials to treat respiratory diseases e.g. MERS-CoV and SARS-CoV [73]. Type I IFNs are have also been proposed for the treatment of COVID-19 [74] . A recent study demonstrated the potential efficacy of human Type I IFN in suppressing SARS-CoV-2 infection [74].

7.9. Antisense oligonucleotides and antisense RNAs: Antisense RNA therapies including antisense oligonucleotides (ASOs), small RNAs or long non-coding RNAs have been considered to specifically treat various disorders including viral diseases. Upon entering the ASOs inside the host cells, they bind to the RNA target, resulting the formation of double-stranded hetero-duplex, which is then cleaved by cellular RNase H1 [75] . Formivirsen (Vitravene) is the first FDA-approved ASO, which inhibits the expression of major immediate early region 2 of the cytomegalovirus [76]. The drug has been approved for the treatment of peripheral cytomegalovirus retinitis in patients with AIDS [77]. Antisense RNAs have been used in clinical trials in various disorders including cancers, myopathies and Huntington's disease [78]. As antisense-based therapies have showed beneficial effects in other diseases and they are easy to design and cost-effective to manufacture compared with small molecules and antibodies, they may hold promise for rapid drug development for SARS-CoV infections [79].

7.10. Other Treatment Modalities and Potential Targets: Animal studies have demonstrated that binding of the coronavirus spike protein to ACE-II down-regulates the receptors and thereby contributes to severe lung injury [80], which raises the possibility that the delivery of an excessive soluble form of ACE-II may provide therapeutic intervention. The soluble ACE-II may competitively bind with SARS-CoV-2, neutralize the virus and rescue cellular ACE-II for the protection of the lung from injury. The recombinant human ACE-II seems to be safe, with no negative hemodynamic effects on healthy subjects [80]. RNA dependent RNA polymerase has also been targeted for investigational drugs such as Remdesivir and Favipiravir. Studies have shown that both agents inhibit RNA dependent RNA polymerase activity and thus may be useful for the treatment of early or mid-stage of coronavirus diseases [81]. The transmembrane protease serine 2 which appears to be essential for entry and viral spread has also been considered as a

potential target [82]. Finally, anti-TMPRSS2 compound such as comostat mesylate has been tested as a potential anti-coronavirus candidate [80].

Protein modelling studies on spike protein suggest that SARS-CoV-2 has a strong binding affinity to human ACE-II receptors. The interactions between ACE-II and spike proteins have been considered as a therapeutic target *in silico* modelling, which identified a natural flavonoid called hesperidin. Hence, a docking-based screening using a quantum mechanical scoring of chemical libraries of approved drugs may identify chemical agents which can be directly tested in Phase II-III clinical trials [83]. Recently, steroids have been found to reduce the risk of death in extremely ill coronavirus patients and increase the survival of one in eight COVID-19 patients on ventilators [84]. Therefore, steroids such as dexamethasone has become the first life-saving treatment for seriously ill COVID-19 patients [85].

8. EXPERT OPINION

Despite the widespread investigations on the recently emerged SARS-CoV-2, there are considerable gaps in our understanding of this virus. Hence, we reviewed extensively different aspects about the virus including pathogenicity, current diagnostic, epidemiology, transmission dynamics, and therapeutic strategies and how they have been applied for the management of SARS-COV-2.

SARS-COV-2 is genetically diverse and has a high tendency to undergo frequent genetic mutations and gene recombination, which increases the risk of interspecies transmission. Furthermore, a number of non-structural and auxiliary proteins encoded by this virus seems to have no known function. Therefore, it is essential to determine the mode of action of these proteins and their roles in viral pathogenesis and replication. It is equally important to learn whether this virus has a greater propensity to jump across species and how it has achieved the non-human to human transmission. This will aid to identify reservoirs of coronaviruses which is likely to provide novel directions to predict where and when future epidemics may occur.

