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# IS THE HOST GENETICS RESPONSIBLE FOR VARIED PRESENTATION OF COVID-19?

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## ABSTRACT

Since COVID-19 caused by SARS CoV-2 began in Wuhan China in December, 2019, the virus is rolling on with all its might with changing modalities and infectivity across continents with more than 86 million confirmed infection and more than 1.8 million deaths. It is more worrying that the strain isolated in the UK and South Africa recently has been found to be 70% more infectious. The severe state of COVID-19 has been correlated with advanced age, diabetes, hypertension and other chronic diseases, nevertheless younger patients and even children are sometimes getting severe infection with mortality. This is sometimes unexplained. This has been widely researched and addressed with postulated genetic makeup, their blood group, immune status of the persons. The host genome, ethnicity, innate and adaptive immune response regarding SARS CoV-2 has been studied very extensively. So this review tries to look at the different insight of the genetics and its manifestations regarding severity of COVID-19, which might subsequently hold its predictability and measure to be adopted.

**KEYWORDS:** COVID-19, Host genetics, ACE-2, TMPRSS2, Immune Response.

## INTRODUCTION

The COVID-19 has so far affected more than 200 countries in the whole world despite having varied postulations of its endurance. The pandemic declared by WHO on March 11, 2020 is still on and with second surges in many places. As of 8th January, 2021 the total infected persons has exceeded 86 million in the world and the total number of deaths has culminated to more than 1.8 million.[1] Such devastating is the impact of the illness that not only has it affected the health sector also the educational, financial and all other spheres of human lives are perturbed with this dangerous virus. Since the outset in Wuhan, China in December-2019, researchers and clinicians are truly baffled with the behavior of this novel corona virus. Some risk factors like old age, diabetes, heart disease etc has been related as reasons for increased susceptibility and severity of COVID-19. Interestingly though, some young healthy people also experience severe illness when they get COVID-19 for reasons which are yet unknown. People vary in their susceptibility to infectious disease and variation in the human genetic get up plays an important role in determining this.[2] Host genetic variations is established as a component regarding pathogenesis of EBV viruses and HIV in a similar way. Deficiency of toll like receptor (TLR) signaling have been associated with herpes virus encephalitis.[3,4,5,6] Severe responses like those seen in other illnesses such as influenza could be also caused by genetic difference between individuals and as such the genetic study of human and corona virus might reveal important clues.[7,8] Keeping all these in mind, this review has been written as an update regarding the host genetics, their susceptibility and clinical manifestations of COVID-19.

### Sars-cov-2

Corona viruses are enveloped, positive sense, single stranded viruses with a crown like appearance under the electron microscope due to the presence of spike glycoproteins on the envelope. They contain the largest genome amongst RNA viruses.[9,10]

SARS COV-2 belong to the *Betacoronaviruses* genera based on its phylogenetic relationship with other Corona viruses such as SARS CoV and MARS CoV.[11,12] Genomic characterization has shown that probably bats and civets are the gene source of Alpha Cov's and Beta Cov's. An intermediate animal host between horse shoe bats and humans has yet not been identified as well as its transmission route in the CoV-2 pandemic.[13] Though most postulated hypotheses is that the virus acquired one or several mutations which allowed it to cross species barriers and infect human cell sometime in autumn 2019,

a few months before the beginning of the current pandemic.[14]

**Clinical presentation of COVID-19**

Presentations of COVID-19 is variable ranging from asymptomatic/ mild symptoms to severe illness and mortality. The commonest symptoms being fever, cough, sore throat, anosmia, respiratory distress and sometimes diarrhea. Symptoms may develop starting from 2 days to 2 weeks following exposure to virus. Mean incubation duration ranges from- 5.1-11.5 days. The frequency of asymptomatic infections has not yet been determined now. However different studies say it to be 60-80%.[15] The CDC report divided the clinical manifestation of the disease by its severity.[16]

**Mild-disease:** Symptomatic patients without evidence of pneumonia or hypoxia.
**Moderate disease:** Symptomatic patients with pneumonia, mild to moderate disease occurs in 81% of cases.
**Severe disease:** Dyspnea, respiratory frequency 30/min or over, Blood oxygen saturation (Spo2) < (93%), PAO2/F102 ratio of P/F and percentage of oxygen supplies, <300, Lung involvement of 50% which occur in 14% of cases.
**Critical disease:** Respiratory failure, Septic Shock, and/ or multiple organ dysfunction (MOD) or multiple organ failure (MOF) in 5% of cases.

