EGYPTIAN ACADEMIC JOURNAL OF

BIOLOGICAL SCIENCES

PHYSIOLOGY & MOLECULARBIOLOGY

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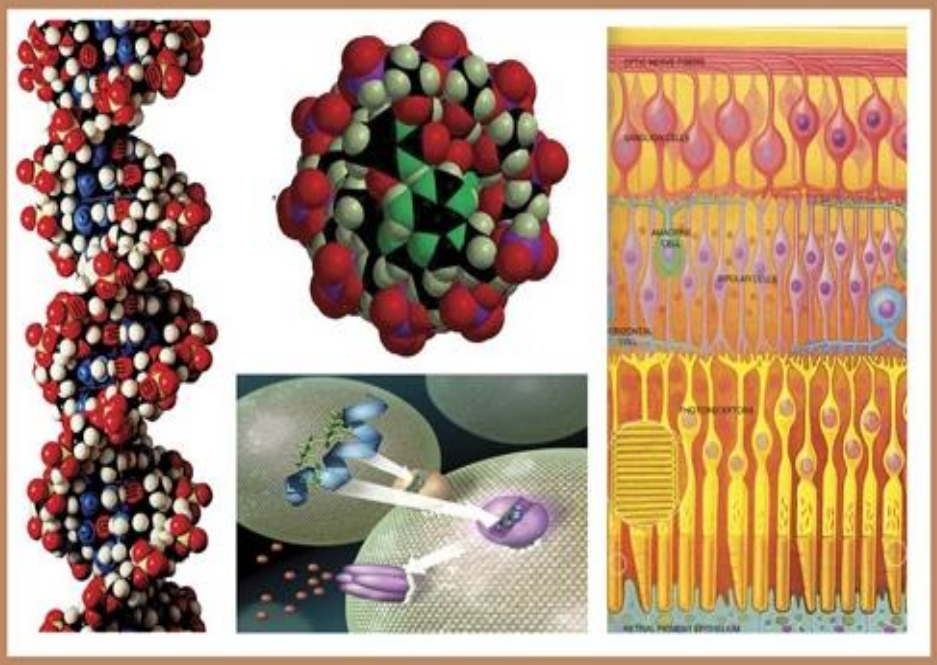


ISSN
2090-0767

WWW.EAJBS.EG.NET

Vol. 13 No. 1 (2021)

Citation: *Egypt.Acad.J.Biolog.Sci. (C.Physiology and Molecular biology) Vol. 13(1) pp133-147 (2021)*

DOI: 10.21608/EAJBSC.2021.173938

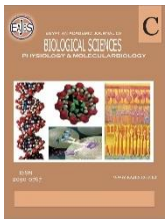
Egypt. Acad. J. Biolog. Sci., 13(1):133-147 (2021)

Egyptian Academic Journal of Biological Sciences

C. Physiology & Molecular Biology

ISSN 2090-0767

www.eajbsc.journals.ekb.eg



COVID-19: Variable Immune Response in Indian Population

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REVIEW INFO

Review History

Received:27/3/2021

Accepted:22/5/2021

Keywords:

COVID-19;

Immune response;

Genetic makeup;

Host gene polymorphism;

Mortality

ABSTRACT

With a year and a half into the COVID-19 pandemic, still, variance in terms of transmission and susceptibility of different populations/ethnicities to the disease remains an enigma. The clinical outcome of COVID-19 disease is poor in patients with associated morbidities; however, the reasons behind significant mortality of immuno-competent healthy individuals attributed to fulminant infection remains to be elucidated. Generally, protective B and T cell-mediated immune responses seem to have a tilted balance causing a sustained inflammatory state in SARS-CoV-2 infected individuals. The genetic makeup of an individual is highly likely to play a major role in elicitation as well as the outcome of the immune response in COVID-19 cases. The Indian response to COVID-19 indicates a potential influence of genetic background on host immune response pathways leading to decreased susceptibility and mortality to SARS-CoV-2 infection. Many host genes are involved in the entry and replication of SARS-CoV-2 and the subsequent host immune response. The current review discusses the potential cytokine gene polymorphisms prevalent in the Indian population that may influence the transmission, severity and mortality due to COVID-19 infection.

