## Review Article

# Update on Immunological aspects of COVID-19 Infection

**Nallasivan Subramanian**[1]

COVID-19 Pandemic has shaken the world since Jan 2020 and countries are struggling now with second wave peaking in eastern nations while vaccine drive is going on in the western world. Exposure to the SAR2 CoV causes multisystem disease and not limited to lungs and airways. After initial viral replication triggers the cytokine storm, the inflammatory cascade sets in and causes multiorgan disease, however lungs bore the brunt of the attack still. Patients develop a dysfunctional immune response with activated macrophages resulting in high levels of plasma cytokines including IL-6, TNF-$\alpha$, IL-8, IL-10 and IL-1RA and altered coagulation pathways. Though the 2 week period of viral infection may settle in most patients without much systemic upset, there are patients who have post covid sequelae and health consequences. Serum CRP, LDH, Ddimer and IL-6 levels have been found to be reasonable biomarkers in patients with COVID-19 infection and many studies have shown direct correlation with clinical profile. Further continued research on the immunological aspects will help elucidate the reasons for widespread disease in spite of efforts by WHO and all nations. Mutant strains, drug availability and the medical expenditure will be the foremost in managing this pandemic. This article gives a summary of immunological aspects of COVID-19 and current understanding of this viral infection.

[*J Indian Med Assoc* 2021; **119(11):** 44-7]

***Key words*** **: COVID-19, Cytokine storm, SARS Cov2, Mutant, Thrombosis, Lung injury.**

COVID-19 pandemic has shaken the World resulting in huge loss to the mankind in 2020 and now spreading fast as second wave although countries have been taking steps to control this pandemic. According to AIIMS (All India Institute of Medical Sciences) Chief on 1st April 2021, COVID second wave has started in India exactly like what UK experienced in Dec 2020 and has the propensity to affect adolescents." COVID Vaccination efforts have been ramped up with more sustained campaigning across the health sector, media and the public.

Exposure to the SAR2 CoV causes multisystem disease and not limited to lungs and airways. Currently patients manifest with fever, fatigue, diarrhea, vomiting, breathlessness and stroke. COVID-19 is spreading with mutant variants and vaccination is also being undertaken across the World. Postcovid, people suffer with multitude of symptoms including arthralgia, myalgia, deep vein thrombosis and breathlessness. In this article we report the concise information on immunological aspects of COVID-19 infection.

### Pathophysiology :

Once a patient becomes infected with SARS Cov2, adaptive immunity develops and serum IGA and IGM antibodies develop by 5 to 7 days and IgG by 10 days. Tcell activation results in specific CD4 cells and CD8 which stay in circulation.Grifoni et al have demonstrated that in patients recovering from COVID-19, specific memory CD4 T cells were seen in 100% and CD8 T cells in 70% of patients[1].

Once virus enters the humans through respiratory epithelium, viral contents are released inside the host cells, mRNA replication occurs and protease cleavage happens resulting in the release of cytokines. Structural and functional analysis showed that the spike for SARS-CoV-2 also bound to ACE2 which are abundant in lung, heart and kidney. Although severe COVID-19 is characterized by high-viral load and dysregulated immune system, antibody-dependent cytokines like- IL-4, IL-5, do not contribute to severity of acute infection. Understanding the important features of B cell and T cell mediated immunity play pivotal role in the management of this infection and

***Editor's Comment :***

- COVID-19 infection has mutant strains and vaccination strategies should focus on the immunological changes while producing the newer vaccines across the different countries.
- SARS-CoV-mediated disease is largely immune driven with complement activation resulting in SIRS- Systemic Inflammatory Response Syndrome and also thrombogenic vasculopathy.
- Social distancing and universal masks would help in reducing the transmission of this covid virus which may be still active over the next few years.

[1]MD, MRCP (UK), MRCP (CCT), Rheumatology, FRCP (Edin), Consultant Rheumatologist, Velammal Medical College Hospital and Research Institute, Madurai Shifa Hospitals, Tirunelveli 627009 and Corresponding Author

***Received on : 29/06/2021***
***Accepted on : 10/09/2021***

the ensuing inflammation[2].

