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SARS-CoV-2 associated pathogenesis, immune dysfunction and involvement of host factors: a comprehensive review

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Abstract. – Infectious diseases, especially viral infections, have emerged as a major concern for public health in recent years. Recently emerged COVID-19, caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), has been declared a pandemic by World Health Organization since March 2020. It was first identified in Wuhan, China, in December 2019 and has since claimed more than a million lives. Complicated symptoms are associated with rising incidence and fatality rates, while many of the vaccine candidates are in the final stages of clinical trials. This review encompasses a summary of existing literature on COVID-19, including the basics of the disease such as the causative agent's genome characterization, modes of transmission of the virus, pathogenesis, and clinical presentations like associated immune responses, neurological manifestations, the variety of host genetic factors influencing the disease and the vulnerability of different groups being affected by COVID-19.

Key Words:
COVID-19, SARS-CoV-2 infection, Pathogenesis, Immune response, Host factors.

Introduction

Infectious diseases, especially viral infections, have emerged as a major concern for public health in recent years. Despite rigorous research efforts, new viral strains emerge with no predictive patterns on when and how the infection appear and cause global havoc. Previous outbreaks of coronaviruses (CoV) include severe acute respiratory syndrome (SARS)-CoV and Middle East Respiratory Syndrome (MERS)-CoV, historically known as pathogens that pose a major threat to public health[1]. COVID-19 is one such viral infection that has changed the global scenario. Serious COVID-19 symptoms are associated with rising numbers of cases and increasing fatality rates. Since its emergence, SARS-CoV-2 has affected an alarming 101,587,488 people in 214 countries and territories worldwide, causing 2,188,094 deaths as of January 28, 2021. Around 73,467,272 people have recovered from the infection, but 25,928,644 people are still battling the disease[2]. This review covers the basics of the COVID-19 disease and highlights the importance of various associated factors.

Methodology

A systematic literature search of original research articles and review articles was performed using PubMed/Medline, Scopus, Google Scholar and Web of Science to search for the latest COVID-19 related articles. Preferred Reporting Items for Systematic reviews and Meta-Analysis (PRISMA) guidelines were strictly followed. To form a comprehensive review on COVID-19, the various search terms used included 'SARS-CoV-2, COVID-19, Coronavirus, Novel coronavirus.

Manual searching was also performed, reviewing the reference lists of comprehensive review articles and relevant clinical trials. From the thousands of articles available on COVID-19 and SARS-CoV-2, around 200 were narrowed

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down to produce a comprehensive review encompassing all topics. A few reports and newspaper articles were also included to obtain necessary information. Mostly the literature was published in the year 2020, but a few studies from previous years were also included where necessary to link COVID-19 data for hypothesis formulation. Original research articles were preferred and studies not conforming to the objectives of the review were excluded.

Genome of COVID-19/ Molecular Biology

Coronaviruses are a family of positive single-stranded RNA viruses that contain large RNA genomes and cause severe upper respiratory tract illnesses[3]. Four humans CoVs are globally endemic and contribute to respiratory tract infection, but severe forms of infection are caused by SARS-CoV, MERS-CoV and the recently discovered SARS-CoV-2 which has caused a pandemic[4].

COVID-19 is caused by a novel coronavirus generally termed as SARS-CoV-2, belonging to the family *Coronaviridae*, sub family *coronavirinae*, and genus *Betacoronavirus*. The genome of SARS-CoV-2 is a positive-sense, non-segmented, single-stranded RNA molecule with the same sense as mRNA. It ranges from 29.8 kb to 30 kb in size and like eukaryotic mRNAs, it contains a 5' cap and a 3' poly-A tail[5,6].

The genome contains multiple open reading frames (ORFs). RNA is translated into 16 nonstructural proteins (nsps) from 2 ORFs; ORF1a and ORF1b. These encode two large polyproteins: pp1a and pp1b, respectively[4]. Pp1a is 440-500kDa and is cleaved into 11 nsps. The -1-frameshift mutation, upstream of ORF1a stop codon leads to the production of a larger polypeptide, pp1ab, because of continued translation of ORF1b. This pp1ab is 740-810kDa and is cleaved into 15 nsps. The proteolytic cleavage of pp1a is done by nsp3, which anchors a papain-like protease domain, while pp1b cleavage is mediated by nsp5, which is a 3C-like protease domain[7]. A replicase transcriptase complex, formed by nonstructural proteins, is an assembly of viral and cellular proteins. It facilitates the synthesis and amplification of genomic and sub-genomic mRNAs within infected cells[4,8].

Other ORFs encode four structural proteins and six accessory proteins. Structural proteins include spike (s), membrane (M), envelope (E) and nucleocapsid (N) protein[9]. The virus binds to the angiotensin-converting enzyme 2 (ACE2) receptor via the S1-S2 heterodimer domains of S glycoprotein expressed on the virus surface[10]. The organization of the genome is generally conserved within a family. According to the current annotation (GenBank: NC_045512.2), it has six accessory proteins 3a-b, 6, 7a-b, 8b, 9b, 10[7]. The genes encoding these accessory proteins are interspersed between the structural genes and the gene order for SARS-CoV-2 is [rep]-[S]-3a,3b [E]-[M]-6-7a,7b-8b-[N],9b,10[11]. Accessory proteins help the virus adapt to a specific host and the expanded genome size is linked to the genes acquired by RNA processing enzymes such as RNA 3'-5' exonuclease and endonuclease. These characteristics of coronavirus are significant and are predicted to have paved the way for crossing species (Figure 1) barriers[12].

Many evolutionary analyses have been done on the coronavirus genome which negate the idea that it is the result of a recent recombination. The mutation rate of SARS-CoV-2 might be higher than 7.23, as calculated from the dominant population's sequences. The mutational events are further supported by the evidence of RNA editing in its genome mediated by the host cell's APOBEC mechanism[13].