1. INTRODUCTION

In late 2019 or the beginning of the year 2020, a novel virus was discovered later named SARS-CoV-2. The disease caused by this 2019 novel coronavirus (2019-nCoV) was termed as COVID-19 disease and a pandemic was declared on 11 March 2020 (Wiersinga *et al.*, 2020). There has been the dramatic spread of the virus across the globe owing to droplet/airborne transmission, international travel, high R_0 and has significantly affected public health and economies worldwide.

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DOI: 10.21608/EAJBSC.2021.173938

The cause of the rapid spread of the virus in the community is likely the viral shedding from asymptomatic or pre-symptomatic individuals; COVID-19 illness can present with varied clinical presentation ranging from asymptomatic carriers to mild to moderate illness to severe respiratory illness, initially thought to be a respiratory virus. Further, as the pandemic progressed, it was observed that it can involve other systems like neurological, cardiovascular etc leading to significant morbidity and mortality and. immune-mediated mechanisms responsible for mortality in COVID-19 pneumonia (Mao *et al.,* 2020).

The disease had led to unprecedented fatal outcomes in the western world; South Asian countries namely India, Afghanistan, Pakistan, Bhutan, Maldives, Bangladesh, Sri Lanka and Nepal were expected to be worst hit by the pandemic owing to dense population and low resource settings but strangely India reported lesser mortality compared to worldwide mortality (Jain *et al.*, 2020). There could be various reasons for a better outcome in this part of the world the most important being immune sensitization of populations by various vaccine drives of which most important being BCG vaccines. The majority of the population in South Asian countries has been exposed to BCG vaccine for over half a century and the immunity elicited by BCG vaccine is making people more resistant to COVID-19 morbidity and mortality than in the western world (A.R. Sharma 2020). The hygiene hypothesis may hold special mention due to early exposure to numerous infections, Indian population has well developed immune regulatory system that might have negated severe illness due to COVID-19 (Sehrawat S 2020). Going back to the classical epidemiological triad which states that disease course depends on agent, host and environmental factors, so the genetic background in various populations might be responsible for variable susceptibility to disease and its outcome. We hypothesize the role of prevailing cytokine polymorphism in Indian population as the reason for lower mortality rates due to COVID-19 in this review.

1.1. COVID-19 Disease: Virology, Pathogenesis:

SARS-CoV-2 belongs to alpha coronaviruses; these are enveloped, positive-sense, single-stranded RNA viruses; disease in human beings is mainly transmitting through infecting peridomestic animals, which serve as intermediate hosts. The droplet transmission is the main mode of transmission, the later airborne route was also confirmed and the virus is known to exist on the surface for 72 hours (Wiersinga et al., 2020). The structural proteins are encoded by the four structural genes, including spike (S), envelope (E), membrane (M) and nucleocapsid (N) genes. The S2 subunit of the spike protein of SARS-CoV-2 is highly conserved; SARS-CoV-2 uses ACE2 (angiotensin-converting enzyme 2) cell receptor for entry into the host cell with enhanced binding affinity for ACE2 (Hoffmann M 2020). Transmembrane protease serine 2 (TMPRSS2), an essential serine protease is required for spike glycoprotein priming after binding to ACE2. Following the binding, the S protein binds to the cellular receptor ACE2. Conformation change in S protein facilitates fusion of viral envelope with the cell membrane through the endosomal pathway via clathrin-dependent endocytosis (Hoffmann M 2020). SARS-CoV-2 releases RNA into the host cell and is translated into viral polyproteins. The polymerase produces subgenomic mRNAs and is translated into relevant viral proteins. Viral proteins and genome RNA are subsequently assembled into virions in the endoplasmic reticulum and golgi, transported via vesicles and finally released out of the cell. After endocytosis of the viral complex, surface ACE2 is

down-regulated, resulting in unopposed angiotensin II accumulation. Local activation of the renin–angiotensin–aldosterone system may mediate lung injury (Vaduganathan M 2020).

Expression of the ACE2 receptor is found in pulmonary and extrapulmonary tissues including heart, kidney, endothelium and intestine resulting in a plethora of clinical symptoms ranging from asymptomatic presentation to mild flu-like symptoms like fever, sore throat, dry cough, body aches, malaise, diarrhea, conjunctivitis; atypical symptoms like olfactory and gustatory dysfunction or more severe and critical conditions manifesting like myocarditis, myocardial infarction, cerebrovascular complications, acute kidney injury, thrombo-embolic episodes, etc ultimately culminating into multiple organ dysfunction (MODS) (Wiersinga et al., 2020). These complications are more commonly seen in the elderly population and patients with comorbidities like diabetes mellitus, hypertension, chronic lung, kidney, liver, or cardiac diseases, immunosuppressed patients like transplant recipients, malignancies etc.

