(Coronavirus infection: overview and immune response)

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Abstract : The initial cases of novel coronavirus (2019-nCoV)–infected pneumonia (NCIP) occurred in Wuhan, China, in December 2019. Since then, it has spread rapidly around the world and become global concern. This outbreak has attracted much attention in medical community due to severe morbidity and mortality worldwide. Coronaviruses (CoVs) are the largest group of known positive-sense RNA viruses having an extensive range of natural hosts. Although several therapeutic agents have been evaluated for the treatment of Covid-19, but there is a lack of effective antiviral agents. In this brief review we summarize the current knowledge on viral structure, clinical features, immune response, management, and treatment options of Covid-19, which may improve our understanding of this infectious disease.

IndexTerms **- COVID-19, immunopathology, Immune response, SARS-CoV-2.**

I. INTRODUCTION

In late December 2019, the Chinese health authorities identified a cluster of pneumonia cases of unknown etiology in Wuhan, the capital city of Hubei province in China (Guan et al., 2020; Jiang et al., 2020). The disease spread rapidly across China and many other countries around the world, enhanced by infected individuals travelling abroad, and became a major global health concern (Grifoni *et al*., 2020). The World Health Organization has confirmed that there were 13,378,853 cases globally with 580,045 deaths as of July 16, 2020 (WHO, 2020).

The pathogen has been identified as a novel enveloped RNA betacoronavirus 2. The virus itself is currently named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), and the disease it causes has been officially called Corona Virus Disease 2019 or 'Covid-19' by the WHO (Lai *et al*., 2020). It was characterized as a pandemic on 11th March 2020 (Abed Alah *et al*., 2020).
Many of the symptoms caused by SARS-CoV-2, such as acute respiratory syndrome, are closely similar to those caused by severe acute respiratory syndrome coronavirus (SARS-CoV) which emerged in 2002-3 and was transmitted between humans, causing over 8,000 reported cases of human infection and about 800 deaths (Wan *et al*.,2020).

It is believed that the primary source for the SARS-CoV-2 is bats, which distinguishes it from the previous SARS CoV and MERS CoV (Middle East Respiratory Syndrome coronavirus) which were transmitted to humans from exotic animals and camels respectively. However, it is not clear yet whether SARS CoV 2 originated in bats and was transmitted to humans directly or if it occurred through an intermediate host (Omrani et al., 2020; Taher *et al*., 2020).

Regarding epidemiological information concerning SARS-CoV-2, infection mainly occurs through human-to-human transmission by close contact and via spraying droplets from infected individuals through their coughing or sneezing (Prompetchara et al., 2020; Taher *et al*., 2020). Transmission from asymptomatic persons can occur throughout the incubation period. Current research suggests estimates of mean incubation for SARS-CoV-2 lasting between 2 to 14 days. Therefore, understanding the period during which infected patients may transmit the virus to others is critical in controlling this contagious infection, and in particular whether transmission can occur prior to the development of symptoms or during incubation (Taher *et al*., 2020).

Virology

The coronaviruses (CoVs) are a large family whose members contain a positive-sense and single-stranded RNA genome. CoVs belong to the subfamily Orthocoronavirinae of the Coronaviridae family, in the order Nidovirales (Lai *et al.*, 2020). The 4 major genera include *Alphacoronavirus* (α-CoV*), Betacoronavirus* (β-CoV), *Gammacoronavirus* (γ-CoV), and *Deltacoronavirus* (δ-CoV). Several α-CoVs and β-CoVs have been identified in mammals, causing mild respiratory infections and common cold symptoms in humans, whereas, γ-CoV infects avian species and the δ-CoVs may infect both mammals and birds (Li, 2016; Grifoni *et al*., 2020). Both SARS-CoV and 2019-nCoV belong to the β-genus.