Currently, significant efforts have been made to improve the detection systems of SARS-CoV-2. The diagnosis of SARS-CoV-2 depends on the detection of the coronavirus RNA or antibodies present in the serum samples. However, each of the methods described in this review has its own unique advantages and unavoidable disadvantages. The RT-PCR is extensively used for different types of virus identification with high specificity as well as sensitivity, but its analysis requires specialised equipment and specialists, which is only conceivable within well-established laboratories. Adopting a combination of multiple diagnostic approaches could be adapted to minimise the variables confounded by single detection methods. Analysis of chest CT imaging findings have been recommended for the diagnosis of SARS-CoV-2 infections. As the CT imaging technique shows the changing pattern of the images over time of disease onset, it provides guidance for clinicians to treat patients effectively. Therefore, it is essential to develop more effective and practical approaches to overcome the shortcomings of the existing methods.

The current management of COVID-19 is based generally on supportive therapy and treatment to prevent respiratory failure. However, the autopsies of some of the COVID-19 patients are indicative of a potential role for coagulopathy in this infection. Moreover, many of the COVID-19 patients admitted to the intensive care units have been found to be deficient in vitamin K. So, it would be worthwhile to investigate the role of vitamin K for countering this infection.

Finally, an exit strategy for a path back to normal life is required, which should involve a multi-prong effort towards development of new treatment and a successful vaccine to protect human health worldwide and control and halt future outbreaks of SARS-CoV-2. Therefore, the bench to bedside translational research as well as reverse translational works focusing bedside to bench is very important and would provide the foundation for the development of targeted drugs and vaccines for SARS-CoV-2 infections.

Disclosure statement

No potential conflict of interest was reported by the author(s).

Figure legends

Figure 1. The life cycle of SARS-CoV-2 in host cells. SARS-CoV-2 enters target cells through an endosomal pathway or membrane fusion. The S protein of SARS-CoV-2 binds to cellular receptor angiotensin-converting enzyme 2 (ACE2) and enters into the host cell by viral fusion. The virus synthesizes its RNA polymerase that produces viral RNAs, this viral RNA transcribes smaller sub-genomic positive RNAs that are used to synthesize structural proteins. The proteins are integrated into the membrane of the Endoplasmic Reticulum (ER) and are assembled in a nucleocapsid, the progeny viruses are then released from the host cell by exocytosis through Golgi vesicles and are transmitted through droplets causing infections.

Figure 2: Females exhibit greater humoral and cell-mediated immune responses to viral infections than males. Disparities in the immune responses can be attributed to sex hormones such as oestrogens and androgens. Sex hormones modify the functions of immune cells by binding to specific receptors expressed by many immune cells, including lymphocytes, macrophages, and dendritic cells. This binding stimulates various cell signalling pathways, resulting in differential production of cytokines and chemokines. After viral exposure, expression and antigen recognition by TLRs, the induction of the innate immune response, the activity of antigen presenting cells (APCs) such as dendritic cells and macrophages and production of inflammatory cytokines (e.g., IFN-β, IFN-γ, and TNF-α) are observed to be much higher in females than males. The initiation of the adaptive immune response, including the activation of lymphocytes and the production of antibodies by B cells are also shown to be much higher in females. The activity of CD4+ and CD8+ T cells along with the expression of antiviral and proinflammatory genes, many of which have oestrogen response elements within their promoters are also elucidated to be much higher in females (data not shown). CCL- chemokine ligand; IFN, interferon; IL, interleukin; iNOS, inducible nitric oxide synthase; ND, not defined; NO, nitric oxide; TLR, toll like receptor; TNF, tumour necrosis factors [25,26].