1.2. Immune Response to SARS-CoV-2 Infection:

Following entry of virus via nasal-oral route, viral antigens are recognized by pathogen recognition receptors (PRR) mainly Toll-like receptors 3,7,8 (TLRs) and presented in complex with MHC class I molecules to T cells leading to activation of helper $CD4^+$ T cells and cytotoxic $CD8^+$ T cells (Shah *et al.,* 2020). Helper T cells, in turn, activated B cell responses. A well-coordinated network of the immune system, in turn, leads to the secretion of pro-inflammatory cytokines mainly IFN-γ, TNF-α and IL-6, production of neutralizing antibodies and cytotoxic T cells helps to clear the virus. The initial release of cytokines and chemokines leads to non-specific activation of mononuclear macrophages that further release excessive pro-inflammatory cytokines in response resulting in a state called hypercytokinemia (also known as cytokine storm). The excessive synthesis of cytokines stimulates the massive proliferation of monocyte-macrophages and induces apoptosis of lymphocytes (Badawi 2020). Indeed, the early stages of COVID-19 are characterized by lymphopenia; lymphocytes progressively decline further during the course of illness.

The pro-inflammatory cytokines drive the recruitment of immune cells including monocytes-macrophages, lymphocytes, and neutrophils at the site of infection, induce pulmonary and vascular injury in lungs and other tissues leading to extensive inflammatory reactions, vascular injury, necrosis, thrombosis, hyaline membrane formation. This immune-mediated damage due to hypercytokinemia may culminate into fatal outcomes characterized as ARDS, coagulopathy and multiorgan damage (Badawi 2020; Xu *et al.,* 2020). Simultaneously natural regulatory T cell (nTreg) and induced regulatory T cell (iTreg) are directed to infected tissues and via secretion of IL-10 and TGF-β inhibit excessive inflammation and repair the tissue. This cytokine milieu decides the outcome of infected patients. The studies have shown that T cells are over-activated and regulatory T cells are down-regulated in COVID-19 patients resulting in cytokine storm leading to immune mediated injury and severe disease; further the period of excessive T cell activation may cause T cell exhaustion and lymphopenia which would result in delayed virus eradication and poor outcomes (Qin *et al.,* 2020).

2. Indian Scenario:

India is a densely populated country with a majority of the population living in a close niche owing to limited resources and cultural beliefs and with a high burden of non-communicable diseases like diabetes mellitus etc. With limited health care infrastructure, it was expected at the beginning of the pandemic

that India will have a very high mortality rate. The first case in India was detected on January 30, a student who returned from Wuhan, the birthplace of SARS-CoV-2, later on, more cases were detected. At the end of March 2020, the nationwide lockdown was imposed which led to a delayed peak of COVID-19 in India but slowly whole country came under the effect of the pandemic. As per the latest WHO COVID-19 data on 29th May 2021, more than 27 million cases are reported from India, while the USA has more than 32 million cases and Brazil has more than 16 million cases (Table 1). The feature to be noted is that India has witnessed only 318,895 cumulative deaths which are 1.16% cumulative deaths of COVID-19 cases; this figure is less compared to Brazil (2.79%) and USA (1.79%), absolute numbers being 454,429 for Brazil and 586,890 for USA. Other less populous countries have also reported higher death percentages due to COVID-19 compared to India (WHO 2020). During the early stages of the pandemic, the Indian government came out with the policy of isolating all positive confirmed cases into healthcare facilities with the primary aim to contain the spread of the pandemic and clinically monitor all patients. Subsequently, as the pandemic progressed, it was observed that the majority of the infected population was asymptomatic or have an only mild illness, mortality rates were low so with increasing burden coming on health infrastructure, the policy was changed and home isolation policy was adopted where asymptomatic or mild cases were put in-home quarantine (Ministry of Health & Family Welfare 2020).

Table 1: COVID-19 situation by WHO Region/Country. Confirmed cases including deaths as of 29 May 2021 reported to WHO of some topmost countries [Source: COVID Intel Database (WHO)].