The genomic organization of SARS-CoV-2 is very similar to bat-SL-CoVZC45, bat-SL-CoVZXC21, and SARS-CoV, as demonstrated by the comparison of coding regions. Only a few deletions or insertions are noted while the lengths of other proteins are similar, except for the longer spike protein (S) in SARS-CoV-2[9].

Mode of Transmission

The absence of evidence to support the various transmission routes has led to great debate since the start of the COVID-19 pandemic. Various pathways have been identified for the spread of viruses from person to person, such as sneezing, coughing, breathing, or even talking with an infected individual[14]. As per the current consensus, SARS-CoV-2 spreads primarily through respiratory droplets (> 5-10 μm)[15] and heavier droplets cannot make it farther than 6 ft. before landing on the ground hence the social distancing guidelines of keeping a 6 ft. distance from others[16].

Despite the uncertainty regarding the relative contribution of different transmission routes of the virus causing COVID-19, airborne transmission was generally regarded as the major mode of its transmission[17]. However, the exposure of humans to droplets of respiratory secretions of an

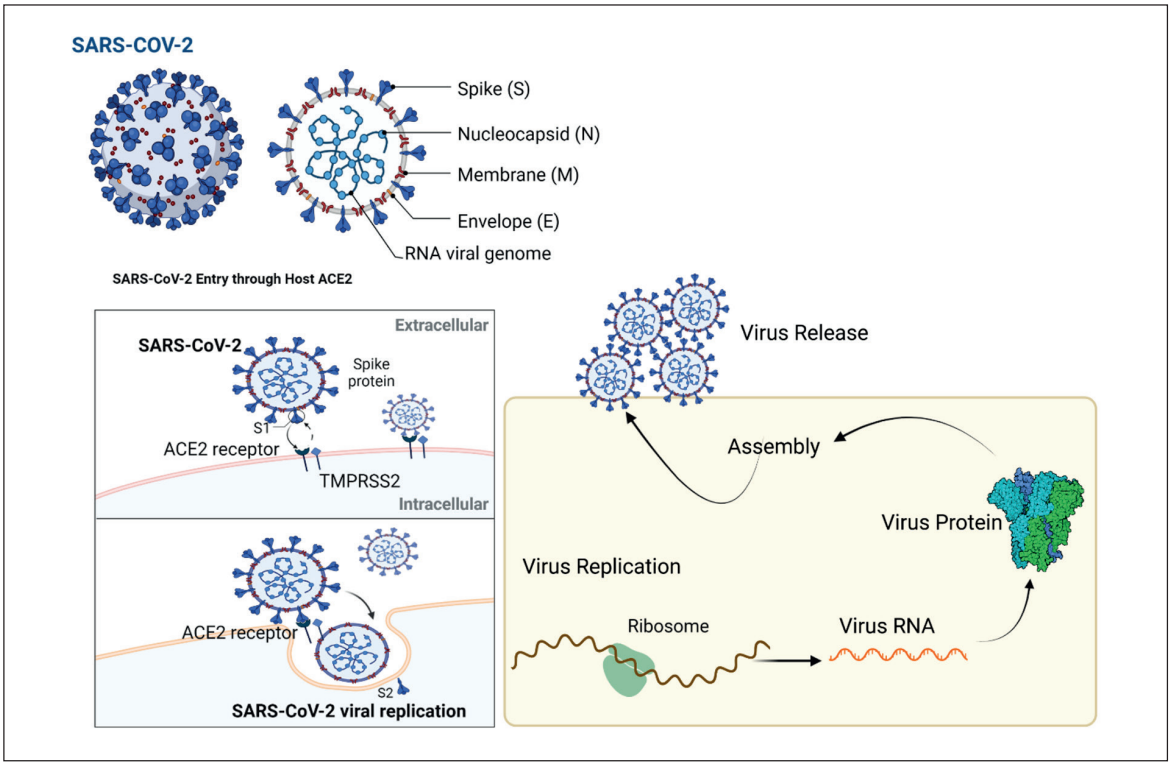

Figure 1. SARS-CoV-2 structure and replication cycle. Coronavirus structure showing the organization of spike (S), membrane (M), and envelope (E) proteins.

infected person, either by airborne transmission or indirectly through contact with contaminated objects, has been recognized as the major mode of SARS-CoV-2 transmission[18].

Being a virus infecting the respiratory tract, SARS-CoV-2 is generally transferred via respiration. Small droplets are created in the air that passes over the respiratory tract fluid of a person. Those droplets may contain the infected virus and can be transmitted to another person or the environment via sneezing or coughing or breathing by the infected person. The size of the droplets, viral concentration within them, and the number of droplets determine the overall disease transmission[16]. The spread, however, is not limited to respiratory droplets alone as indicated by the evidence.

Viral shedding by these pathways forms large droplets which cause person-object contamination frequently and smaller aerosols readily disperse in the air[14]. The distinct efficiency of dispersal and deposition patterns within the human respiratory tract are among the characteristic features that stem from the >5 μm size of droplets and inhalation of virus-containing aerosols (< 5 μm)[19].

SARS-CoV-2 has the ability to stay on surfaces or objects for several days while it has infectious characteristics in aerosols for hours. This virus remains viable on the surface of objects for longer time periods compared to other viruses; it was recently reported to stay on plastic surfaces for around 6.8 h and on stainless steel surfaces for about 5-6 h[20]. It is shown to be more virulent than other viruses due to its higher affinity for ACE2 receptors, hence, fewer virus-containing droplets are required to cause infection[21].

There is not enough evidence to prove that fecal oral routes can be a cause of COVID-19 viral spread; however, it can be a potential risk in confined spaces such as public transportation, dormitories or hostels[22]. Staying longer in the environment indicates it can spread via indirect transmission routes as well, such as fomites or airborne transmission[23]. Viral shedding depends upon the stage of SARS-CoV-2 infection. The highest rate of shedding is at or before symptom onset, and the probability of viral spread also differs between symptomatic and asymptomatic carriers.