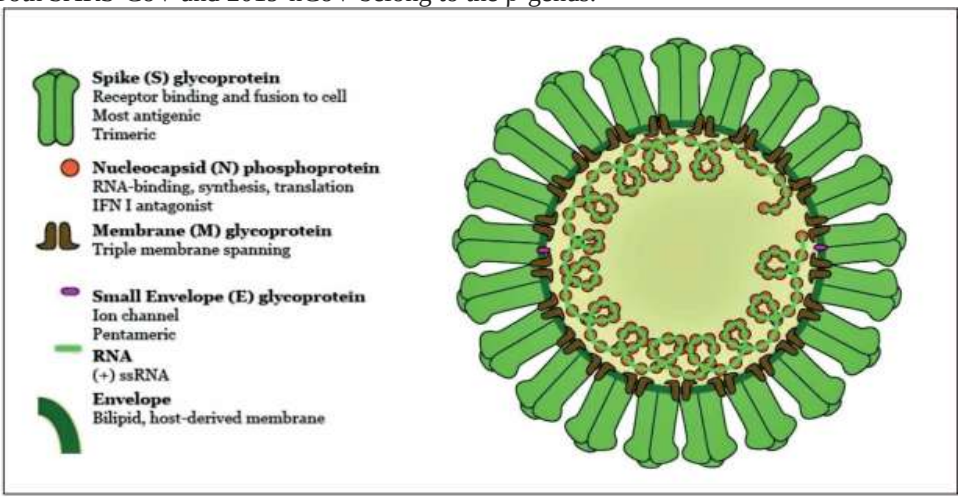

Figure 1: Schematic diagram of a coronavirus (Kannan *et al*., 2020).

Coronaviruses have the largest genomes among all RNA viruses, of 27 to 32 kilobases in size packed inside a helical capsid which consists of nucleocapsid protein (N) surrounded by a lipid layer envelope. The latter contains three structural proteins. A membrane protein (M) and an envelope protein (E) (Figure 1) are associated with the virus assembly (Kannan *et al*., 2020), whereas the spike protein (S) forms a crown-like viral particle, hence being called the corona which in Latin means crown (Fan *et al*.,2019; Khan & Fahad, 2020). The corona is a multifunctional molecular mediator for coronavirus attachment and entry into host cells, interacting with a host receptor and then fusing the viral and host membranes, as well as a critical inducer of host immune responses (Wan *et al*., 2020; Wang *et al*., 2020).

Clinical features and immunopathology of Covid-19

The pathogenesis of Covid-19 is still under investigation. Scientists and clinicians believe that not all people exposed to SARS-CoV-2 become infected and may present as asymptomatic while other cases can be critical, leading to the development of severe respiratory illness and even death. Covid-19 is mainly a respiratory disease and in the majority of patients associated events of physiological instability include fever, fatigue, and respiratory symptoms such as a cough or sore throat and shortness of breath (Prompetchara *et al*., 2020).