Name	WHO Region	COVID-19 cases (cumulative total)	COVID-19 related deaths (cumulative total)	Deaths per million of COVID-19 cases	Percentage of deaths
Global		168,599,045	3,507,477	20803.66	2.08
United States of America	Americas	32,869,009	586,890	17855.42	1.79
India	**South-East Asia**	**27,555,457**	**318,895**	**11572.84**	**1.16**
Brazil	Americas	16,274,695	454,429	27922.43	2.79
France	Europe	5,535,701	108,354	19573.67	1.96
Russian Federation	Europe	5,044,459	120,406	23868.96	2.39
The United Kingdom	Europe	4,473,681	127,758	28557.69	2.86
Italy	Europe	4,205,970	125,793	29908.20	2.99
Germany	Europe	3,669,870	88,187	24030.01	2.40
Spain	Europe	3,663,176	79,888	21808.40	2.18

During the period of the year into a pandemic, studies have shown genetic variability in various factors which may result in differential epidemiology of disease across the globe or differential clinical presentations or outcomes. These include polymorphism in ACE2 receptor, genetic variability across three HLA molecules (HLA B* 46:01 variant vulnerable to SARS-CoV-2 infection while HLA B* 15:03 variant as protective), locus 3p31.21 being associated to the disease susceptibility gene cluster on ABO group with O blood group conferring protection (Severe Covid *et al.,* 2020). Recently one author has hypothesized the genetic variability exacerbating NET formation resulting in exaggerated

inflammatory response and coagulopathy (Thierry 2020).Any imbalance between the protective immune response and immune dysregulation determines the final outcome of the disease (Fig. 1), so what is favoring the Indian population towards a better outcome; is the Indian population harboring any protective immune response needs to be elicited. In the upcoming era of precision medicine, it becomes important to study immunogenetics at individual levels to determine the treatment of disease.

Therefore, understanding the dynamics of immune response in patients with different outcomes of the disease may provide the immunological blueprint of protective immunity against COVID-19. Although there is little evidence available on the characteristics of humoral immune response to SARS-CoV-2, the crucial role of antibodies in conferring protection is slowly emerging. Though recent data on healthy blood donors and mild cases of COVID-19 suggested that 70% of the Indian population have strong traits of durable immune memory (Ansari *et al.*, 2020).

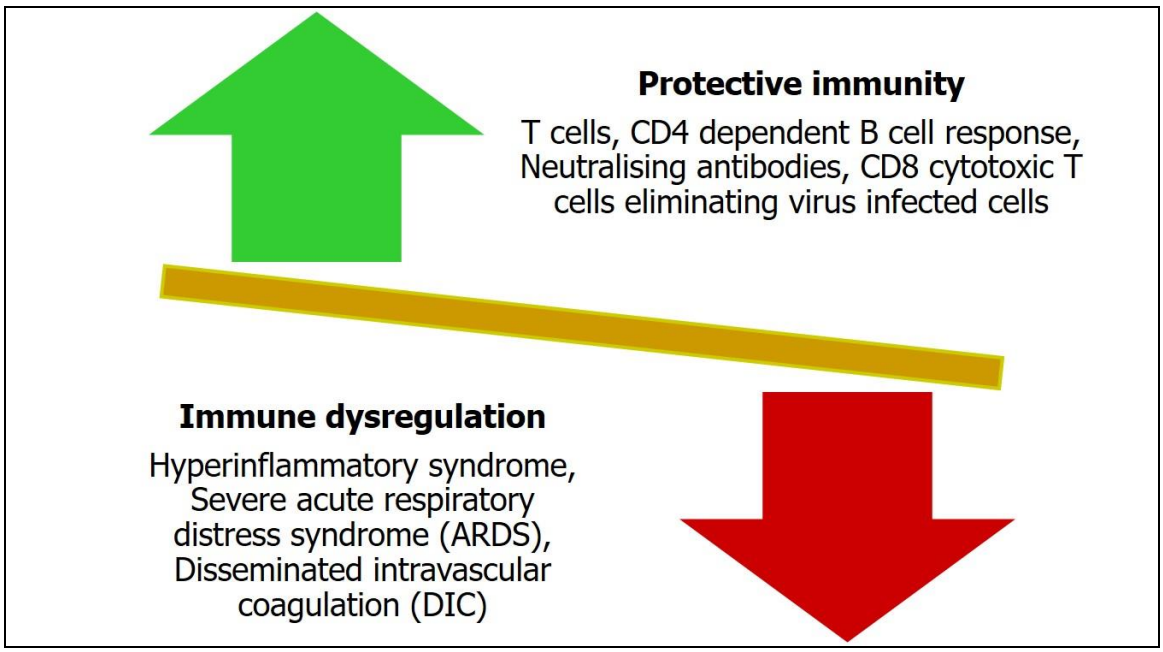

Fig. 1: COVID-19 Protective immunity and inflammatory spectra.