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Figure 1

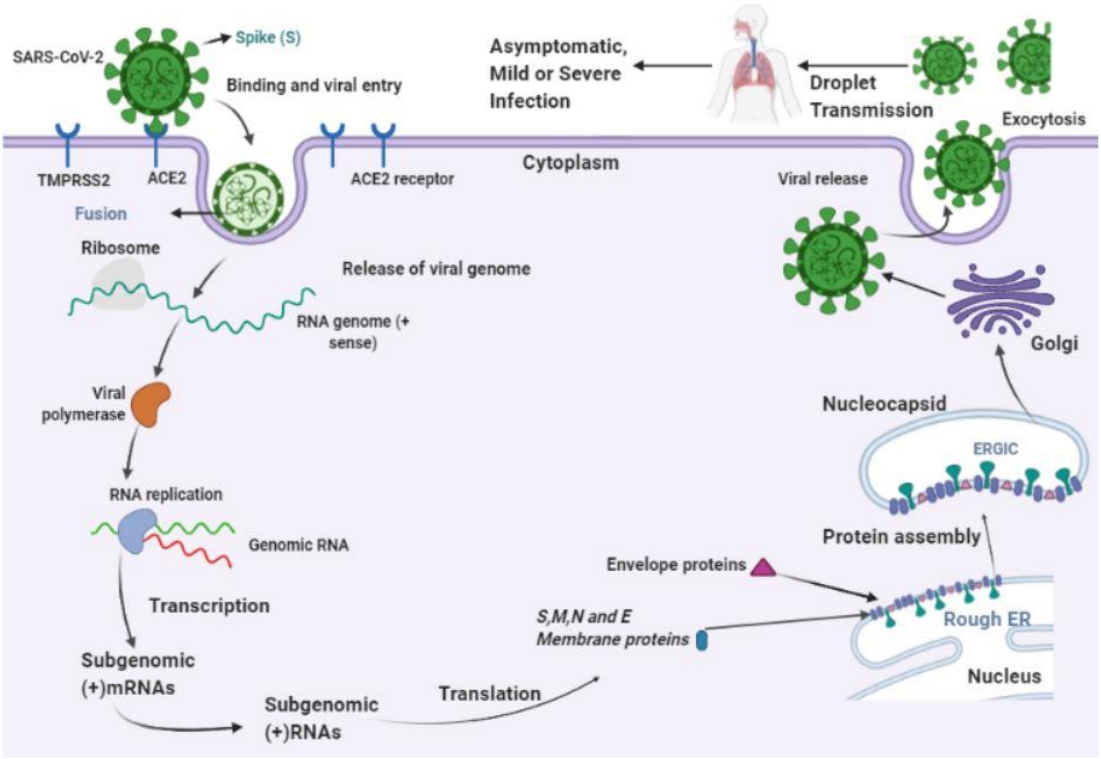
SARS-CoV-2
Spike (S)
Binding and viral entry
Asymptomatic,
Mild or Severe
Infection
Droplet
Transmission
Exocytosis
TMPRSS2
ACE2
ACE2 receptor
Cytoplasm
Viral release
Fusion
Ribosome
Release of viral genome
RNA genome (+
sense)
Golgi
Viral
polymerase
Nucleocapsid
ERGIC
RNA replication
Protein assembly
Genomic RNA
Envelope proteins
Transcription
S,M,N and E
Membrane proteins
Rough ER
Subgenomic
(+)mRNAs
Nucleus
Subgenomic
(+)RNAs
Translation

