Review Article

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The Role and Delicate Balance of Host Immunity in Coronavirus Disease-19

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ABSTRACT

Severe Acute Respiratory Syndrome (SARS) associated with SARS-CoV-2, causes a severe form of the respiratory illness known as Coronavirus Disease-19 (COVID-19). COVID-19 has emerged as a worldwide pandemic with a high number of fatalities. Approximately 112,654,202 people have been infected so far with this disease which has led to the death of more than one point seven million (2,496,749) till 24th Feb, 2021. Measures to counter this disease have led to a global economic slowdown. Multiple drug trials are ongoing and several putative candidates for vaccination against the virus have been approved and are in the pipeline. Many studies have also characterized the immunological profile of patients infected with COVID-19. Some studies suggest that the severity of the COVID-19 infection is directly associated with the cytokine storm. In this review, we aim to compile the available knowledge and describe the nature of immune responses in patients infected with COVID-19 infection in different age groups, comorbidity, and immune-compromised state and their association with disease severity.

Keywords: COVID-19, Immune Response, COVID-19 Infection, and Immune Cells

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INTRODUCTION

Coronaviruses that were mainly known to infect birds and mammals (1, 2) have been found to infect humans as well since mid of 1960s (3). The first two strains 229E and OC43 were first independently isolated and identified by Hamre, Procknow, and McIntosh respectively in the 1960s. These viruses were morphologically similar and were grouped as coronaviruses by Tyrrell. Later on, they were segregated on a serological basis into three groups. I (229E), II (OC43), and III (Avian infectious bronchitis virus). They were classified in coronaviridae family having two subfamilies (i.e. coronavirinae and torovirinae). The coronavirinae four genera alpha, beta, gamma, and delta. After three decades, new HCoV-HKV1 was discovered in 2001. All these viruses were not causing any severely diseased condition (4) but the first major outbreak of severe acute respiratory syndrome (SARS) caused by coronaviruses occurred in 2002-2003 emerged from

Southern China which caused about10% mortality among the infected individuals. This was followed by the spread of an infection in the middle-east region known as Middle-East respiratory syndrome (MERS), which emerged from Saudi Arabia which had a higher lethality of approximately 34% (5, 6).

In December 2019, several cases with symptoms similar to pneumonia emerged in Wuhan, China. Early genome-wide sequencing analysis in these patients revealed a new virus with unknown origins that were later termed SARS-CoV-2 due to its resemblance to coronaviruses and disease manifestation similar to human SARS and MERS. While a study (72,314 cases) by the Chinese Centers for Disease Control and Prevention showed that the majority of patients infected patients with COVID-19 (81%) had mild symptoms (7, 8) with about 2-5% fatality due to respiratory and multi-organ failure. However, the severity and mortality of this infection were dependent upon age, comorbidity, and particularly, immunity of the patients (6). The mildness of COVID-19 in children has been suggested to be due to differences in the immune responses in this age group (9). Measures to counter this disease have led to a global economic slowdown.

Understanding the immunity of individuals that manifest mild symptoms could be crucial to containing the human costs of this pandemic. Thus, this review will systematically present the critical features of the immunological profile of COVID-19 patients and propose target molecules and possible avenues for further research that may aid the prevention and treatment of this disease.

IMMUNE RESPONSES TOWARDS COVID-19

Some of the features of the immunological profile of COVID-19 patients are consistent with those seen in the previous SARS and MERS infections. Immune responses under innate and adaptive immunity are briefly described in this review for COVID-19.