**Host-Genetics and Susceptibility of COVID-19 patients**

The Human genome is made up of 6.4 billion nucleotides which are individually positioned in the human DNA denoted by the letters "A"T"C" and "G". In comparison the SARS-COV-2 Genome is much smaller with only about 2900 Nucleotides; although corona viruses possess the largest genomes among all known RNA viruses.[17,18,19,20] Genotyping is the technology that detects small variations in the genetic sequence, known as single nucleotide polymorphism, that can lead to physical difference making us unique with pathological changes which lead to disease. Human genome genotyping has given rise to the fields of pharmacogenetics and personalized medicine. It also allow the study of individual predisposition to develop certain disease, the disease severity and the response to treatment.[21]

COVID-19 symptoms range from very mild to severe. To understand the individual variability in the response to SARS-CoV-2 infection, genotyping can be useful. Polymorphism or variation in the Human Leukocyte Antigen (HLA) on the surface of the human cell have been shown to play a role in the spread and severity of COVID-19. Additionally blood group variants have been associated with the development of COVID-19. A study in China found particular variants (SNP rs 505922) in the ABO gene that determines the blood group and COVID-19 susceptibility and a second report from a genome wide association study (GWAS) conducted in Italy and Spain found an association between blood group types on severity of COVID-19. The meta-analysis of around 8.5 million SNPS single nucleotide polymorphism revealed that some variants may help to identify severe COVID-19 cases and as to this study people with blood group "O" have a protective effect while blood group "A" has a higher risk of being severely affected.[21]

In a preprint posted to med Rxiv on 2nd June 2020, research describe a GWAS of sample from 1610 hospitalized patients with COVID-19 and 2505 healthy controls. The authors identified variants in two regions- the locus that encodes blood type and a multi gene cluster on chromosome 3 that were linked to respiratory failure during SARS-CoV-2. For the locus that encodes for blood type, blood group "A" was at a higher risk for respiratory failure while blood group "O" seemed to be protective. The odds for those with types "A" to be hospitalized with severe respiratory symptoms were nearly 1.5 times that for other blood types and those with type "O" had almost 2/3 PDS- odds of being hospitalized as those with other blood type.[22,23]

The other genomic region shows up on the human chromosome 3 and contain several genes of interest. One is SLL6A20 which encodes an amino acid transporter that interact with ACE2, the main receptor that SARS-CoV-2 uses to get into human cells. Two other genes in the cluster encodes immune system related chemokine receptor 6 and the CC motif chemokine receptors. Both proteins play a role in T cell differentiation and recruitment in influenza viral infection. So this region has been related to the COVID-19 as well.[22]

In the earlier SARS CoV epidemics S (spike) protein was shown to facilitate cellular entry by binding to angiotensin converting enzyme 2 (ACE-2) present on target cells[24] In addition the cellular serine protease transmembrane protease Serine-2 (TMPRSS2) is needed for priming of S protein and subsequent fusion of the SARS CoV with host cell membrane.[25,26] Over expression of ACE2 enhances disease severity in mice upon SARS-COV-2 infection, indicating its importance in viral entry.[27] Several studies had shown that S protein of SARS-CoV-2 also uses ACE2 and TMPRSS 2 for cell-entry and has much higher affinity than the early SARS CoV-S protein and also ACE2 is highly expressed by type II alveolar epithelial cells which can be related to pulmonary symptoms.[28,29,30,31]

**Ace 2 and Tmprss 2**

Earlier it was mentioned that SARS-CoV-2 infection depends on host cell factors- angiotensin converting enzyme-2 (ACE 2) for entry into cells. The host transmembrane serine protease TMPRSS 2 for SARS-COV-2 spike (S) protein priming ACE-2 encoded on the-X-chromosome catalyzes the conversion of angiotensin II to angiotensin (1-7) which acts as a vasodilator and exerts important modulatory effects on cardiovascular

system. TMPRSS2 is a key gene in prostate cancer. The distribution of ACE2 expression has recently been investigated by single cell RNA sequencing and the expression of both, ACE2 and TMPRSS 2 are likely to dictate SARS-CoV-2 tissue tropism.[22]