Figure 2

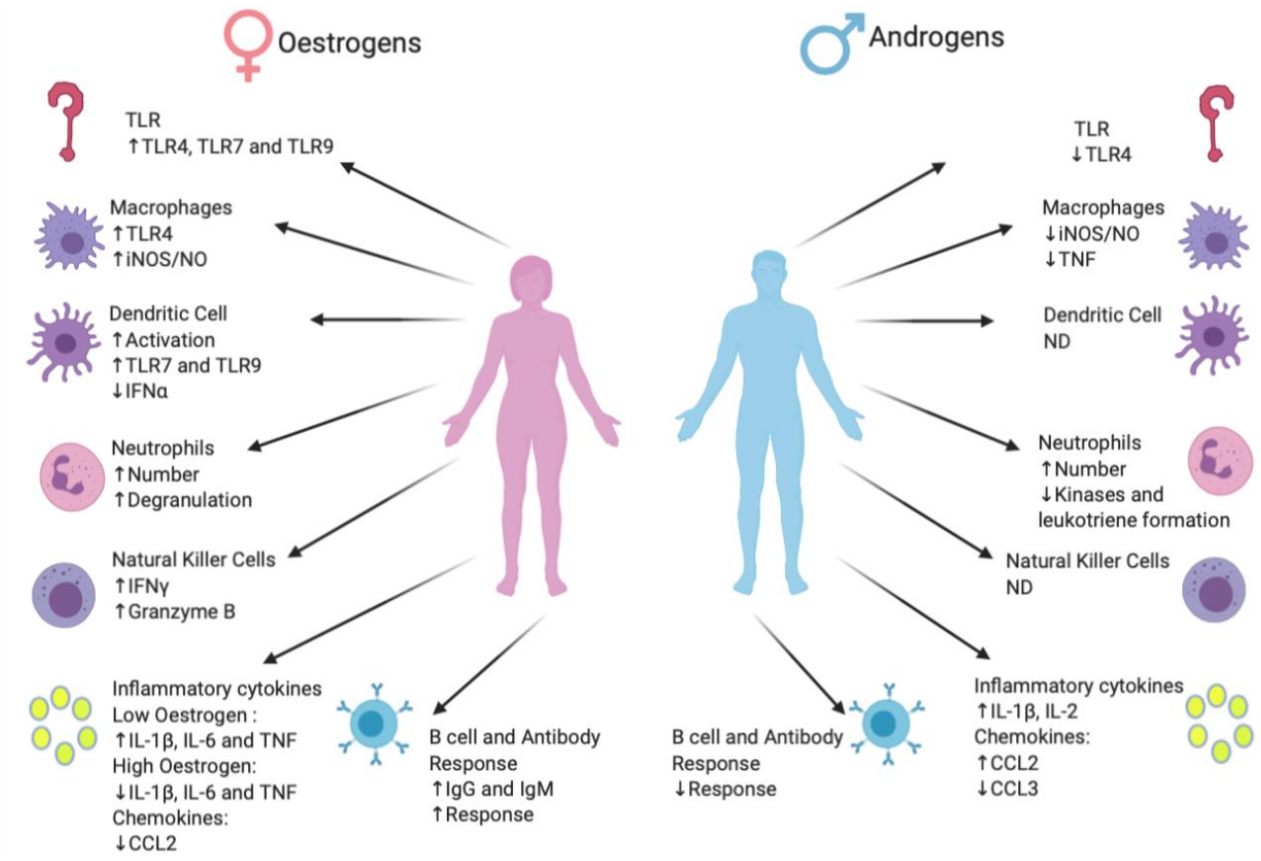
Oestrogens
TLR
↑TLR4, TLR7 and TLR9
Macrophages
↑TLR4
↑iNOS/NO
Dendritic Cell
↑Activation
↑TLR7 and TLR9
↓IFNα
Neutrophils
↑Number
↑Degranulation
Natural Killer Cells
↑IFNγ
↑Granzyme B
Inflammatory cytokines
Low Oestrogen :
↑IL-1β, IL-6 and TNF
High Oestrogen:
↓IL-1β, IL-6 and TNF
Chemokines:
↓CCL2
B cell and Antibody
Response
↑IgG and IgM
↑Response
Androgens
TLR
↓TLR4
Macrophages
↓iNOS/NO
↓TNF
Dendritic Cell
ND
Neutrophils
↑Number
↓Kinases and
leukotriene formation
Natural Killer Cells
ND
Inflammatory cytokines
↑IL-1β, IL-2
Chemokines:
↑CCL2
↓CCL3
B cell and Antibody
Response
↓Response