INNATE IMMUNE RESPONSE

Innate immunity is rapid but does not have a memory and it is mediated by dendritic cells, NK cells, monocytes, macrophages, and neutrophils. For instance, higher total neutrophil count and reduced lymphocyte count are common features of all three syndromes (10). Endosomal and cytosolic pattern recognition receptors (PRRs) which are RIG-1 and TLRs (TLR 3,4,7 and 8) respectively recognize the ssRNA of the virus and activate the downstream cascade mediated by TRIF and MyD88 which finally lead to activation of transcription factors NF-kB and IRF3 that lead to the transcription of genes associated with proinflammatory cytokines (IL-6, TNFa), chemokines (MCP1, IP-10) and Type I interferons (IFN**α, β, γ**), together called "Cytokine storm". These PRRs are mainly expressed on innate immune cells like TLR7 is highly expressed on pDC and B cells whereas TLR8 is expressed in myeloid cells (11). Furthermore, a cytokine storm comprising of high levels of inflammatory cytokines is also observed in infected patients and is correlated with increased severity of the disease (12, 13). These immune responses can be used in addition to consistent rapid viral tests for differential diagnosis of COVID-19 patients and to assess the severity of the infection.

Neutrophils

An Increased neutrophil count is reported in severe cases and nonsurvivors. In addition to this extravasation and infiltration of neutrophils was also observed in the lung tissues of autopsies. Excessive neutrophils are the major contributor to lung injury mediated by oxidative burst, phagocytosis and the formation of Neutrophil NETs also called NETosis. Whether the NETosis contributes to the cytokine storm is yet to be explored (14). Monocytes and Macrophages- Reduced monocytes were observed in severe cases of COVID-19. There was extensive infiltration of monocytes revealed

in autopsies of COVID-19 patients. The mechanistic role of the macrophages in SARS-CoV-2 can be similar to SARS. The ORF8 of SARS activates autophagy through activation of inflammasome which leads to the inflammatory response. Inflammasome recruits the pro-caspase 1 which proteolytically cleaves and activates pro-IL1**β** and Pro-IL18 as well as initiates a particular kind of programmed cell death called pyroptosis (15).

NK Cells

NK cells also showed a remarkable reduction in count in severe COVID-19 patients. There are discrepancies regarding the functionality of NK cells. Recently NK cells were showed to have up-regulated NK group 2 member A (NKG2A) receptors, inhibitory to cytokine secretion by NKT cells, and cytotoxic function. Cytotoxic function reported being also impaired by elevated IL-6 and IL-10. By contrast, a high levels of NK cells were found in BALF of COVID-19 patients indicating the trafficking of NK cells in lungs (16).

Mast Cells

There are increasing evidence that asymptomatic and mild symptomatic COVID-19 patients after recovery exhibit conditions similar to multi-organ inflammatory syndrome-A (MIS-A) similar to mast cell activating syndrome. Therefore, mast cells can have some role in complications after recovery (17).

ADAPTIVE IMMUNE RESPONSE

The total cell count, $CD4^+$, and $CD8^+$ were found to be significantly reduced in COVID-19. Diao et al. suggested cytokine (TNF**α**, IL-6, and IL-10) mediated necrosis or apoptosis of T cells causes a decrease in number. The functional exhaustion of CD4 and CD8 cells was also reported indicated by increased expression of exhaustion markers Tim-3 and PD-1 on the cell surface. CD4 cells rapidly turn to Th1 cells and secrete GCSF associated with mortality due to COVID-19. CD8 cells of ICU patients have higher GM-CSF expression compared to healthy or Non-ICU patients (18).

HUMORAL IMMUNITY

B cell response starts at 7-10 days post-exposure and neutralizing antibodies formed in some but not all patients after 30 days past exposure. There is lymphopenia in which B cells were also reduced in number. The SARS-CoV-2 showed polyclonal response with receptor binding domain and spike protein-specific IgG class-switched from IgM. To a lesser extent, IgA was also reported. The little somatic hyper-mutation in antibodies against spike protein makes it a favourable candidate for vaccine (19).