Following the social distancing guidelines, the use of hand sanitizers, quarantine and minimal

contact with infected people or infected surfaces reduces the spread of SARS-CoV-2, but airborne transmission is only averted by a face covering which prevents viral-infected aerosol inhalation and viral shedding[18].

Pathogenesis

Proinflammatory Cytokine Storm

Standard laboratory abnormalities found during extremely pathogenic coronavirus infections, such as extreme acute respiratory syndrome, coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV), are lymphopenia and inflammatory cytokine storm, and are considered consistent with disease seriousness[24]. Higher numbers of leukocytes, elevated respiratory findings, and increased levels of plasma proinflammatory cytokinesis were recorded in patients infected with COVID-19. In the majority of severe cases, serum concentrations of pro-inflammatory cytokines, including IL-1β, IL-6, and TNF-alpha are increased, indicating cytokine storm syndrome could be correlated with disease severity. An analysis of immunological features in peripheral blood in patients with COVID-19 reveals that neutrophil and T cell numbers, in particular CD8+ T cells, as well as inflammatory cytokine levels in peripheral blood are dynamically associated with the severity of the disease[25].

Lung Injury

Recently, individuals with life-threatening SARS-CoV-2 disease have been found to have related cytokine release syndrome (CRS)[26]. Early predictors of severe lung involvement and mortality include lymphocytopenia and elevated levels of inflammatory mediators[27]. In particular, neurogenic pulmonary edema could appear in patients with extreme COVID-19 pneumonia, it could not be defined as a type of ARDS, but rather as a non-cardiogenic interstitial pulmonary edema with a distribution of the peripheral lung zone that could be found in viral pneumonitis. For clinical purposes, this non-cardiogenic pulmonary edema was mainly a diagnosis of viral pneumonitis[28]. The key distribution pattern of ground-glass opacities and consolidation is peripheral in COVID-19, and atypical lung involvement patterns may occur in the lower lung lobes as recorded by various chest computed tomography (CT) studies[29]. The involvement of the lungs in COVID-19 might result in ARDS, requiring intubation and admission to the intensive care unit. Various pathways can be linked to the pathogenesis of lung involvement, including lung parenchymal damage which might be caused by the virus, resulting in pneumonitis that causes interstitial lung and/or alveolar inflammation. The virus might also bind directly to the receptors of ACE-2, promoting endothelial dysfunction. Lung parenchymal and microvascular inflammation might be aggravated by the resulting CRS, thereby encouraging refractory modes of ARDS with related hypercoagulable conditions and microthrombosis[30].

Liver Injury

In patients with COVID-19 infection, multiple studies have reported clinical features and laboratory tests consistent with various degrees of liver injury. Prior studies have found that the frequency of liver damage ranged from 58% to 78% in significant COVID-19 cases[31].

The virus predominantly attacks the respiratory system causing signs of fever, exhaustion, cough, dyspnea, lack of appetite, and muscle and joint pain. However, the occurrence of vomiting, nausea, and diarrhea, showing the involvement of the gastrointestinal and hepatobiliary systems[32,33], has also been reported. The angiotensin-converting enzyme 2 (ACE-2) is used by COVID-19 as the binding site for the lungs, kidneys, and heart to join the host cell[9]. The ACE-2 protein is also found in bile duct cells, as well as in type II alveolar epithelial cells of the lungs. This means that SARS-Cov-2 could theoretically infect bile duct cells and cause irregular tests of liver function[31,34]. However, it is not clear if liver damage in patients with COVID-19 infection is due to overt liver participation by the virus or due to multiorgan failure.

Asthma

None of the patient reports concluded that allergic diseases and asthma were risk factors for infection with SARS-CoV-2. The intensity of COVID-19 was linked to older age and a high number of comorbidities, i.e., cardiovascular, and metabolic disorders[33].

Heart Injury

COVID-19, which primarily induces acute respiratory failure, is not limited to the respiratory system alone; it can also affect other organs, such as the kidneys, heart, gastrointestinal tract, im-

mune system, blood, and nervous system. There have also been clear effects of SARS-CoV-2 on the myocardium, leading to adverse heart outcomes in patients with SARS-CoV-2[35]. Two case reports from China and Italy recently showed that, even without symptoms and signs of interstitial pneumonia, COVID-19 may lead to fulminant myocarditis[36,37]. There is an increased risk of life-threatening acute heart failure associated with more serious COVID-19 infection in a systematic study and meta-analysis[38].

Kidney Injury

The effect of COVID-19 on the kidneys has also been shown in several research studies, with an emphasis on vulnerable dialysis and renal transplantation patients. As several anecdotal studies have identified coronavirus PCR fragments in the blood and urine of infected patients with SARS and COVID-19, a novel coronavirus may have a direct cytopathic influence on kidney-resident cells[39]. A case of COVID-19 infection has recently been documented by Guillen et al[40] in a patient with a renal allograft (RAR) who was initially diagnosed as having clinical signs of gastrointestinal disease with fever and subsequently acquired respiratory symptoms.

Diarrhea

Some COVID-19 patients had diarrhea, while only a limited percentage had stomach signs, such as diarrhea, anorexia and fatigue, while vomiting[41]. In the US, the first COVID-19 patient endured fever and cough and contracted diarrhea within two days of hospital admission[42]. An analysis found 14 publications describing COVID-19-related diarrhea and the prevalence ranged significantly, varying from 2% to 49.5%[43]. SARS-CoV-2 specifically or indirectly harms the digestive system by an inflammatory response. Inflammatory disruption to the stomach can also be induced by hyperactivate cytokines, immune dysregulation, and inflammatory floods, culminating in diarrhea[25].