**ACE 2 polymorphism**

Yuan hou et al 2020 investigated genetic susceptibility to COVID-19 by examining DNA polymorphism in ACE2 (OMIM 300355) and TMPRSS (OMI 602060) genes.[22] A total of 437 non synonymous single nucleotide variants (SNV) in the protein coding regions of ACE 2 and TMPRSS 2 from three database from 9 geographical areas were studied by applying polyphen 2 and CADD (combined annotation dependent depletion) scores, 63 potentially deleterious variants in ACE2 and 68 deleterious variants in TMPRSS2 were identified. African/African-American (AFR) and Non-Finnish European (EUR) populations had deleterious variants of ACE2 occuring in 39% and 54% respectively. Prevalence of deleterious variants among Latino/ Admixed American, East Asian (EAS) Finnish (FIN) and South Asian population (SAS) is 2-10% while Amish (AM) and Ashkenazi Jewish (AJJ) do not carry such variants in ACE2 coding. These ACE2 variants located in the Angiotensinogen AGT- ACE2 interaction surface which is anticipated to influence rennin angiotensin system (RAS) function.[22]

So these comparative genetic analysis show that ACE2 genomic variants may play important roles in the susceptibilities to COVID-19 and its associate of cardiovascular conditions by altering AGT-ACE2 pathway. Additionally different polymorphisms may explain susceptibility and even outcome in different ethnic populations and also the fact that ACE2 is localized to XP22.2 explain the observed male associated risk.

**Tmprss 2 polymorphism**

TMPRSS2 enzyme activity is important for corona virus spread and pathogenesis in the infected host.[32] The analysis by Hou et al indicated 4% of non synonymous variants of TMPRSS 2 are stop-gained mutations and carried by AFR and EUR with low alveolar frequency. Mean while 35% and 39% of deleterious variants in TMPRSS2 coding regions are carried by the AFR and EUR population.[22] So these polymorphism difference in population offer potential explanation for different genetic susceptibility also because TMPRSS2 is located on 21/q22.2. It could be speculated that individuals with Down syndrome would be in high risk for COVID-19 infection. Additionally, oncological role of TMPRSS2 may be linked to poor outcome with COVID-19 as well.[33] Shuler et al showed that TMPRSS expression is highest in ciliated cells and Type I alveolar epithelial cells and increases with age in hosts. So this correlates well with relative protection of infants and child**.** A unique polymorphism in TMPRSS like p.Val160Met (rs1239760) may provide potential explanations for different genetic susceptibility to COVID-19.[19]

**Innate immune response to sars cov-2**

The innate immune response works against a wide range of pathogens particularly viruses. Specifically the interferon takes an important part which as we all know is the first line of defence against pathogens particularly viruses. The innate immune response is crucial. The interferon in general (IFN I, IFN III) activate hundreds of antiviral proteins and prime adaptive immune response. As for corona viruses they are recognized by two groups of pattern recognition receptors, namely the toll like receptors (TLRS) and the retinoic acid inducible gene 1 (RIG-1) like receptors (RTRS).[34]

These receptors in turn induce downstream signaling and results in production of IFN Type I & III and pro-inflammatory cytokines. The TLRS for SARS CoV so far implicated are TLR 3, -4 and -7. TLR 3 recognizes double standard RNA (dsRNA) the TLR 4 usually recognize lipopolysaccharide from gram negative bacteria, SARS COV genome activates TLR 7.[35]

TLR 7, TLR 3 and TLR 4 activate the adaptor inducing INF-β; whereas myeloid differentiation primary response (MY D88) is the adaptor used by all other receptors. Several studies have suggested that infection of the TLRS MY-D88 with SARS Cov- causes viral replication, enhanced pathology in the lungs and increased morbidity. This might suggest that lack of control of viral replication could lead to exaggerated immune response and immune pathology during later infection.[36,37,38,39]

Additionally corona viruses are also recognized by RLRs. They are cytosolic RNA sensors where RIG-1 short ds RNA with 5 triphosphate and Melanoma differentiation associated protein-5 (MDAs). MDAs is protective in mice infected with the murine coronavirus mouse hepatitis virus (MHV).[40] Furthermore several authors implicated neutrophil extra cellular trap (NET) in organ damage, pulmonary pathology, microthrombosis and mortality in COVID-19.[41,42]