Germinal Centre Response

The fate of effective antigen-specific neutralizing antibody secretion depends upon germinal center reaction in the secondary lymphoid organs. A recent study by Kaneko et al., observed the $Bcl6^+$ T follicular helper cells (Tfh cells), $Bcl6^+$ B cells, and $Bcl6^+$ T follicular regulatory cells (TFreg cells) are sparsed in secondary lymphoid organ, hence defective or absence of germinal center response in fatal COVID-19. Although it is unclear that GC response is impaired in survivors of COVID-19 that may lead to inefficient and short-lived antibody response (20). The durability of antibody response against SARS-CoV-2 and what titter of Abs prevent reinfection is yet to be known. The previous experience with SARS exhibit that T cells response lasts up to 6 years. In the case of SARS-CoV-2 Spike protein-specific antibodies, memory B cells and circulating Tfh cells have been found in recovered patients (21). SARS-CoV-2 generates the Abs response but Ab titer depends upon the severity of the disease and initial inoculum. IgG and IgM titres in asymptomatic cases are

much lower than the severe cases.

Cytokine storm triggered the plasmablast nonspecific expansion of B cells also evidenced by in vitro study (22) and a decrease in memory B cells differentiation. The pre-existing and nonspecific Abs against coronavirus may cause an immunopathological condition in SARSCov2 called Antibody-dependent enhancement (23).

IMMUNOPATHOGENESIS

Immune Cell Counts and Function

Initial immune studies on COVID-19 infection were focused on the analysis of immune cell count or percentages. COVID-19 infection leads to alteration in the levels of innate as well as adaptive immune cells. Consistent with other viral infection studies, a recent report showed that patients infected with COVID-19 had reduced numbers of circulating lymphocytes. Wang et al. reported that a decrease in lymphocyte number was observed in the majority of patients (72%) infected with COVID-19. Other than the number of total lymphocytes, patients also showed lower numbers of other immune cells such as CD4 T, CD8 T, B, and NK cells. Although, adaptive immunity mediated T and B lymphocytes have an advantage of memory formation capacity.

Similar immune cell impairment has been also reported previously in patients infected with MERS or SARS-CoV (24). Similarly, Cui et al. had shown the occurrence of lymphopenia (reduction in the number of lymphocytes in 84% of patients), and decrease in immune cells such as CD4 T (in 100% of patients), CD8 T (87%), B cells (76%), and NK (55%) in SARS patients. Interestingly, Wang et al. also observed that severe cases of COVID-19 were associated with a decreased level of these lymphocytes compared to mild cases (25, 26). However, the number of CD8 T cells found to be negatively associated with the clinically pro-inflammatory markers such as Erythrocyte Sedimentation Rate (ESR), C-reactive protein (CRP), and Interleukin-6 (IL-6). Based on these findings, a change in the number of immune cells, particularly CD8 T cells, could be a reliable predictor of disease progression and disease severity in COVID-19 patients (27).

Additionally, patients of COVID-19 had decreased percentages of NK, CD8 T cell secreting IFN-γ, and IL-2 compared to healthy controls. Consistent with these results, these patients also showed lower frequencies of CD107a+, CD8+, CD107a+ NK cells compared to healthy controls (28). Another recent report by Guang Chen and co-authors showed that patients infected with COVID-19 exhibited defective functionality of these lymphocytes in addition to lymphopenia (29). This study showed that the production of IFN-γ, one of the most important antiviral cytokines, by CD4 T cells was reduced in patients infected with COVID-19. This suppression of the immune function of CD4 T cells was particularly pronounced in severe cases compared to moderate cases (29).

IMMUNE CELL INFILTRATION AND EXHAUSTION

SARS-CoV-2 is transmitting through the respiratory route, the initial site of infection for the virus is the respiratory epithelium. However, after infecting the epithelium of the lung, the inflammation spills over to the circulation generating an immune response mediated by leukocytes and cellular mediators of innate immunity including macrophages, dendritic cells (DCs). The severity of lung injury due to this disease is directly correlated with infiltration of immune cells such as neutrophils and macrophages as revealed by autopsies (30, 31). Infiltration of inflammatory cells into the lungs may be induced by the excessive production of cytokines such as IFNs through Fas and Trail-death receptor pathways that result in apoptosis

of epithelial cells of respiratory surfaces (12). This damage results in leakage of cells and hypoxia which causes the Acute Respiratory Distress Syndrome (ARDS) seen in severely affected COVID-19 patients (12). While corticosteroids can mitigate the inflammatory effects and the accompanying infiltration of cells, early administration of corticosteroid therapy involves risks of aggravation in some patients (32). Alternatively, neutrophil extracellular traps (NETs) which facilitate migration and infiltration may be a potential target of intervention, and therapeutics such as colchicine and IL1β blockers that are used to treat known pathologies of NETs may be useful in the treatment of COVID-19 as well (31).