Bacterial and Fungal Coinfections

In COVID-19 patients, medicinal medications and antibiotics can also lead to diarrhea. Antiviral substances, such as umifenovir, a broad-spectrum drug, can also induce diarrhea. In the treatment of COVID-19, antibiotics and antiviral drugs have been widely used, but there are few studies on drug-induced diarrhea, and prospective studies are required. In COVID-19 cases, diarrhea disrupts the equilibrium of the intestinal flora, influences the inflammatory response, raises the incidence of COVID-19, and disturbs the prognosis[44]. During the treatment of COVID-19, antimicrobials have many possible functions. In hospital patients, SARS-CoV-2 infection can also be hard to differentiate from non-acquired and ventilator-associated pneumonia. Of the studies documenting SARS-1, bacterial/fungal coinfection occurred in 42 of 135 (31%) reported cases. Broad-spectrum antimicrobial therapy has been generally documented, with antibacterial therapy being administered in 72% of COVID-19 cases[45].

Stroke

During the ongoing global pandemic, there is growing evidence that patients afflicted by COVID-19 may experience clinically relevant coagulopathy with thromboembolic complications, including ischemic stroke. Out of 3556 admitted patients with a diagnosis of COVID-19 infection, 32 patients (0.9%) had proven ischemic stroke imaging during the research period in 2020[46]. Patients have a lower mean age than historical non-COVID-19 stroke patients. The number of patients diagnosed with cerebrovascular stroke as an early occurrence of COVID-19 was noticeable[47].

During the COVID-19 pandemic, with a rising strain on healthcare systems, a general evidence base is needed to establish antimicrobial prescribing and stewardship policies to facilitate optimum patient results and to avoid the adverse effects of antimicrobial use on patients and the community as a whole.

Immune Responses

Cytokine Storm

In COVID-19 patients, cytokine storm is one of the critical features in worsening the disease state. It is a condition in which excessive cytokines are produced by hyper-activated immune cells, leading to hyperinflammation and multiple organ failure, further increasing the mortality rate[10].

During viral infection, a prompt and systemic innate immune response is the first line of defense, and cytokines are known to play a major role in the immunopathology of viral diseases[48]. The viral mRNA acts as pathogen-associated molecular patterns (PAMP) and activates Pat-

tern Recognition receptors (PRRs), initiating a robust cytolytic immune response mediated by Natural killer (NK) cells and type I interferons (IFN)[49]. In the adaptive immune response, cytotoxic T lymphocytes target virus-infected cells facilitating viral clearance, and B cells produce antibodies against virus-specific antigens (Figure 2).

However, in the case of critically ill COVID-19 patients, there is an excessive production of inflammatory cytokines, including tumor necrosis factor (TNF), interleukin-6 (IL-6) and IL-1β while lymphocyte counts are extremely low, thus damaging the host tissues[50]. As implicated in SARS-CoV infection, this storm is suggested to be mediated by the activating signals received by the IFN receptors present on the surface of mononuclear macrophages. The target for SARS-CoV-2 infection is primarily alveolar macrophages expressing the ACE-2 receptors that mediate the cytokine storm[51]. This results in the production of enormous amounts of chemo-attractants, including CCL-2, CCL-3 and CCL-5, resulting in further accumulation of these macrophages producing the aforementioned proinflammatory cytokines and aggravating the disease state[48].

A substantial reduction in CD4+ T cells, CD8+ T cells, and NK cells was observed in critically ill COVID-19 patients compared to those exhibiting mild symptoms[52]. Moreover, the cell count of proinflammatory Th17 cells and perforin and granzyme expressing T lymphocytes increased, which is believed to be involved in causing lung injury in these patients[53].

Increased concentrations of T helper cells (Th1 and Th2) cytokines including TNF, IL-10, IL-2, IL-7, MIP-1 α, MCP-1, and GM-CSF have been observed in the plasma of critically ill COVID-19 patients. IL-6 concentration is also reportedly above the normal range in COVID-19 patients exhibiting severe symptoms compared with those with milder or no symptoms[52,54]. Apart from being associated with ARDS, the cytokine storm in COVID-19 cases has also been linked to a secondary form of haemophagocytic lymphohistiocytosis (HLH). It is characterized by the unrestrained growth of tissue macrophages or histiocytes having haemophagocytic activity and the uncontrolled cytokine storm[55]. Seriously ill patients with COVID-19 have also reportedly shown the major features of HLH, such as continuous fever, hyperferritinaemia, hypercytokinaemia, reduced blood cell counts and severe multiple organ damage[56].