The high level of anti–SARS-CoV-2 IgG and IgA titers to the spike protein correlates well in patients with CD4+ T-cell responses and the level of IgG1 and IgG3 Enzyme-Linked Immunosorbent Assay (ELISA) titres correlates well with viral neutralization[3].

### Immunological aspects :

SARS-CoV propagates within type II cells, large number of viral particles are released, and the cells undergo apoptosis and die. The end result is likely a self-replicating pulmonary toxin as the released viral particles infect type II cells (precursor for type I cells).

Monocytes/macrophages play a crucial role in anti-viral responses by linking innate and adaptive immunity. Peripheral activation and accumulation of activated pro-inflammatory monocytes/macrophages within lungs has become one hallmark of symptomatic SARS-CoV-2 infection.

In severe cases, fatality is due to severe lung injury characteristic of Acute Respiratory Distress Syndrome (ARDS). This pathology is characterized by intense, rapid stimulation of the immune response that triggers activation of the Nod-like receptor family, pyrin domain-containing 3 (NLRP3) inflammasome pathways and release of its products including the proinflammatory cytokines IL-6 and IL-1β[4].

### What is NLRP3 Pathway ?

The NLRP3 (NOD-, LRR-, and pyrin domain-containing protein 3) inflammasome consists of a sensor (NLRP3), an adaptor (ASC; also known as PYCARD), and an effector (caspase 1). NLRP3 contains an amino-terminal pyrin domain (PYD), a central NACHT domain (domain present in NAIP, CIITA, HET-E, and TP1) and a carboxy-terminal leucine-rich repeat domain (LRR domain). The NACHT domain mediates ATPase function that is vital for NLRP3 self-association and function and the LRR domains auto regulate through folding back onto the NACHT domain. ASC has two protein binding domains, an amino-terminal PYD and a carboxy-terminal caspase recruitment domain (CARD). NLRP3 can oligomerize between NACHT domains upon stimulation which leads to ASC recruitment through PYD–PYD interactions[5].

### Cytokine Storm :

In SARS-CoV-2 infection, a cytokine storm occurs resulting in elevated inflammatory biomarkers including C-reactive protein, D-dimer, and ferritin[6]. Patients experience altered immune response with activated macrophages resulting in high levels of cytokines including IL-6 and TNF-α[7]. Patients develop acute lung injury, acute respiratory distress syndrome, systemic inflammatory response syndrome (SIRS), Macrophage activation syndrome and coagulopathy[8]. Patients affected with SAR Cov2 who had biopsy studies showed infiltration in pulmonary capillaries by neutrophils and extravasation into the alveolar space[9]. Neutrophil Extracellular Traps (NETs) can be released. Although this is a way to ensnare pathogens, NET formation is linked to pulmonary diseases, particularly acute respiratory distress syndrome.

While eosinophils have protective effects in different viral infections, a significant amount of COVID-19 patients present with eosinopenia, although it is not reported in all cohorts. The pathophysiological mechanism of eosinopenia in COVID-19 patients may be related to increased apoptosis, and decreased eosinophil egression from the bone marrow[10].

### Complement and SARS-CoV-2 :

The complement system is involved in both coagulation and inflammatory pathways. Histologic and immunohistochemical analysis of lung and skin have been conducted in patients with COVID-19-induced ARDS. The specific lung findings for ARDS were accompanied with deposits of C5b-9 (membrane attack complex), C4d, and mannose binding lectin (MBL) - associated serine protease (MASP) 2, in the microvessels[11].

Skin biopsies showed a pauci-inflammatory thrombogenic vasculopathy, with deposition of complements C5b-9 and C4d. Severe COVID-19 patients develop catastrophic microvascular injury syndrome with complement activation and coagulopathy. Therefore SARS-CoV-mediated disease is largely immune driven with complement activation resulting in SIRS- Systemic Inflammatory Response Syndrome.