Moreover, it has been documented that T cells showed greater expression of inhibitory markers such as Tim3 and PD-1 (33). These inhibitory markers, which are features of exhaustion, were particularly higher in ICU patients. T cell exhaustion is a state of dysfunction which is seen in chronic infections. This suggests that T cells become dysfunctional in severe cases of COVID-19. The cause of immune exhaustion in ICU patients could be the continued exposure of SARS-CoV-2 antigens and the resultant increase in inflammatory responses by T cells via GM-CSF and IL-6 secretion. Moreover, IL-10 has also been causatively implicated in immune cell exhaustion (33). Hence, trials of anti-inflammatory drugs such as Remdesivir have proved reasonably successful for the treatment of COVID-19 (34, 35).

These studies and observational reports conclude that patients infected with COVID-19 exhibit altered immune cell profile and functional exhaustion. The severity of the infection may also be associated with early impairment inactivation and later immune exhaustion. Therefore, targeting of immune cells (CD8 T and NK) could slow disease progression and contribute to virus elimination in the early stage of the COVID-19 infection.

CYTOKINE STORM AND HYPER INFLAMMATION IN COVID-19

Cytokines play a key role in immunity as well as in the immunopathology of viral infections. A consistent feature of disease progression and mortality observed with COVID-19 infection was the association with enhanced levels of proinflammatory cytokines. Patients who had been admitted to the ICU and were subsequently discharged from the hospital after improvement in their condition showed decreased proinflammatory cytokine levels compared to those who succumbed to the infection. Moreover, severely ill patients had a higher concentration of pro-inflammatory cytokines (TNF-α, IL-1β, IL-6, and IL-8), and chemokine's in circulation compared to patients with the mild manifestation of symptoms (36).

Multiple studies have also reported that the IL-6 level can predict the severity of the disease. Consequently, a clinical trial using Tocilizumab drug (ChiCTR2000029765) to block the IL-6 receptor has been started to investigate the possibility of IL-6 as a viable target of intervention for COVID-19 patients that can mitigate the adverse effects of the infection (37). This drug is known to bind to both membrane-bound and soluble IL-6 receptors thereby leading to the inhibition of downstream signal transduction. The study by Zhang et al. 2020 reported that Tocilizumab had a better efficacy for the treatment of severely ill patients infected with COVID-19 (38). However, this study was conducted with a relatively small sample size and therefore, larger studies are required to validate this treatment. In brief differential immune and clinical parameters among severe vs. mild COVID-19 patients have been summarized in the Table 1 and the Figures 1 and 2.

COMORBIDITY AND COVID-19

The fate of COVID-19 majorly dependent on the comorbidity of patients. A recent report

Table 1. Immune and clinical parameter to differentiate Severe vs. Mild COVID-19 Infection

S. No.	Immune and clinical parameters to differentiate Severe Vs. Mild COVID-19 Infection	
	Immune and Clinical parameters	Severe COVID-19 patients compared to Mild
1	Neutrophil	↑
2	Lymphocyte and WBC	↓
3	Natural Killer Cell	↓
4	T Cell (CD4 and CD8)	↓
5	Cytokine Levels (IL-6,IL-8,TNF-α and IFN-γ)	↑
6	ALT,AST and Total Bilirubin	↑
7	D-Dimer and LDH	↑
8	Hemoglobin and Albumin	↓
9	Troponin, Myoglobin and Procalcitonin	↑

White Blood Cell (WBC), Interleukin 6 (IL-6), Interleukin 8 (IL-8), Interferon Gama (IFN-γ), Tumor Necrosis Factor Alpha (TNF-α), Alanine aminotransferase (ALT), Aspartate aminotransferase (AST), and Lactate Dehydrogenase (LDH).