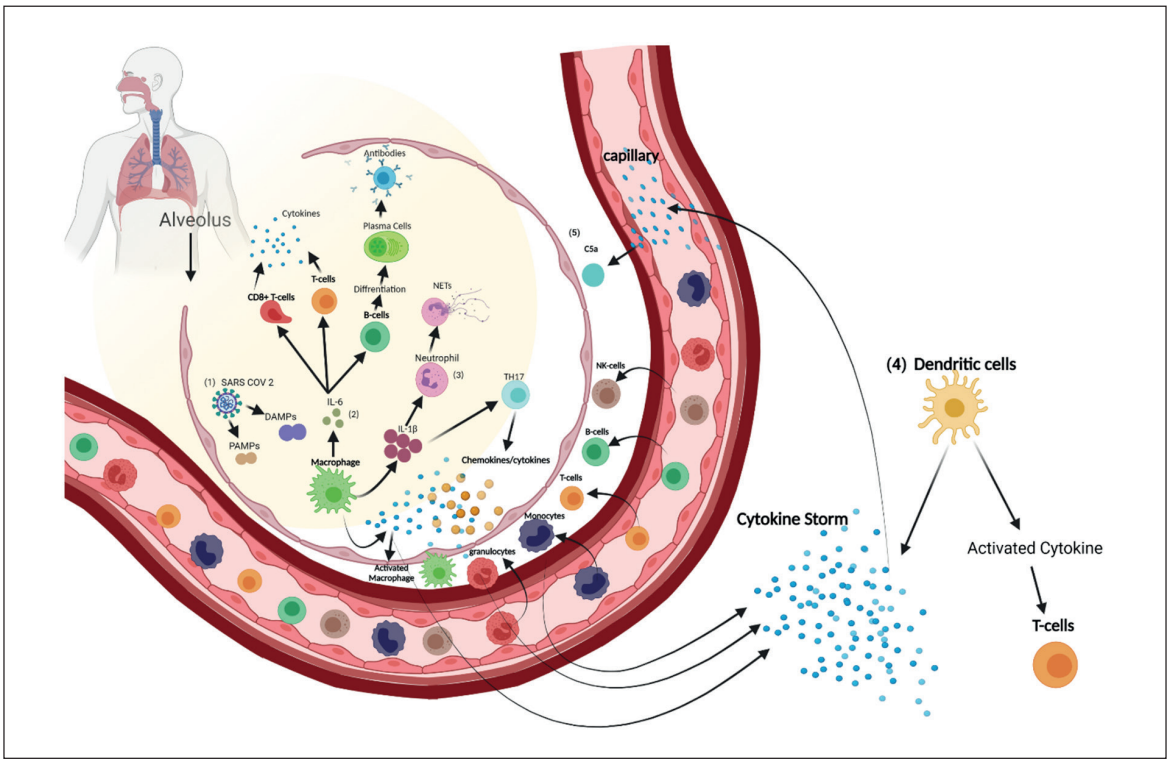

Figure 2. Immune response to SARS-CoV-2 infection leading to cytokine storm.

An excess of, or any, dysregulation in the organization of immune reactions leads to disruption of normal bodily functions. Hence, in SARS-CoV-2 infection, earlier identification and timely suppression of cytokine storm and hyperinflammation is imperative to counter the deteriorating condition of COVID-19 patients and reduce the mortality rate.

Interleukin-6 (IL-6)

Interleukin-6 (IL-6) is a proinflammatory cytokine and a major mediator of the immune response during infection. It is reportedly increased in the serum of COVID-19 patients and data from retrospective studies indicate its association with the high case fatality rate (CFR) of SARS-CoV-2 infected patients[57].

Currently, there is no effective biomarker for the diagnosis of COVID-19 and the analysis of disease progression relies solely on the clinical presentation. Growing evidence suggests the potential of IL-6 as a predictive biomarker for COVID-19 disease progression.

One of the major components showing enhanced expression during the cytokine storm is IL-6 and it is associated with a fulminant inflammatory response, mechanical ventilation, and mortality in COVID-19 patients[58]. Similarly, increased IL-6 has also been observed in patients with respiratory dysfunction, suggesting a correlation between cytokine-mediated lung damage and COVID-19[59].

Immune dysregulation by the cytokine storm during COVID-19 has also found a root in elevated IL-6 levels. In severely ill patients, a much greater increase in IL-6, as high as 1000-fold above the normal value, has been reported compared to other inflammatory cytokines such as IL-10 and IL-1[60]. During severe COVID-19, the serum level of IL-6 was three times higher than that of noncomplicated stages of infection[61].

The data from recent studies indicate that clinical measurements of the serum levels of IL-6 at the time of hospital admission may be an important prognosticator for revealing the disease progression and severity in COVID-19. It can also indicate the prospects of survival in hospital admitted cases. These studies also reveal the importance of using anti-IL-6 drugs as a therapeutic strategy for improving the outcome in patients suffering from COVID-19[62]. Many attempts have been made to block IL-6 as it is highly expressed in COVID-19 related cytokine storm and is frequently associated with a poor outcome.

Regulatory T Cells

Regulatory T cells, also known as Tregs, are a subgroup of T cells that can diminish the immune response. Fulminant immune responses in cases of infection can sometimes lead to tissue damage in the host, hence Tregs are nature's way of keeping inflammatory responses under control[63]. Two subsets of Tregs are present; one is derived from the thymus and called natural Tregs (nTregs) while the other is induced in the periphery from naïve T cells and is known as induced Treg (iTregs). Both subtypes are equally important and play an indispensable role in maintaining homeostasis and eliciting immune tolerance, thereby preventing the development of inflammatory illnesses and autoimmunity[64].

Tregs suppresses innate and adaptive immune system activation by secreting of immunosuppressive cytokines including TGF-β, IL-35 and IL-10 and by presentation of inhibitory molecules expressed on their surface, such as cytotoxic T-lymphocyte antigen-4 (CTLA-4) and lymphocyte-activation gene-3. In severely ill COVID-19 patients, the level of Tregs is significantly reduced in comparison to those with mild disease, as shown by various studies[65,66]. One reason for this can be that the Tregs have gone to the site of infection to counter the tissue damage induced by a heightened immune response. The expression of IL-2 is lowered in severe cases with COVID-19[67], which could potentially cause enhanced Tregs apoptosis and is confirmed by the reduction in the levels of FoxP3 levels.

As regulatory T cells are important in dampening the immune response, their lower frequency in severe COVID-19 cases can be responsible for cytokine storm and dysregulation of immune system causing lung damage. The levels of IL-2R, also known as CD25, have also been augmented in severe patients with COVID-19[66] which potentially interferes with the bioavailability of IL-2 and might lead to enhanced Tregs apoptosis[68].

Based on the evidence of Tregs' importance in COVID-19 and immune system dysregulation, it has been suggested that Tregs-based therapeutic strategies might prove to be beneficial for patients with severe forms of this disease. Trials are underway on the use of HLA-matched umbilical cord-derived Tregs (NCT02932826 and NCT03011021) for inflammatory conditions[69,70] and can provide an option for COVID-19 therapy, upon successful results. Reportedly, a noteworthy decline in inflammatory cytokines such as IL-6, IFN-γ, IL-12, TNF-α and IL-8 was observed in

two COVID-19 associated ARDS patients who were treated with allogenic, *ex vivo* expanded Tregs derived from the umbilical cord[70]. This highlighted a temporal relation between patient recovery and the infusion of Tregs.