Table 1: Classification of COVID-19 patients based on clinical features/lab investigation (adapted from [32])

Classifications	**Clinical features/laboratory investigation**
Asymptomatic	COVID-19 nucleic acid test positive. No clinical symptoms and signs. Chest imaging – normal.
Mild	Symptoms of acute upper respiratory tract infection: fever, fatigue, myalgia, cough, sore throat, runny nose, sneezing) or digestive symptoms (nausea, vomiting, abdominal pain, diarrhoea
Moderate	Pneumonia (frequent fever, cough) with no obvious hypoxemia. Chest CT with lesions.
Severe	Pneumonia with hypoxemia (SpO2 < 92%)
Critical	Acute respiratory distress syndrome (ARDS), may have shock, encephalopathy, myocardial injury, heart failure, coagulation dysfunction and acute kidney injury

Table 2. Recent diagnostic evaluation techniques of SARS-CoV2

Product	**Sample type**	**Target**	**Technology**	**Company name**
Xpert SARSCoV-2	Nasopharyngeal swab, nasal aspirate	SARS-CoV2 RNA	RT-PCR	Cepheid
RapiPrep COVID19	Sputum or swabs	SARS-CoV2	LAMP amplification technology	Rapid pre
Vita PCR COVID19 assay	Nasopharyngeal or oropharyngeal swabs	SARS-CoV2	RT-PCR	Credo Diagnostics
3D Medicines	Upper and lower respiratory specimens	SARS-CoV-2 RNA	RT-qPCR	3D Medicines
ePlex SARSCoV-2	Nasopharyngeal swab	SARS-CoV2 RNA	RT-PCR	GeneMark DX
Accula SARSCoV-2	Throat and nasal swabs	SARS-CoV2 RNA	RT-PCR and lateral flow	Mesabiotech
AIT Laboratories	Nasal, mid turbinate, nasopharyngeal, and oropharyngeal swab	SARS-CoV-2	RT-PCR	AIT Laboratories
ID NOW COVID-19	Throat, nasal, nasopharyngeal and oropharyngeal swabs	SARS-CoV-2 RdRp Gene	Isothermal nucleic acid amplification	Abbott
Viva Diag COVID19 IgG - IgM test	finger prick / venous blood, plasma or serum	IgG / IgM	Colloidal gold immunochromatography	VivaChek
COVID19 IgM IgG Rapid Test	Finger prick / venous blood	IgG / IgM	Lateral flow immunoassay	BioMedomics, BD
GT-100 SARSCoV-2 IgG/IgM kit	Human serum and plasma	IgG / IgM	Time resolved fluorescence immunoassay	Goldsite Diagnostics Inc
Rapid Response COVID-19 IgG/IgM Test Cassette	Finger-prick, whole blood, serum or plasma	IgG / IgM	Lateral Flow Immunoassay	BTNX
qSARS-CoV-2 IgG/IgM Rapid Test	Whole blood, serum or plasma	IgG / IgM	Lateral Flow Immunoassay	Cellex Inc
Anti-SARS-CoV-2 ELISA (IgG)	Serum or plasma	IgG	Lateral Flow Immunoassay	EUROIMMUN US Inc

Table 3: Examples of drugs that are being trialled to explore their repurposing potential for the treatment of COVID 19