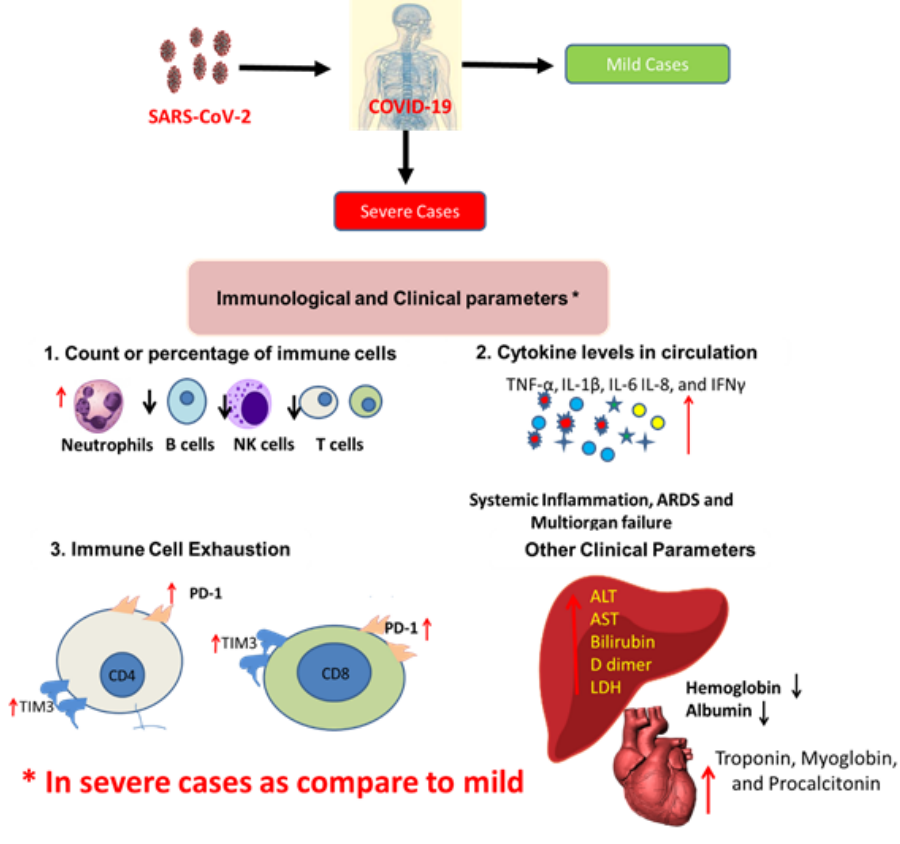

Figure 1. Immune and clinical representation of COVID-19 patients- Inflammatory and host immune marker in response to SARS-CoV-2 infection.

from China investigated the out of 1590 cases, 399 (25.1%) had at least one comorbidity. The commonness comorbidities are: hypertension (n=269, 16.9%), cardiovascular diseases (n=59, 3.7%), cerebrovascular diseases (n=30, 1.9%), diabetes (n=30, 8.2%), hepatitis B infections (n=28, 1.8%), COPD (n=24, 1.5%), chronic kidney diseases (n=21, 1.3%), malignancy