Another approach for COVID-19 patient management could be the use of Tregs-derived immunomodulatory molecules such as CTLA-4, which can potentially keep the COVID-19 associated hyperinflammation in check[66]. A lower incidence of COVID-19 in patients treated with a CTLA-4-linked drug named abatacept highlights its potential role in therapeutic activity. These observations regarding abatacept were concluded from two separate epidemiological surveys done in Spain (Barcelona and Madrid) where the lowest frequency of COVID-19 symptoms was noted in people treated with disease-modifying anti-rheumatic drugs (DMARDs) and specifically abatacept[71,72]. Similar results were obtained in Italy (Siena) where only two out of 779 DMARD-treated patients tested positive for SARS-Cov-2[73].

CTLA-4-based treatments or those involving other Tregs-related molecules are promising sources for immune regulation in COVID-19 patients. Hence, further studies need to be performed on the efficacy of various immunotherapies to prevent the aggravation of immune system damage in COVID-19.

Natural Killer Cells

Natural killer (NK) cells are cytotoxic lymphocytes that provide an efficient and robust immune response to viral infections, but they may also be involved in immunopathology. They are generally divided into two groups: cytotoxic $CD56^{dim}$ NK cells and cytokine producing $CD56^{bright}$ NK cells[74]. A rapid response of NK cells has previously been reported in the acute phase of many viral infections, including dengue virus, encephalitis and hanta virus[75-77]. Little is known about the role of NK cells in SARS-CoV-2 infection but given their crucial importance in viral clearance and immunomodulation, they may prove to be strong allies in the fight against COVID-19.

Many studies are now being conducted to examine the role of NK cells in SARS-CoV-2 infection. Emerging evidence shows the presence of lower NK cell counts in the peripheral blood of COVID-19 patients suffering from moderate or severe forms of the disease[52]. This suggests the association of a reduction in the number of NK cells in COVID-19 with disease severity and progression.

Based on the results of flow cytometry analysis, activation of distinct NK cell immunophenotypes has been linked to disease severity. It was also noted that NKG2C, granzyme B, HLA-DR, perforin, and Ksp37 were highly expressed in responding $CD56^{bright}$ NK cells, while responding $CD56^{dim}$ NK cells showed higher expression of HLA-DR and Tim-3. The data indicated that adaptive NK cell subsets are present in the circulation of COVID-19 patients[78].

In a study by Zheng et al[79], a striking finding was reported that the expression of activation markers including IFNɣ, TNFα, CD107a and IL-2 was significantly reduced on T and NK cells while the NKG2A receptor, which is an inhibitory molecule involved in repressing T-cells and NK cells function, is markedly increased in COVID-19 patients. The data from these studies indicates the functional exhaustion of cytotoxic NK and T cells and a severely compromised immune response in patients having severe COVID-19[80]. Conversely, only two studies have reported an increase in NK cells in the bronchoalveolar lavage (BAL) fluid of patients affected with COVID-19[81,82].

Besides working as friends, NK cells are also thought to work as foes in the case of COVID-19. A study revealed that NK cells were strongly activated in response to SARS-CoV-2 infection and may be involved in the hyperinflammation in some severe cases of COVID-19[78]. This hyperresponsiveness in COVID-19 patients may stem from the overexpression of inhibitory molecules like TGF-β[80]. Evidence of NK cells acting as a double-edged sword necessitates the deciphering of their involvement in coronavirus disease.

NK cell exhaustion could be targeted by blocking the inhibitory markers for restoration of COVID-19 patients. A vaccine designed to block NKG2A, Monalizumab[83], could be a therapeutic candidate to restore the functions of NK and T cells.

A clinical trial is proceeding in China (NCT04264533) to evaluate the effectiveness of Vitamin C infusion in patients with COVID-19 pneumonia, based on the evidence that Vitamin C led to more than 10-fold expansion of NK cells *ex vivo* while maintaining the tumor killing capability[84]. The regulatory role of NK cells can be exploited as an adjunct therapy. To control the T cell response, regulatory NK cells can be induced by IFN-β therapy. Triple therapy based on IFN-β1b therapy and the antivirals lopinavir-ritonavir and ribavirin showed promising results in viral clearance from COVID-19 patients in a randomized Phase II trial conducted in Hong Kong[85].

Further studies need to be performed to clearly understand the role of NK cells in COVID-19 infection to effectively utilize NK-cell based targeted therapies to improve the disease status in severely ill patients as well as to counter the pandemic.

Macrophage Activation Syndrome

It has been suggested that macrophage activation syndrome (MAS), a component of the cytokine storm, is associated with COVID-19 related pneumonia[86]. There is a possibility that SARS-CoV-2 infects particular cell types such as macrophages, cells in the alveolar wall or endothelial vessels, which leads to the development of MAS. It is a hyperinflammatory state of the immune system and has been previously observed in patients suffering from viral infections, pediatric rheumatological illnesses like systemic juvenile idiopathic arthritis (SJIA) and malignancies[87]. One of the prognomonic features of MAS is that macrophages produce an excess of proinflammatory cytokines. SARS-CoV-2 infection alongside MAS is usually reported in patients suffering from ARDS and mortality has been associated with the upregulated expression of IL-1 and IL-6[88].

Apart from hypercytokinemia, MAS-like symptoms exhibited in some COVID-19 patients included higher levels of C-reactive protein (CRP), D-dimer and ferritin in the serum, and development of severe fibrinolysis and inflammation[89]. In COVID-19 patients, hyperferritinemia is less common than MAS and mostly only the D-dimer is increased, unlike the reduced platelet counts and fibrinogen commonly seen in MAS. Similarly, the hepatosplenomegaly present in MAS is not observed in SARS-CoV-2 infected patients[20].