Since viruses are host-dependent, they co-evolve with the hosts and devise many strategies to evade the host immune response. The spike (S) glycoprotein of SARS-CoV-2 has a strong affinity for ACE-2 host receptor. The Receptor binding domain (RBD) is variable and differs between SARS-CoV-2 and SARS-CoV, but remains an appropriate target for a vaccine, alongside S protein (Chiu and Openshaw 2015; Figgett *et al.*, 2013; Smulski and Eibel 2018). Antibodies against S protein may play a crucial role in controlling the virus dissemination by inhibiting its interaction with ACE-2 receptor on host cells, however, it is too early to speculate that whether the antibodies formed during SARS-CoV-2 infection have a long-lasting immunity or if non-neutralizing in nature, the antibodies can prove to be detrimental during reinfections, facilitating antibody-dependent enhancement (Chiu and Openshaw 2015; Figgett et al., 2013; Hotez *et al.*, 2020; Jartti *et al.*, 2005).

There are similarities between fatal SARS-CoV and H5N1 influenza virus infections with associated lung infiltration by macrophages (Gu and Korteweg 2007; Ng *et al.*, 2006; van den

Brand *et al.,* 2014). However, the observed virus clearance from the lungs of SARS or fatal H5N1 infection patients at the time of death raises doubts regarding mortality due to the virus in the lungs (Channappanavar and Perlman 2017; Hendrickson and Matthay 2013; Korteweg and Gu 2008). SARS-CoV-2 did not show widespread infection amongst children nor many fatalities were reported (Zimmermann and Curtis 2020). Unlike other infections, the transmission to children in the Indian population has shown a dramatic resistance in acquiring SARS-CoV-2. On comparison of immune phenotypes, a study by Rathore et al. observed a significantly high number of monocytes, NK cells, $CD4^+$ T cells, naïve B cells and memory $CD4^+$ T cells prominent amongst Indian infants as compared to infants born in US (Rathore *et al.,* 2018).

2.1. Role of Cytokine Gene Polymorphisms in Disease Susceptibility and Severity:

Considering that India has a diverse ethnicity and is endemic to several parasitic and viral infections, it is difficult to unequivocally establish the role of T and B cells in defense against SARS-COV-2. A team of researchers observed better survival capacity amongst Indians, probably possessing unique KIR (killer cell immunoglobulin-like receptors) genes as a result of natural selection to survive the environmental challenges (2008; Mukherjee *et al.,* 2009; Rajalingam *et al.,* 2008). Furthermore, childhood immunization and exposure to diverse microbes challenge the immune system and evolve various mechanisms to defend against the pathogens. The haplotype HLA variability can occur under stress as a compensatory mechanism during infection and determines the eventual outcome of a disease. On the other hand, immune-related genes for cytokines are polymorphic and the cytokine gene expression and disease manifestation may vary in different ethnic populations. Cytokines have a key role to play not only in the defense against pathogens but their genes are the candidates for host susceptibility to the onset of an active disease too (Wu *et al.,* 2019). It is evident from previous studies that cytokine production may vary during disease progression which is strictly under genetic control. Several polymorphisms of promoter and coding regions of cytokines influence not only their production and risk of disease but also disturbs the balance between pro-inflammatory and anti-inflammatory cytokines production (Jarduli *et al.,* 2013). Hence, the genetic background of an individual may influence the onset and progression of the disease and the cytokine release storm (CRS), leading to critical illness and fatal outcome is the hallmark of severe COVID-19 infection.