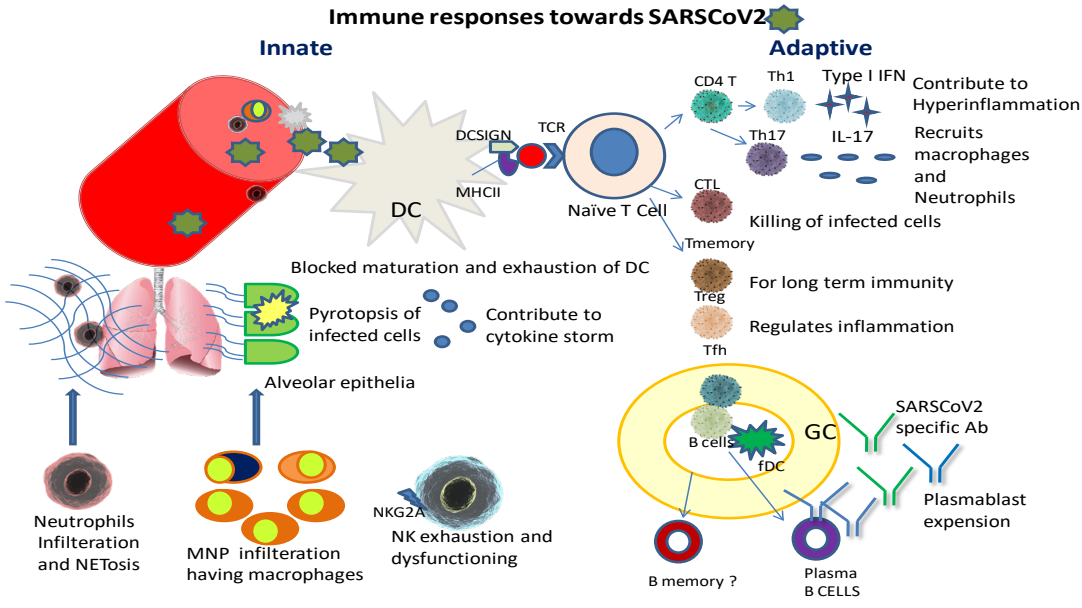

Figure 2. Innate and Adaptive immune responses in SARS-CoV-2 Infections:- A representative figure showed the immune responses mediated by innate and adaptive immunity in patients infected with SARS-CoV-2.

(n=18, 1.1%) and immunodeficiency (n=3, 0.2%). According to the observation of Wei-jie Guan et al at least one comorbidity was associated with severity of the disease. The majority of severe cases had previous history compared to non-severe cases (32.8% versus 10.3%). According to current knowledge, it has been well documented that the age of subjects also plays a key role in the outcome of the disease (39).

Another observational study by PengPengXu et al evaluated the risk factors associated with COVID-19 severity. In this investigation, authors had enrolled 703 patients of confirmed COVID-19 virus infection and they identified that numerous comorbidities, leukocytosis, lymphopenia, and higher CT severity scores on admission were associated with higher rates of in-hospital death, while adverse outcomes were associated with older age, multiple comorbidities, leukocytosis, lymphopenia, and higher CT severity scores (40).

IMMUNE COMPROMISED STATE AND COVID-19

The rate of co-infection and severity increases in immunocompromised patients because of impaired immune defences specifically in patients suffering from respiratory diseases. Analogous concerns occur about immunosuppressed patients infected with SARS-CoV-2. Future research should focus to delineate the attributable risk of immunosuppression and their association with disease severity (41).

Another well-established immunocompromised state is pregnancy. All existing indication suggests that pregnant women are at no larger risk of becoming severely ill than other healthy adults if they progress coronavirus disease. Recent studies also found that the utmost pregnant women admitted to hospital with SARS-CoV-2 infection were in the late second or third trimester, and they had good consequences, however, the transmission of SARS-CoV-2 to newborns was rare. Further larger studies are required to establish the fact of mother to baby vertical transmission of SARS-CoV2 (42).

IMMUNE ESCAPE OF COVID-19

There are various immune evasion

mechanisms adapted by CoVs like SARS-CoV-2 and MERS-CoV hide their PAMPs inside a double membrane vesicle from PRRs of innate immune response similar mechanism may be adopted by SARS-CoV-2. The SARS-CoV-2 may increase infectivity by IFN driven upregulation of ACE2 which is an ISG (43). Another study by Paces et al. reported that SARS-CoV-2 directly binds to the MHC class I molecules and downregulates in surface expression. SARS-CoV-2 also interferes with DCs maturation as well as the JAK/STAT pathway of IFN signaling. The nsp1 prevents phosphorylation and translocation of STAT1 to nucleus (44). The NLRP3 mediated inflammasome over activation is also reported in COVID-19 cases causes persistent viral release by pyroptosis and IFN levels (45).