The suspicion of MAS complicating COVID-19-associated pneumonia spurs interest in testing the anti-cytokine strategies being used in MAS to effectively suppress heightened immune responses. However, MAS aggravates COVID-19 pneumonia and the immunopathological manifestations were mainly observed in the lungs and thorax, which makes the differentiation from ARDS difficult. A preliminary trial conducted by University of Science and Technology of China using anti-IL6R blockage with tocilizumab, used generally in MAS, showed success when conducted on COVID-19 patients thus providing evidence for its efficacy[90]. It is imperative to do further studies on COVID-19-associated MAS, which may highlight new molecular targets for better COVID-19 management.

Multisystem Inflammatory Syndrome in Children (MIS-C)

Various studies have established a strong link between COVID-19 and multisystem inflammatory syndrome in children (MIS-C)[91,92]. Before being admitted to the hospital for MIS-C management, the majority of children in a reported series had been infected with SARS-CoV-2 within the past two weeks and displayed hyperinflammatory manifestation comparable to those of adults suffering from COVID-19[65]. The interval between symptom onset of COVID-19 and hospitalization of MIS-C was noted to be 25 days in a subgroup of these children. Although one-third of the studied groups had negative RT-PCR results for COVID-19 infection antibodies were detectable, hence confirming the presence of SARS-CoV-2 previously[93,94].

Primarily originating and being reported in Europe and USA, MIS-C is also referred to as a pediatric inflammatory multisystem syndrome temporally associated with severe acute respiratory syndrome coronavirus 2 (PIMS-TS)[91]. The symptoms of MIS-C are reportedly comparable to those observed in other rare paediatric disorders, such as toxic shock syndrome or mucocutaneous manifestations and constant fever similar to Kawasaki disease, but the differences in clinical presentation separate it from these conditions[95]. MIS-C affects adolescents and older children above 5 years of age, unlike Kawasaki disease, and has substantial cardiovascular involvement[96]. Children suffering from MIS-C are also reported to suffer from severe consequences like kidney injury, poor heart functionality, and thrombosis[93]. Like Kawasaki disease, however, MIS-C presents with a range of clinical manifestations with no diagnostic tests or characteristic findings[95].

Reportedly, aside from common symptoms such as fever, abdominal pain, and body aches, there are two major subdivisions of children with MIS; 75% are patients with typical or atypical Kawasaki disease and the other 25% have a severe form of the disease with reduced cardiac activity[97]. This published literature reports acute heart failure, acute myocarditis in PIMS-TS children and involvement of coronary artery dilation in two-thirds of the group, which is contradictory to the data from other countries where the incidence is only 36% in UK, 17% in France, 20% in Italy and 9% in the USA[95,96,98,99].

It is important to understand the pathogenesis of MIS-C and the association with SARS-CoV-2 infection to formulate effective preventive and therapeutic measures to reduce the burden of COVID-19 morbidity and mortality.

Neurological Manifestation

As the number of cases affected by coronavirus grows, the reports of patients with an affected nervous system are also increasing. Even though SARS-CoV-2 primarily affects the respiratory and cardiovascular systems, it is also reported to have various neurological manifestations[100]. Identification of these neurological symptoms is, however, challenging, especially in patients with mild or no symptoms of COVID-19 or those having been infected weeks earlier. Many COVID-19 patients reportedly experienced dizziness, headache, neuralgia and some also faced severe complications such as acute encephalitis, impaired consciousness, Guillainn Barré syndrome, skeletal muscle injury and cerebrovascular accidents. Ageusia and anosmia are common among patients even in the absence of other clinical features. The neurological complications might stem from a direct effect of SARS-CoV-2 on the nervous system or an indirect effect of the dysregulated immune system during or after the infection[100].

Two cases of COVID-19 patients, middle-aged women with acute disseminated encephalomyelitis have been reported, among whom one required intubation and experienced seizures, and impaired consciousness while the other presented with dysarthria, dysphagia and encephalitis after myalgia and headache[101,102]. COVID-19 patients presenting with the characteristics of Guillainn Barré syndrome show symptoms such as symmetrical and progressive weakness of the limbs, facial weakness and areflexia in some patients, while a few cases report its variants as well[103]. Viruses generally utilize two routes for neuro-invasion: neuronal retrograde dissemination and hematogenous dissemination. In neuronal retrograde dissemination, the virus infects peripheral neurons and utilizes the transport machinery of these cells to reach the CNS while in hematogenous dissemination, it spreads via the bloodstream throughout the body and crosses the blood-brain barrier (BBB) to reach the brain[103].

Neurological damage caused by COVID-19 occurs mainly via two mechanisms: immune-mediated injury to the CNS and hypoxic brain injury. Immune mediated impairment results from hyperactivation of immune cells and the cytokine storm, in which overproduction of IL-6 causes complement activation and a coagulation cascade, leakage from the vessels and end organ damage[89]. The hypoxic condition causing brain damage can be a result of severe pneumonia in the case of critically ill COVID-19 patients. Resulting vasodilation and accumulation of toxic compounds can lead to neuronal swelling and edema, causing further severe damage to the nervous system[104]. Hypoxic encephalopathy leads to the death of many COVID-19 patients[105].

The presence of SARS-CoV-2 RNA was first detected in the CSF of a patient with encephalopathy and COVID-19 comorbidity using real-time reverse transcription PCR (RT-PCR) and has been reported in various studies[106]. However, the virus was not detected in the CSF of the majority of patients exhibiting neurological symptoms[107] thus indicating an indirect impact on the nervous system and the need for the development of more specific diagnostic methods.

Host Genetic Factors

Although the detection of comorbidities in COVID-19 patients has helped stratify the risk groups, the distinct responses of individual cases make it difficult for physicians to handle the clinical complications. Evidence from previous studies strongly suggests that the variability in clinical outcome depends largely on variations in host genetic factors and partially on gender differences, comorbidities and viral factors. Viral genome variations do not affect the clinical outcome of COVID-19 significantly, as demonstrated by Zhang et al[108]. Therefore, it is of prime importance to identify the prominent host genetic factors that alter the susceptibility to SARS-CoV-2 infection, govern the pathogenesis, and determine the outcome of the disease.