Gastrointestinal symptoms including nausea, vomiting, and diarrhea have rarely been reported in patients (Omrani, 2020). Pulmonary parenchymal opacity has also been observed among Covid-19 patients in chest radiography (Chung *et al*., 2020). Abnormalities identified in the laboratory, like lymphocytopenia, thrombocytopenia, and high C-reactive protein (CRP) scores, are common (Guan *et al*., 2020). Computed tomography scans show ground-glass opacity and patchy infiltrates in over 85% of cases, while plain X-rays are abnormal in approximately 60% of patients (Omrani *et al*., 2020). It has been found that 5–10% of patients may develop severe pneumonia with hypoxia, acute respiratory distress syndrome, and multi-organ failure. Such patients often require admission to an intensive care unit (ICU) for critical support and mechanical ventilation (Tiruvoipati & Botha, 2020). Interestingly, it has been shown that severe cases with Covid-19 have high-levels of proinflammatory cytokines, including IL-2, IL-7, IL-10, G-CSF, IP-10, MCP-1, MIP-1A, and TNFα.Moreover, Covid-19 patients can exhibit extensive alveolar edema, proteinaceous exudate, and patchy inflammatory cellular infiltration (Omrani., 2020; Prompetchara *et al*., 2020). Basically, immune cells sense viral infection through the identification of virus-derived pattern-associated molecular patterns (PAMPs) that are unique to pathogens. This binding results in the activation of pattern recognition receptors (PRRs) expressed by epithelial cells and other immune cells, leading to immune cell activation. The detection of SARSCoV2 (and other single-stranded RNA viruses) occurs by endosomal RNA, and PRRs including the Toll-like receptors TLR7, TLR 3 and TLR8, and RIG-I-like (RLRs), and NLR receptors. Upon ligand binding, the PRRs recruit adaptor proteins which trigger crucial downstream transcription factors, including interferon regulatory factor (IRF), NF-κB, and AP-1, leading to the production of Types I and III antiviral interferons and various chemokines. The latter activate further innate response cells such as monocytes, NK cells, and dendritic cells (DCs), leading to the production of chemokines such as MIG, IP-10, and MCP-1 which are capable of recruiting lymphocytes that recognize the viral antigens presented by the DCs. Studies show that SARS-CoV-2 induces significant levels of the proinflammatory chemokines IL-1B, IL-6, TNF, and IL1RA. Their presence is further confirmed by the increased serum levels of these molecules in Covid-19 patients (García, 2020).

Furthermore, the production of chemokines and other cytokines attract cells such as neutrophils and macrophages to sites of infection which release cytotoxic substances such as matrix metalloproteinases. These innate and adaptive immune response mediators are critical in pathogen clearance and recovery but can contribute to damage to normal host tissues (Felsenstein *et al*., 2020, Perlman & Dandekar, 2005).

The phenomenon associated with elevated inflammatory mediators called a “cytokine storm” may lead to viral sepsis and the initiation of other clinical complications such as pneumonitis, acute respiratory distress syndrome (ARDS), respiratory failure, shock, organ failure, and potentially death, especially in elderly people and those with chronic diseases such as hypertension, cardiovascular disease and diabetes (Prompetchara *et al*., 2020). In addition, immunohistochemical studies show that levels of CD4, T cells, CD8 and T cells in spleen and lymph nodes may be reduced. Besides this, in a lung with characteristic diffused alveolar damage (DAD), the major infiltrating cells are monocytes and macrophages, with moderate numbers of multinucleated giant cells but very few lymphocytes this suggests that the pulmonary pathology associated with severe Covid-19 represents a dysregulated host immune response (Qin *et al*., 2020).

Immune response induced by Covid-19

The immune response induced by SARS-CoV-2 can be generated by innate and adaptive immune responses. Generally, cells respond to a viral infection by elevating the innate antiviral response to limit the spread of infection and to help in inducing an adaptive immune response that will eradicate the virus (de Wilde *et al*., 2018). Adaptive responses are mainly T cell-dependent, with CD4 helping B cells toward the production of specific neutralizing antibodies that limit the infection at a later phase and prevent reinfection (García, 2020).

The immune response against Covid-19 in humans awaits characterization and it is still unknown whether or not antibody or T-cell responses in infected patients provide protective immunity. CD8+ T cells are the main inflammatory cells and play an important role in eliminating the virus. Numbers present of total lymphocytes, CD4+ T cells, CD8+ T cells, B cells, and natural killer cells show a significant association with inflammatory status in Covid-19, particularly CD8+ T cell levels and the CD4+/CD8+ ratio (García, 2020).