### Clinical Features :

The median incubation period from initial infection to symptom onset is 5 days with the majority (97.5%) developing symptoms within 11.5 days. Common symptoms of infection include fever (72%), Shortness of breath (71%), Cough (69%), Tiredness (46%), coughing up sputum (26%), Aching muscles or joints (21%), Headache (13%) and Sore throat (10%)[12] (Table 1). Other symptoms reported include loss of Taste (50%) and Smell (66%). Patients with mild disease recover in 7 days. In more severe cases, patients may continue to cough with malaise for 2 to 4 weeks. In severe infection, breathlessness becomes marked 7–10 days after symptom onset as the infection causes inflammation in the lungs that impairs oxygen exchange. Vascular involvement like deep vein

Table1 — *Showing manifestations of acute SARS Cov 2 infection*

| Clinical features | Percentage |
|---|---|
| Fever | 72% |
| Shortness of breath, cough | 70% |
| Fatigue | 46% |
| Loss of taste | 50% |
| Loss of smell | 66% |
| Myalgia | 21% |
| Headache and sorethroat | 13% |

thrombosis and mesenteric ischemia have been reported during the second week of infection. Those who were discharged may need home oxygen support while convalescing from lung injury.

## Systemic Manifestations following COVID-19 Infection :

While COVID-19 was initially considered a respiratory illness, it is now evident that inflammation and fibrosis shall affect multiple organs including lung, heart, kidneys, liver, and gastrointestinal tract and even cause stroke and vasculitis. The extent of disease partly reflects the distribution of the cellular receptor for SARS-CoV-2, Angiotensin-Converting Enzyme 2 (ACE-2), but also the indirect effects of inflammatory cytokines with complement activation leading to thrombotic complications, pulmonary embolism and stroke. Ningombom and colleagues have shown that countries with higher prevalence of exposed obese individuals (with higher ACE2 levels) experienced the highest number of mortalities[13].

## Long Term Health Issues of COVID-19 Infection :

Avila et all have reported that 31% of ICU patients with Covid 19 have developed thrombotic complications including acute cerebrovascular events, impaired consciousness and muscle injury. These complications were seen in patients with severe respiratory impairment, affecting up to 45% of such patients[14]. The cardiac manifestations included myocarditis, acute myocardial infarction, heart failure, dysrhythmias, and venous thrombosis. Few patients after recovery from severe infection present with features of chronic fatigue syndrome.

## Can Patients Get Reinfection ?

Patients who had contracted COVID-19 and treated, also have susceptibility to reinfection as the immune response is not sustained for long. Researchers have demonstrated a decline in IgG neutralizing antibodies to SARS-CoV-2 in convalescence, raising a possibility to repeat infection. Antibody levels always decline too after the acute illness, because most of the plasmablasts, the “effector” response of B cells, induced during the first week after infection are short-lived. A similar response is seen with the effector CD8+ T-cell response[15]. Patients are now manifesting with recurrent infection even though they were treated for COVID-19 and then got vaccinated.

## Mutant Strains :

Various strains of the novel corona virus have been spreading in different countries and according to WHO they have been labelled as per Greek letters. Alpha strain (B 1.1.7 – UK), Beta (B 1.351- South Africa), Gamma (P.1-US), Delta (B.1.617.2- India) have been named and two more- Epsilon and Iota have been identified in the United States. Scientists are wondering if the mass vaccination will help control this mutant virus of SARS Cov 2 across the world.

## Conclusions :

World is living on the edge with 18 months of human life curtailed by this pandemic with economical and social impact and 2021 will most likely be swamped by more aggressive disease. Further continued research on the immunological aspects will help elucidate the reasons for widespread disease in spite of efforts by WHO and all nations. Mutant strains, drug availability and the medical expenditure will be the foremost in managing this pandemic. The pandemic demands action on multiple strategies, from prevention to testing to treatment. Still lot of unknowns in this covid 19 infections and further research to develop virus neutralising antibodies may help to contain this pandemic to a reasonable extent.