Various comorbidities have been reported to increase the susceptibility to severe forms of COVID-19 significantly. From the most prevalent to lesser incidents in COVID-19 patients, the reported comorbidities include chronic obstructive pulmonary disease (COPD), diabetes, coronary heart disease (CHD), kidney disease and hypertension[109]. A study by Liu et al[110] demonstrated that there are differences in risk factors for the development of severe COVID-19 based on gender. As males are more susceptible, when compared with females, to CHD and hypertension which are predisposing conditions to SARS-CoV-2 infection[110] they are more vulnerable to development of fulminating COVID-19. Irrespective of

the comorbid conditions, still a wide spectrum can be seen in COVID-19 infected individuals and raises many questions for the scientific community to explain this diversity.

Information from studies carried out on other coronaviruses, like SARS-CoV-1, has paved the way for researchers to narrow down the inherited risk factors for SARS-CoV-2. Variants in the most well-characterized genes, coding for the receptor of a new pandemic-causing virus, i.e., ACE-2 receptor gene variants have been implicated in differential susceptibility to infection[111]. The differences in worldwide prevalence and COVID-19 epidemiology can be explained by the geographical differences in the distribution of variants, such as a suggested correlation between the polymorphisms in ACE-2 and COVID-19 prevalence[112].

It was recently reported by using large genomic datasets that resistance to COVID-19 infection can result from the presence of ACE-2 variants which depict lower binding affinity for SARS-CoV-2. The identified variants include K31R, Y83H, G326E, M62V, E35K, D509Y, G352V, Y50F, N51S, K68E, N33I, E37K, D38V, F72V, H34R, Q388L and D355N[113].

Transmembrane protease serine-type 2 (TMPRSS2) protein is also involved in the entry of SARS-CoV-2 via S protein priming and polymorphisms in this gene are suggested to cause differences in disease susceptibility[114]. Moreover, a missense mutation in the novel binding receptor for the spike protein of SARS-CoV-2, known as CD147/BSG, is also indicated to have clinical implications. The anti-CD147 antibody, known as meplazumab, has been effective in the recovery of patients with COVID-19-associated pneumonia[115,116] thus indicating its ability to prevent viral entry in host cells.

Another study on major histocompatibility complex (MHC) class I genes, including HLA-A, B, and C, also demonstrated that variability in these genes leads to the predisposition of the host to contracting the virus. For example, people carrying the HLA-B * 46:01 variant are more susceptible to COVID-19 infection, while the variant HLA-B * 15:03 confers the ability to present conserved SARS-CoV-2 peptides, common in human coronaviruses, hence providing protection to the host via cross-protective T-cell-based immunity[117].

As hypoxic conditions develop in cases of severe COVID-19 disease, hypoxia-inducible transcription factors (HIFs) can also possibly alter the host vulnerability to infection[118]. The genetic variant rs12252-C in the Interferon-Induced Transmembrane Protein 3 (IFITM3) was found to be associated with COVID-19 severity depending on age[119].

Coronavirus genomes and intermediates are recognized by Toll-like receptors (TLRs), mainly TLR3 and TLR7, and several retinoic acid inducible gene I (RIG-I)-like receptors, referred to as RLRs, which lead to downstream signaling cascades for generating an immune response. Any genetic variance in the molecules involved in viral recognition, such as TLRs (TLR3 and TLR7) and RIG-I, or in the downstream pathways that lead to a dysregulation in this immune response can act as a predisposition to COVID-19 severity and alter the course of the disease[120].

In the case of SARS-CoV-2 infection, the innate immune response is mediated by the production of antiviral type I IFN. Single nucleotide polymorphisms (SNPs) in IFN-inducible genes such as MX1 and OAS1 have previously been associated with SARS-CoV infection[121,122] and hence suspected involvement in COVID-19 infection. Complement system activation has also been suggested to contribute to COVID-19 lung pathology[123].

A correlation between COVID-19 susceptibility and ABO blood group was investigated in a Chinese population. Blood group A was associated with an increased risk of contracting the virus and developing COVID-19, while people with blood group O presented with a lower risk of infection[124]. Another study generated similar results of association between the risk of SARS-CoV-2 pneumonia and ABO blood groups[125]. DSTN, MUC5B, CFL1, CFL2, DPP4 and TERT are some of the other genes reported in the literature, in which variations can potentially lead to differential COVID-19 vulnerability or clinical outcome[126].

The critical importance of deciphering host genetic factors can be assessed from the fact that a 'COVID-19 host genetics initiative' has been launched on a global scale where the scientific community can share and analyze data on genetic determinants of susceptibility to SARS-CoV-2, disease severity and clinical outcomes[127].

The identification of varied host genetic factors involved in COVID-19 would have far ranging benefits, not only for drug repurposing, precision medicine, and clinical trial design, but also for reducing fatality rates in the pandemic by better disease management. Early screening for

susceptibility factors can also help forecast the clinical outcomes and disease severity for timely intervention, as well as to prioritize people based on their need for vaccination when it is available.

Conclusions

Coronaviruses have posed a major threat to public health in the past few years. Emergence of the current pandemic was led by a new strain of coronavirus known as SARS-CoV-2. The wholesale market of seafood and exotic animals in Wuhan, China was the epicenter of the disease. The robust spread of COVID-19 infection claiming more than a million lives and its high case fatality ratio demonstrates the unpreparedness of nations across the globe to tackle a health crisis. The novelty of the virus, non-responsiveness or varied outcomes from existing treatment and the unavailability of a vaccine to contain the pandemic further necessitates the in-depth analysis of the associated features of the virus as well as the disease for better patient management and improved healthcare for COVID-19 patients.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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