The three new variants of COVID-19 came to existence from October 2020. Variant with high mutations B1.1.7 was first reported in UK, followed by variants like B1.351 was reported in South Africa and P.1 in Brazil. The key mutation D614G is present in all three variants which makes them more infectious than parent strain. In India the COVID-19 cases are again rising, currently active cases in India are 1.45 lakh, with 1.56 lakh deaths till date (1% of the total cases). Inspite it, The progress of vaccination is good in India as 14 million people has been vaccinated. All three variants have gained access in India.

THE COMPLEMENT SYSTEM AND ITS ASSOCIATED THROMBOSIS

Microvascular thrombosis has been indicated by elevation of D-Dimer, thrombocytopenia, Low fibrinogen levels, and prolonged prothrombin time. There are two theories about the thrombosis in COVID-19 (i) direct viral invasion in endothelial cells and (ii) Indirect complement-mediated activation. Apart from this the cytokine storm also leads to the proliferation of megakaryocytes promoting thrombosis (46). Host innate immune responses consist of a complement system which is the first response against certain pathogens and consists of serine proteases. This system works mainly by the generation of several pro-inflammatory mediators, enhancement of humoral and T cell-mediated immunity, opsonization, and formation of membrane attack complexes. However, hyperactivation of the complement system leads to inflammation, intravascular coagulation that can lead to multiple organ failure and death. This system is mediated basically via three pathways: the classical, the lectin, and the alternative pathway that leads to the formation of C3 convertase that leads to the formation of C3a and C3b. further C3b leads to the generation of C5 convertase that converts C5 into C5a and C5b. C5b along with other complement proteins leads to the formation of membrane attack complexes resulting in the influx of calcium ions leading to cell lysis. Skin and lung tissue of 5 patients with severe COVID-19 with respiratory failure and purpuric skin rashes were examined, which showed the Deposition of C5b-9, C4d, and (MASP)-2 in the microvasculature of lung tissue whereas deposition of C5b-9 and C4d was observed in the purpuric skin lesions samples. When two severe patients were treated with an anti-C5a monoclonal antibody, its suppressive activity was observed. Whereas activation of the classical complement pathway and deposition of the immune complex was also observed in COVID-19 erythrocytes (47). Several studies have shown that excessive coagulation occurs among COVID-19 patients resulting in increased thrombosis (48).

VACCINE AND COVID-19

The persistent destruction by COVID-19 globally has led many researchers to rapidly identify and develop a viable vaccine against the same. The predicted third wave of COVID-19 coinciding with the entry in the winter season can be critical during this

pandemic and therefore it is important to identify the suitable vaccine development to prevent the worsening of this disease.

The spike protein found on the surface of SARS-CoV-2 is used as the main target protein for the development of a vaccine against this virus. This protein is used by the virus for the attachment to the host cell receptors, allowing it to enter into the host cell. Therefore targeting it can lead to the blocking of the entry mechanism of the virus and can ultimately prevent the infection caused by it. As per the WHO update on 24th Feb 2021 in the document titled "COVID-19- Landscape of novel coronavirus candidate vaccine development worldwide", 63 and 173 vaccine candidates are in clinical and pre-clinical stages of development respectively. In India, 2 vaccines have been granted emergency approval till date, viz. Covishield (developed by University of Oxford/AstraZeneca and manufactured by M/s Serum Institute of India) and Covaxin (developed and manufactured by M/s Bharart BioTech). Among these 2 vaccines, beneficiaries in the state of Madhya Pradesh are being administered the Covishield vaccine.