There is evidence that high IL-2, IFN-γ, granulocyte colony-stimulating factor (G-CSF), IL-17, monocyte chemo-attractant protein (MCP)-1,TNF-α, macrophage inflammatory protein (MIP)-1 alpha and IL-6 production after viral infection have been found to be associated with poor outcomes (Tisoncik *et al.,* 2012). The IL-1β secreted by endothelial cells through the nucleotide-binding domain of (NOD)-like receptor protein 3 (NLRP3), inflammasome mechanisms contribute to flu-induced inflammation in lung cells observed after H1N1 infection. This implies that with a polymorphism in IL-1β promoter, T to C transition at position -31 (rs16944), can result in high IL-1β production inducing significantly higher lung damage after influenza A virus infection (Chan *et al.,* 2020). Evidently, influenza viruses take advantage of single nucleotide polymorphism (SNP)-driven variations in host cytokines that alter the transcriptional activity of their genes. Additionally, rs2275913 SNP of the IL-17 gene leading to altered IL-17 expression is related to the increased severity of acute bronchiolitis severity (El-Omar *et al.,* 2000; Griffiths *et al.,* 2015; Kim *et al.,*

2015; Pinto *et al.,* 2017).

One of the most important responses to viral respiratory infections in airway cells is interferon secretion and the gene IL-28 is shown to play an important role in augmenting cytotoxic $CD8^+$ T cells thus affecting the disease outcome (Daneshvar *et al.,* 2016). The contribution of SNP polymorphisms located at rs8099917 site near the IL-28b gene; of type III interferon in spontaneous clearance and sustained virological response to IFN-α and ribavirin treatment in hepatitis C virus (HCV) patients is exhibited as a unique anti-inflammatory property of IFN-λ (Rauch *et al.,* 2010; Shaker and Sadik 2012).

Meanwhile, the function of other anti-inflammatory cytokines cannot be underestimated. IL-10 regulates and suppresses the expression of pro-inflammatory cytokines by macrophages to limit the damage caused by viral and bacterial infections (Rojas *et al.,* 2017). The frequency of certain IL-10 SNPs renders Mexican patients susceptible to severe disease, while other SNPs seem protective in nature (Martinez-Ocana *et al.,* 2013). The rs1800872 polymorphism, located at the 5′-flanking regions of IL-10 promoter controlling the transcription and expression of IL-10, is related to increased intensity of autoimmune and infectious diseases (Zhang *et al.,* 2012; Zhao *et al.,* 2017). It has been shown that rs1800872 SNP enhanced resistance to severe RSV infection and IL-10 balance could reduce the harmful effects of the immune system (Schuurhof *et al.,* 2011; Yu *et al.,* 2017). Therefore, evaluation of these polymorphisms in relation to SARS-CoV-2 may be useful in identifying and distinguishing the degree of immune reactivity in different populations across the globe as studied earlier in the case of influenza.

High serum levels of pro-inflammatory cytokines (IFN-γ, IL-1, IL-6, IL-12, TGF-β) and chemokines (CCL2, CXCL-10, CXCL-9, IL-8) were found in SARS patients with severe disease compared to individuals with uncomplicated SARS. Conversely, SARS patients with severe disease had very low levels of anti-inflammatory cytokines and chemokines. Early studies have shown that IL-1β, IL-10, IL-17 and IL-28 gene polymorphisms are associated with the inflammatory process affecting the outcome of influenza virus A/H3N2 infection (Keshavarz *et al.,* 2019; Rogo *et al.,* 2016). It was observed that in a dominant mode, IL-10 rs1800896 G allele was significantly negatively associated with disease severity during H1N1 pandemic (Choudhary *et al.,* 2018). Hence, there is enough evidence to speculate a varied response of cytokine gene polymorphism in COVID-19 patients of different ethnicities.

2.2. Cytokine Gene Polymorphisms Underpinning Indian COVID-19 Response?

Till now no study has reported on the role of host gene polymorphism and the impact of defense on SARS-CoV-2. Polymorphisms (SNPs) in the TNF-α, IFN-γ, IL-10, and CCL2 have been shown to be associated with variations in the levels of the respective cytokines. An overview of genome data on the Indian population shows a significant allele and genotype distribution in IL-10 -819 C/T and -592 C/A and IFN-γ +874 A/T gene polymorphisms leading to dermatological manifestations in Indian subjects. The resultant haplotypes were responsible for high IL-10 and low IFN-γ production in the Indian population (Jain *et al.,* 2017).