Drug	CAS Number	Currently licensing	Mechanism of Action	Common Adverse Reactions	Company	Stage of Trial
Hydroxychloroquine (Plaquenil)	118-42-3	Prophylaxix of Malaria, uncomplicated malaria, rheumatoid arthritis, chronic discoid lupus erythematosus, and systemic lupus erythematosus	Interferes with the parasite's ability to proteolyse hemoglobin, preventing the normal growth and replication of the parasite.	Headache, drowsiness, visual disturbances, cardiovascular collapse, convulsions, hypokalemia, rhythm and conduction disorders including QT prolongation, torsades de pointes, ventricular tachycardia, and ventricular fibrillation.		Clinical trial ORCHID Study by the Prevention and Early Treatment of Acute Lung Injury (PETAL) Clinical Trials Network of the National Heart, Lung, and Blood Institute (NHLBI), part of the National Institutes of Health [68]. Emergency use authorization provided by FDA for unapproved use
Tocilizumab (Actimera) Monoclonal antibody	375823-41-9	rheumatoid arthritis (RA), active polyarticular juvenile idiopathic arthritis (PJIA) and active systemic juvenile idiopathic arthritis (SJIA)	Inhibits IL-6-mediated signalling by binding to both soluble and membrane-bound IL-6 receptors	Upper respiratory tract infections, nasopharyngitis, headache, hypertension, increased ALT.	Roche	Approved for phase 3 trial by FDA
Umifenovir (Arbidol) Antiviral	131707-25-0	Currently used for the prophylaxis and treatment of influenza and other respiratory viral infections (Currently licensed in	Inhibition of virus-mediated fusion with target membrane and a resulting block of virus entry into target cells	Dermatitis, gastrointestinal upset, central nervous system events, hepatotoxicity, etc.		Trials in China by Dr Hu Bo from the Huazhong University of Science and Technology

		China and Russia)				
Sarilumab (Kevzara) monoclonal antibody	1189541-98-7	used in treatment of Rheumatoid arthritis in adult patients who are irresponsive, respond inadequately or exhibit intolerance to disease-modifying anti-rheumatic drugs (DMARDs)	It specifically binds to interleukin-6 receptors and blocks the activity of pro-inflammatory cytokines	Dyslipidaemia; increased risk of infection; neutropenia; thrombocytopenia	Sanofi and Regeneron	Phase 2/3 trial
Siltuximab(Sylvant) Monoclonal antibody	541502-14-1	Patients with multicentric Castleman's disease (MCD) who are human immunodeficiency virus negative and human herpesvirus-8 negative.	Inhibits IL-6-mediated signalling by binding to both soluble and membrane-bound IL-6 receptors	Abdominal pain; hypersensitivity; hypertension; hypertriglyceridaemia; increased risk of infection; infusion related reaction; localised oedema; neutropenia; renal impairment; skin reactions; thrombocytopenia; weight increased	EUSA Pharma	Observational case-control trial Italy
Favipiravir (Avigan) Antiviral	259793-96-9	Resistant cases of influenza	It selectively inhibits RNA polymerase and prevents replication of the viral genome	Decreased red blood cell (RBC) production, and increases in liver function parameters such as aspartate aminotransferase (AST), alkaline phosphatase (ALP), alanine aminotransferase (ALT) and total bilirubin, and	FUJIFILM Toyama Chemical Co. Ltd.	Phase III trial

				increased vacuolization in hepatocytes. Teratogenic; therefore, should be avoid ed in pregnancy		
lopinavir-ritonavir (Kaletra) protese inhibitors	192725-17-0 and 155213-67-5	HIV infection	Lopinavir is an antiretroviral protease inhibitor which prevents HIV-1 protease activity, and thus the proteolysis of the Gag polyprotein, lopinavir results in the production of immature, non-infectious viral particles. Ritonavir, an inhibitor of the enzymes responsible for lopinavir metabolism. It improves lopinavir's antiviral activity.	Alopecia; anaemia; an gioedema; anxiety; ap petite abnormal; arthralgia; a sthenia; diabetes mellitus; diarrhoea; di zziness; dry mouth; dyslipidaemia; dyspnoea; fever; gastr ointestinal discomfort; gastrointes tinal disorders; headache; h epatic disorders; hypersensiti vity; hypertension; ma laise; muscle complaints; nausea; ne utropenia; oral ulceration; pancreatitis ; peripheral neuropathy; seizure; s kin reactions; sleep disorders; taste altered; vomiting	AbbVie	Randomised Evaluation of COVid-19 thERapY (RECOVERY) trial, China