Majority of the vaccine candidates employ the S (Spike) protein of the virus as the vaccine antigen and generation of neutralizing anti-S antibodies is considered to be the harbinger of protective immunity.

Though the published reports on phase 3 clinical trials of the 3 COVID-19 vaccines; viz. Moderna mRNA vaccine, Pfizer BioNTech mRNA vaccine and Oxford-AstraZeneca viral vector vaccine; have recorded vaccine efficacy of 94.1% (95% CI=89.3-96.8%), 95% (95% CI=90.3-97.6%), 70·4% (95% CI=54·8–80·6) respectively (49-52).

PROPHYLAXIS AND TREATMENT AGAINST COVID-19

Large numbers of randomized control trials are undergoing to determine the potential treatment against COVID-19. This includes certain monoclonal antibodies against cytokines, antiviral nucleotide analog.

Remedesvir is an antiviral drug that has been approved by the FDA on 22 October 2020 for treating COVID-19 positive patients of age 12 or more. The drug is given by intravenous infusion. Favipiravir and Lopinavir/ritonavir are certain other antiviral drugs used for COVID-19 patients. Dexamethasone is a common corticosteroid medication used to treat several autoimmune disorders, several randomized control trials have suggested its potential effects in treating COVID-19 patients especially those who required ventilator or needed extra oxygen.

Hydroxychloroquine and chloroquine are medications used against several autoimmune disorders. However, these are used along with the azithromycin in patients during the early outbreak of COVID-19 in China, and Europe. Several RCTs have been conducted to see the therapeutic effect of these drugs among the COVID-19 patients which resulted in several contradictory results. WHO solidarity, recovery did not found any significant benefit of HCQ in the treatment of COVID-19 and discontinued their HCQ arm (53).

The occurrence of cytokine storm is a common feature among COVID-19 patients. Cytokine storm is a hyper-activation of the immune system that creates pro-inflammatory conditions beyond control. It generally occurs by the secretion of IL-6 cytokine that triggers the immune response and activates different immune cells. Therefore several studies were conducted to see the effects of drugs that lead to blockage of IL-6. Tocilizumab and sarilumab are such drugs that also have shown conflicting results. Similar to these IL-6 inhibitors several kinase inhibitors are being also tested for COVID-19 that includes: acalabrutinib, baricitinib, ruxolitinib tofacitinib they act by blocking several cytokine signaling pathways and have shown to play role in dealing with cytokine storm. Certain trials are to see its effect among COVID-19 patients (54-57).

Plasma therapy is another treatment

therapy used in COVID-19. On March 24, 2020, this was issued by the FDA as an Emergency Investigational New Drug (eIND) application to treat people with COVID-19. In this therapy COVID-19 convalescent plasma (CCP) as it contains antibodies was donated from the recovered patients (58). However, this therapy has limitations and not applicable to all the COVID-19 patients.

CONCLUSION AND RECOMMENDATIONS

The impact of any epidemic viral infection may be determined by three factors: 1. the infectivity-virulence of the virus, 2. Immunity of host, and 3. the environment or geographical favourability of the virus. While the virulence and transmission of the virus are based on its innate nature and cannot be controlled and managing the environment comes with economic and social constraints, the best strategy to contain the damage caused by the virus would be to target the immunity of the host. However, this would require a clearer understanding of the immunological profiles of diseased individuals and the differential immune function in asymptomatic, mildly diseased, severely diseased, and fatal individuals. Identifying key differences in these profiles could help in narrowing down targets of intervention such as lymphocytes and cytokines. Hence, mechanistic studies of factors associated with a decline in lymphocyte counts, specifically T lymphocytes and NK cells, as well as the increase in cytokine levels in severely ill patients are required for the management of COVID-19 patients. Upcoming vaccines and therapeutics molecules could lead to a better understanding of the diseases and strategies for management of SARS-CoV-2 infection. Likewise, long-term potential studies are also essential to define the real likelihood of vertical transmission of this virus.

Conflicts of Interest: None declared.

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