Our previous cytokine polymorphism study showed higher IL-10 -1082 AG and lower AA genotype with decreased A allele frequency; higher IL-10 -819 CC and lower TT genotype frequency with decreased T allele frequency; and lower IL-10 -592 AC genotype frequency in healthy subjects in North India (Dar *et al.,* 2016). The most frequent haplotype detected was GCC (-1082G, -819C, and -592C) in these healthy individuals

depicting an ability of higher IL-10 secretion. IL-10 promoter -1082G allele or GCC haplotype is associated with increased IL-10 production, while ATA and ACC haplotypes are generally assumed to be a responder for low IL-10. Considering the immunosuppressive role of IL-10, we suggest that the high carriage of high producer GCC rather than low producers ATA and ACC haplotypes by the Indian population most likely have a role in protection against COVID-19. It will be interesting to understand that high IL-10 manifested in the Indian population may be a reason for the mild manifestation of SARS-CoV-2 amongst Indians.

Conversely, a decreased IFN-γ +874 AT genotype frequency in the same healthy Indian population pointed towards lower IFN-γ production during subsequent antigen exposure (Dar et al., 2016). Further, antigen-promoted high IL-10 production exerts an immune regulatory effect by suppressing IFN-γ production. IL-10 is known to affect B cell survival, proliferation, differentiation and immunoglobulin production. In addition to IFN-γ, IL-10 also inhibits IL-2 secretion by Th1 cells (de Moreno de Leblanc *et al.*, 2011), thereby, decreasing T cell-mediated immunity but augmenting humoral immunity. Effects of IL-10 on antigen uptake by dendritic cells, increasing expression of TLRs, and stimulating NK cell cytotoxicity to suggest its importance in limiting inflammation, executing control over the regulation of immune reactions and supporting immunoglobulin production by B cells. This probably explains the manifestation of mild infection with rapid recovery amongst Indian patients. Hence, large-scale epidemiological data would be beneficial to study SARS-COV-2 infection in Indian adults.

The cytokines are expressed de novo in response to pathogens and a gene polymorphism may affect transcriptional regulation and severity of the disease. Inhibition of IFN-γ by high IL-10 production delays the clearance of intracellular bacteria. Genomics and SNP database suggest that Indian population homozygous (AA) for IFN-γ +874 have a low production of IFN-γ in comparison to AT/TT genotypes carriers as evident in mycobacterial tuberculosis. The T allele correlates with high IFN-γ expression. The homozygous TT genotype is associated with the ability to produce high levels of IFN-γ, the heterozygous TA genotype with intermediate levels, and the homozygous AA genotype with lower levels (López-Maderuelo *et al.,* 2003). A significant percentage of the Indian population carrying the lower IFN-γ producing genotype (Dar et al., 2016), may provide an advantage for not producing exaggerated immune response during mild to moderate infection. The lower IFN-γ production further cause's poor macrophage activation and slow disease progression. Early inhibition of IFN-β may prove beneficial in reducing inflammation and T cell apoptosis. So, we may hypothesize that polymorphisms of IL-10 and IFN-γ contribute to control over disease progression and early resolution of symptoms in COVID-19 in the Indian population.

Recently, Th17 cells became the center of extensive research and its hallmark cytokine IL-17 dysregulation has contributed to the progression of cancer, inflammatory disease, autoimmune disorder, and clearance of viral or microbial pathogens (Long *et al.,* 2015; Lukacs *et al.,* 2010; Mukherjee *et al.,* 2011). In viral diseases, the presence of the G allele in IL-17 rs2275913 SNP increases the risk of influenza A (H1N1) infection. In contrast, these variations may also regulate immune response and provide protection against severe infection. Early data suggest that patients carrying allele 'A' of IL-17 rs2275913 SNP lack the ability to control their inflammatory response resulting in ineffective immune T cells response against influenza virus infection.

Furthermore, H1N1 pandemic influenza virus-induced Th17-secreted IL-17 resulting in mild and severe disease shows that flu viruses actually benefitted from IL-17 SNPs in developing infection and lung injury. Briefly, IL-10 rs1800872 and IL-28; rs8099917 SNPs are not associated with the risk of infection (Echeverria *et al.*, 2018; Peresi *et al.*, 2013).