SARS coronaviruses enter the cell via the angiotensin converting enzyme 2 (ACE2) receptor and infect the lower airways by binding to ACE2 on alveolar epithelial cells and enhancing the inflammatory cytokines. ACE2 is also expressed on the intestinal epithelium, cardiac cells and vascular endothelia, which may explain the cardiovascular complications experienced by some patients. Furthermore, ACE2 is also expressed on monocytes and macrophages, but at lower levels, thus providing an entry mechanism into immune cells for SARS-CoV-2 (Felsenstein *et al*., 2020). It has been reported that SARS-CoV-2 differs from other coronaviruses in its capacity to replicate within pulmonary tissue, avoid the antiviral effects of IFN-I and IFN-III, activate innate responses, and induce high levels of production of the cytokines essential for the recruitment of adaptive immunity cells (García, 2020). Increased levels of total neutrophils (38%), serum IL-6 (52%) and c-reactive protein (84%) and reduced total lymphocytes (35%) have been observed in SARS-CoV-2 patients. Patients requiring ICU care have elevated plasma levels of

many innate cytokines such as IP-10, MCP-1, MIP-1A, and TNFα.2. These clinical features suggest the involvement of pro-inflammatory conditions in disease progression and severity (Prompetchara *et al*., 2020).

It has been shown that Covid-19 patients have higher T-cell responses against the SARS-CoV-2 spike protein. This correlates well with IgG and IgA antibody titres, which has significant implications for vaccine design and the long-term immune response (Grifoni *et al*. 2020). Furthermore, neutralizing IgA has also been demonstrated in bronchoalveolar lavages in Covid-19 patients. These findings support the importance of investigating the presence of sIgA in secretions of patients with Covid-19 and its possible anti-viral neutralizing activity in the respiratory tract mucosa (García, 2020). Staines *et al*. (2020) showed that Covid-19 antibodies remain stable in the blood of the majority of infected individuals almost two months after diagnosis. Furthermore, patients with severe infections developing the strongest inflammatory response have been found to be more likely to produce high antibody levels. It was suggested that this may be due to antibody responses being associated with an inflammatory response to severe disease, or that the stimulation of the inflammatory response and antibody development pathways could be proportional to higher viral load. Such findings might relate to how long people remain immune after exposure to Covid-19 and may provide useful insights into how different age and ethnic groups respond to infection.

Management and treatment

So far there are no registered drugs or vaccines to treat Covid-19 disease. Management is based mainly on supportive therapy, treating symptoms and trying to prevent complications and respiratory failure (Pascarella *et al*., 2020). The prevention of infection is currently based on standard measures for respiratory viral pathologies, including the use of medical masks and gloves, frequent hand hygiene, travel restrictions, and avoiding contact with people suspected or confirmed to be infected. Quarantine measures to isolate both symptomatic and asymptomatic patients and anyone who may have been in contact with them are essential in order to avoid transmission amplification events (D'Amico *et al*., 2020). Self-isolation at home in mild cases is necessary while maintaining adequate hydration and nutrition and treating symptoms such as fever, sore throat or cough. Hence, hospital beds can be kept available for critically ill patients (Pascarella *et al*., 2020). It is important to detect potentially critical cases at the primary stage so that they can be transferred to the ICU in a timely manner for the required respiratory or circulatory support to be provided so as to reduce mortality rates (Maves *et al*. 2019). In efforts to provide accurate knowledge and to clarify misinformation or fake news for the public in order to tackle this novel infection, governments should be responsible for providing precise information and improved online communication (Lai *et al*., 2020).

Severely critical patients require oxygen therapy and intensive care, since the disease frequently progresses to induce complications such as acute respiratory distress syndrome (ARDS) and septic shock, followed by anemia, acute heart injury, and secondary infections (D'Amico *et al*., 2020; Shi *et al*., 2020). The current treatment of patients infected with SARS-CoV-2 is mainly symptomatic, and most of the pharmacological data available was obtained for medications used during the SARS-CoV or MERS-CoV pandemics or from *in vitro* observations (Pascarella *et al*., 2020). Several clinical trials testing treatments for Covid-19 are being undertaken based on antiviral, anti-inflammatory and immunomodulatory drugs, cell therapy, antioxidants and other therapies.