**Conflict of interest :** None

**Funding :** None

## References

1 Grifoni A, Weiskopf D, Ramirez SI, Mateus J, Dan JM, Moderbacher CR, *et al* — Targets of T Cell Responses to SARS-CoV-2 Corona virus in Humans with COVID-19 Disease and Unexposed Individuals. *Cell* 2020 Jun 25; **181(7):** 1489-1501.e15. Doi: 10.1016/j.cell.2020.05.015.

2 Tang Y, Liu J, Zhang D, Xu Z, Ji J, Wen C — Cytokine Storm in COVID-19: The Current Evidence and Treatment Strategies. *Frontiers in Immunology* 2020; **11:** 1708. https://doi.org/10.3389/fimmu.2020.01708

3 Stephens DS, McElrath MJ — COVID-19 and the Path to Immunity. *JAMA* 2020; **324(13):** 1279-81. doi:10.1001/jama.2020.16656

4 Freeman TL, Swartz TH — Targeting the NLRP3 Inflammasome in Severe COVID-19. *Front Immunol* 2020; **11:** 1518. Doi: 10.3389/fimmu.2020.01518.

5 Swanson KV, Deng M, Ting JP — The NLRP3 inflammasome: molecular activation and regulation to therapeutics. Nature reviews. *Immunology* 2019; **19(8):** 477-89. https://doi.org/

10.1038/s41577-019-0165-0

6 Stringer D, Braude P, Myint PK, Evans L, Collins JT, Verduri A, *et al* — COPE Study Collaborators. The role of C-reactive protein as a prognostic marker in COVID-19. *Int J Epidemiol* 2021; **50(2):** 420-9. Doi: 10.1093/ije/dyab012.

7 Mehta P, McAuley DF, Brown M, Sanchez E, Tattersall RS, Manson JJ, *et al* — COVID-19: consider cytokine storm syndromes and immunosuppression. *Lancet* 2020; **395:**1033–1034. 10.1016/S0140-6736(20)30628-0.

8 Tufan A, Avanoðlu Güler A, Matucci-Cerinic M — COVID-19, immune system response, hyper inflammation and repurposing antirheumatic drugs. Turkish journal of medical sciences 2020; **50(SI-1):** 620-632. https://doi.org/10.3906/sag-2004-168

9 Batah SS, Fabro AT — Pulmonary pathology of ARDS in COVID-19: A pathological review for clinicians. *Respiratory medicine* 2021; **176:** 106239. https://doi.org/10.1016/j.rmed.2020.106239

10 Qilin Li, Xiuli Ding, Geqing Xia, Heng-Gui Chen, Fenghua Chen, Zhi Geng, *et al* — Eosinopenia and elevated C-reactive protein facilitate triage of COVID-19 patients in fever clinic: A retrospective case-control study. *E Clinical Medicine* 2020; **23:** 100375. Doi: 10.1016/j.eclinm.2020.100375

11 Cynthia M, Mulvey J, David B, Gerard N, Steven S, Harp, *et al* — Complement associated micro vascular injury and thrombosis in the pathogenesis of severe COVID-19 infection: A report of five cases. *Translational Research* 2020: 220. 10.1016/j.trsl.2020.04.007

12 Zhou F, Yu T, Du R — Clinical course and risk factors for mortality of adult in patients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet* 2020; **395:** 1054-62.

13 Ningombam SS, Kumar R, Tanwar P — Mutant strains of SARS-CoV-2 are more prone to infect obese patient: a review. *Wiener Klinische Wochenschrift* 2021; **133(7-8):** 383-92. DOI: 10.1007/s00508-021-01819-w.

14 Avila J, Long B, Holladay D, Gottlieb M — Thrombotic complications of COVID-19. *Am J Emerg Med* 2021; **39:** 213-218. Doi: 10.1016/j.ajem.2020.09.065. *Epub* 2020 Oct 1.

15 Stephens DS, McElrath MJ — COVID-19 and the Path to Immunity. *JAMA* 2020; **324(13):** 1279-81. doi:10.1001/jama.2020.16656.