Meanwhile, IL-28, a member of the IFN-γ family has IL-10 like antiviral properties and induces survival signaling in host cells. An early study showed significantly higher rates of seroconversion after influenza vaccination of transplant patients harboring minor-alleles in the IL-28b gene (rs8099917; TG or GG) (Egli *et al.,* 2014; Linnik and Egli 2016). TG or GG, minor-allele genotypes of IL-28b seem strongly associated with the immune suppressive property and host protection when compared with the major-allele TT with severe influenza infections. However, few studies have also shown that IL-28 rs8099917 SNP is associated with flu A (H3N2) and HCV infections in Iranian and Italian patients, respectively (Keshavarz et al., 2019; Rogo et al., 2016; Sticchi *et al.,* 2013). In HCV patients achieving sustained virologic response (SVR), 63% had protective TT genotype of IL-28b gene polymorphism while 37% carried TG/GG genotypes (Egli et al., 2014; Mi *et al.,* 2014). Hence, the involvement of IL-28b polymorphism in the Indian population has to be defined for their protective role in COVID-19 patients.

2.3. Heterologous Immunity:

There is a wide spectrum of clinical disease and the varied immune response is a consequence of multiple factors which include the host genetics, epidemiological variables, duration of viral exposure and other co-morbidities. Due to the diverse microbial community, cross-reactive memory T cell population to various recall antigens provides an additional advantage in minimizing the severity of infections amongst the Indian population. It is well described that the high rate of viral mutation makes the conventional B-cell-based vaccines against RNA respiratory viruses virtually impossible; but T-cell epitopes shown to be cross-reactive in RV may prove to be useful (Selin *et al.,* 2004). However, the use of T-cell-based vaccines may paradoxically enhance disease pathology (Panagioti *et al.,* 2018). Alternatively, the use of anti-inflammatory drugs or blocking or depleting of cytokines (TNF, IL-4, IL-13 and IL-12) and chemokines including CCL11 (eotaxin), CCL5 (RANTES), or the receptor CCR1 ICOS and OX40L (Stegelmeier *et al.,* 2019); are effective in reducing disease burden though should be used with caution.

The general aspects of immune-mediated pathogenesis in COVID-19 have been enumerated well. Nevertheless, multiple pieces of evidence suggest that a host genotype database can generate useful predictions of a disease progression in a particular population. Furthermore, it may also assist in predicting the response to the treatment and outcome of an infectious disease. Antiviral host-miRNAs may likely control the viral pathogenesis as a part of host responses to viral infection. A recent study revealed that nine host miRNAs that can potentially target SARS-CoV-2 genes, do not have targets in SARS and MERS genomes. Hence, human microRNA-27b (hsa-miR-27b) is the only unique miRNA that has a target gene in the Indian SARS-CoV-2 genome (Liang *et al.,* 2018; Rahila Sardar 2020). As observed earlier in *M. tuberculosis* infection, miRNAs play an important role in regulating host anti-mycobacterial defense through an inflammatory response. MicroRNA-27b mediated by the TLR-2/ MyD88/ NF-kB signaling pathway suppresses the production of pro-inflammatory factors (IL-1β, IL-6, TNF-α, iNOS), prevents excessive inflammation during *M. tuberculosis* infection (Liang et al., 2018). The study revealed a novel role of the miR-27b in the regulation of inflammatory response, worth exploring in

COVID-19 cases for a potential molecular host defense mechanism.

Environmental and socio-economic factors such as tropical humidity, overcrowding, and close contacts of infected household members constitute well-known risks. Despite several reasons for an impending rise in the number of cases, the fatalities have been proportionately low. Considering the genetic composition and non-synonymous cytokine polymorphisms, a certain link between SARS-CoV-2 severity, clinical spectrum and outcome of the disease defines a distinct predisposition amongst the Indian population. To know the extent of morbidity and mortality associated with SARS-CoV-2, it is important to investigate cytokine gene polymorphism in asymptomatic and symptomatic patients which may offer a ray of hope of containing this simmering pandemic.

3. Conclusion:

The genetic make-up of the Indian population is likely modulating immunopathology associated with COVID-19. Cytokine polymorphisms prevalent in the Indian population seem to mellow down the cytokine storm which may be responsible for the lower rate of severe illness and mortality. However, further genetic epidemiology studies are required to substantiate the hypothesis.

Declarations

Funding: Not applicable

Conflicts of interest/Competing interests: Shukla DAS, Chhavi GUPTA, Naseem AKHTER, Charu JAIN, Sidharth SONTHALIA, Saif AHMAD and Sajad Ahmad DAR have no conflicts of interest to declare that are relevant to the content of this article.

Ethics approval: Not applicable

Consent to participate: Not applicable

Consent for publication: Not applicable

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