Remdesivir is a nucleotide analogue that prevents viral replication and was effective in the treatment of several Covid-19 patients in China (D'Amico *et al*., 2020). It was effective in blocking SARS-CoV-2 infection through incorporation into the nascent viral RNA chain, leading to its premature termination. It has been reported to be active in preclinical studies of SARS-CoV and MERS-CoV infections, acting on the viral polymerase of coronaviruses. The effectiveness of remdesivir in reducing viral load and improving lung function parameters has also been described (Frediansyah *et al*. 2020; Pascarella *et al*., 2020)

Chloroquine and its phosphate and sulphate derivatives are used for the treatment of malaria and amoebiasis, while hydroxychloroquine is widely used as an immunomodulatory agent in systemic lupus erythematosus (Felsenstein *et al*., 2020). Both drugs were found to be active *in vitro* against SARS-CoV-2 replication, but hydroxychloroquine had greater inhibitory power compared to chloroquine for Covid-19 treatment (D'Amico *et al*., 2020). They also exhibit immunomodulatory activity which interferes with the ACE2 cell receptor (Pascarella *et al*., 2020). The US Food and Drug Administration (FDA) has recently approved the efficacy of hydroxychloroquine as a therapeutic option for SARS-CoV-2 infection (D'Amico *et al*., 2020). However, clinical studies suggest that chloroquine and hydroxychloroquine are associated with an increased risk of heart problems in Covid-9 patients, including arrhythmia and cardiac arrest (Esakandari *et al*., 2020)

Lopinavir-ritonavir (LPV/r) is an HIV protease inhibitor used in antiretroviral treatment for HIV and has proven exhibit *in vitro* activity against coronaviruses, including SARS, MERS-CoV, and SARS-CoV-2 (Omrani, 2020). The combination of two protease inhibitors limits otherwise extensive CYP3A4 activation and drug metabolism, thus substantially improving the bioavailability of LPV. LPV/r in combination with Ribavirin has been shown to be associated with a significant reduction in the severity of the disease compared to ribavirin alone (2.4% versus 28.8%) in SARS patients (Felsenstein *et al*., 2020).

Vitamin D and Zinc as adjunctive agents can reduce the risk of viral infection and prevent lung damage. Vitamin D is effective in reducing the levels of pro-inflammatory cytokines and increasing the concentration of anti-inflammatory cytokines. Zinc has antiviral, antibacterial, and anti-inflammatory properties and is involved in a range of mechanisms such as the inhibition of NF-κB signalling, regulation of T-cells, and restriction of cytokine storms. Therefore, it may be effective in reducing the severity of Covid-19 disease (Esakandari *et al*., 2020).

Finally, there is huge interest in the potential use of convalescent plasma (CP) transfusion to rescue severe Covid-19 patients. Patients who have recovered from Covid-19 whose plasma contains specific antibodies or immunoglobulins may be a valuable donation source of CP. However, it is not yet clear when patients who have recovered from Covid-19 produce antibodies neutralizing SARS-CoV-2, or if antibodies are produced in adequate concentrations to be used in plasma therapy (Omrani, 2020). So, the potential clinical advantages and risks of convalescent plasma therapy for Covid-19 remain uncertain.

Conclusion

Covid-19 has significantly impacted people's health and lives. The disease has led to a pandemic, having spread worldwide. While much information is now available regarding this virus, extensive further study and morphological and histopathological research is required which will help in the understanding of the disease and its diagnosis and treatment. Even though many treatments have been proposed, there are currently no specific options for treating Covid-19 or preventing infection. Furthermore, there is no conclusive evidence yet that patients who have recovered from Covid-19 are immune to a second infection. However, the most important methods to control the disease and safeguard populations are regular hand-washing, the use of disinfectants, maintaining social distancing, and the quarantining of individuals with Covid-19 or those suspected of being infected.

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