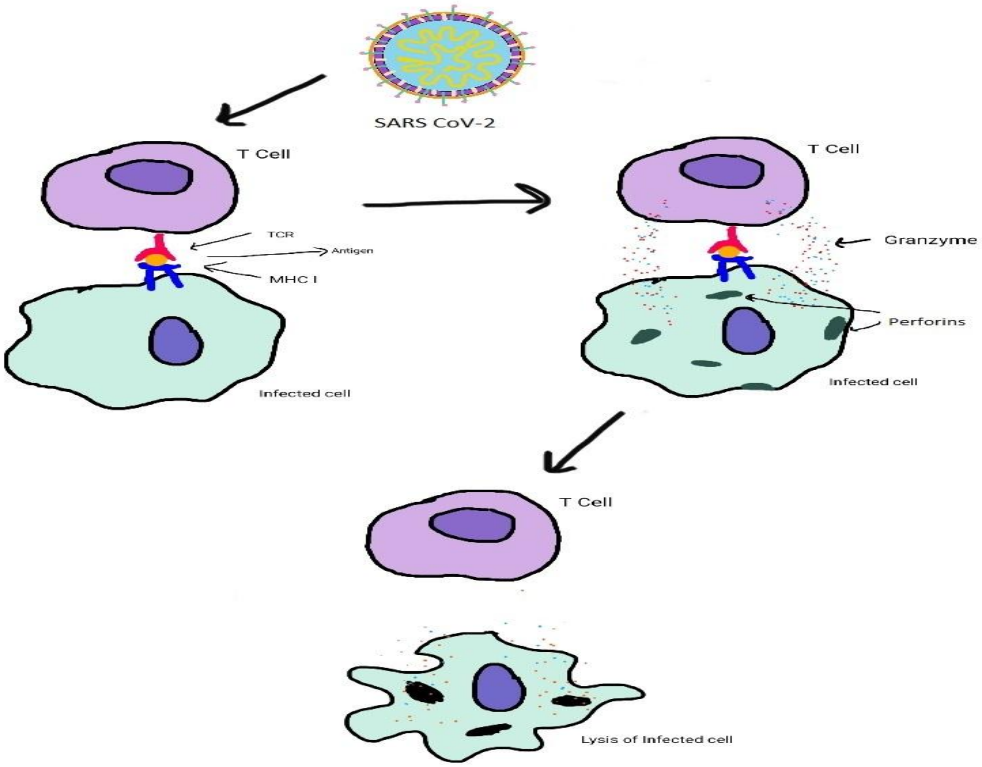
Although interferons are considered most important effector of innate immune system, a recent study had demonstrated that SARS CoV-2 induces significantly less alveolar cell IFN and ISG expression compared to influenza and respiratory syncytial viruses.[43]

**Adaptive immune respone**

The transition between innate and adaptive immune response is critical for the clinical progression of SARS CoV2 infection. The cell mediated immune response plays a crucial role in antiviral immunity and development of robust CD 8 and CD4 T cell responses, which correlate well with positive outcome during SARS-COV infection. This is a bit poorly understood as it might lead either to a development of a protective

response or an exaggerated inflammatory response. The protective response is T-cell dependent with CD4 helping B cells, whose job is processing antibodies.[44, 45] The immune response leads towards production of specific antibodies and cytotoxic CD8 cells capable of eliminating infected cells.

Fig. Adaptive immune response by CD8+ T cells




Clinical investigation of severe COVID-19 patients consistently report neutrophilia and lymphopenia with significantly decreased CD4 + T cells and decreased IFN-γ expression as well as reduced number of regulatory and memory T cells.[46,47,48]

Additionally increased levels of plasma pro inflammatory cytokines such as interleukin (IL)-Iβ,IL-6,IL-8 and Tumor necrosis factor alpha– (TNF) are seen in severely affected COVID-19 patients, which is indicative of a cytokine storm and subsequent ARDS development.[49,50] Cytotoxic T cells are important for clearing respiratory virus and providing long term protection which should be well controlled for prevention of pathological consequence.[51,52] The pathological features of COVID-19 resemble those of SARS and MERS both of which are thought to be largely caused by immune dysregulation rather than direct pathology induced by high viral load similarly for SARS COV-2.[53,54]

Quite a number of studies had demonstrated that SARS COV-2 initiate an antibody response and sero conversion is observed between 10 and 14 days post infection.[55,56,57,58,59] A Chinese study in Chongqing region reported simultaneously or sequential sero conversion ( IgM & IgG) against spike protein of SARS COV-2. It is of interest that IgG titres were higher in patients with severe COVID-19 compared to the non-severe cases.[60] However SARS COV-2 isolated from critically ill patients can be neutralised by sera from severely affected patient, which favours the COVID-19 development of therapeutic neutralizing antibodies. The efficacy and longevity of immunity to SARS COV-2 is highly dependent on the rate by which the virus alters its composition (which is the mutation rate).

Fig. Adaptive immune response in CD4+ T cells and B cells

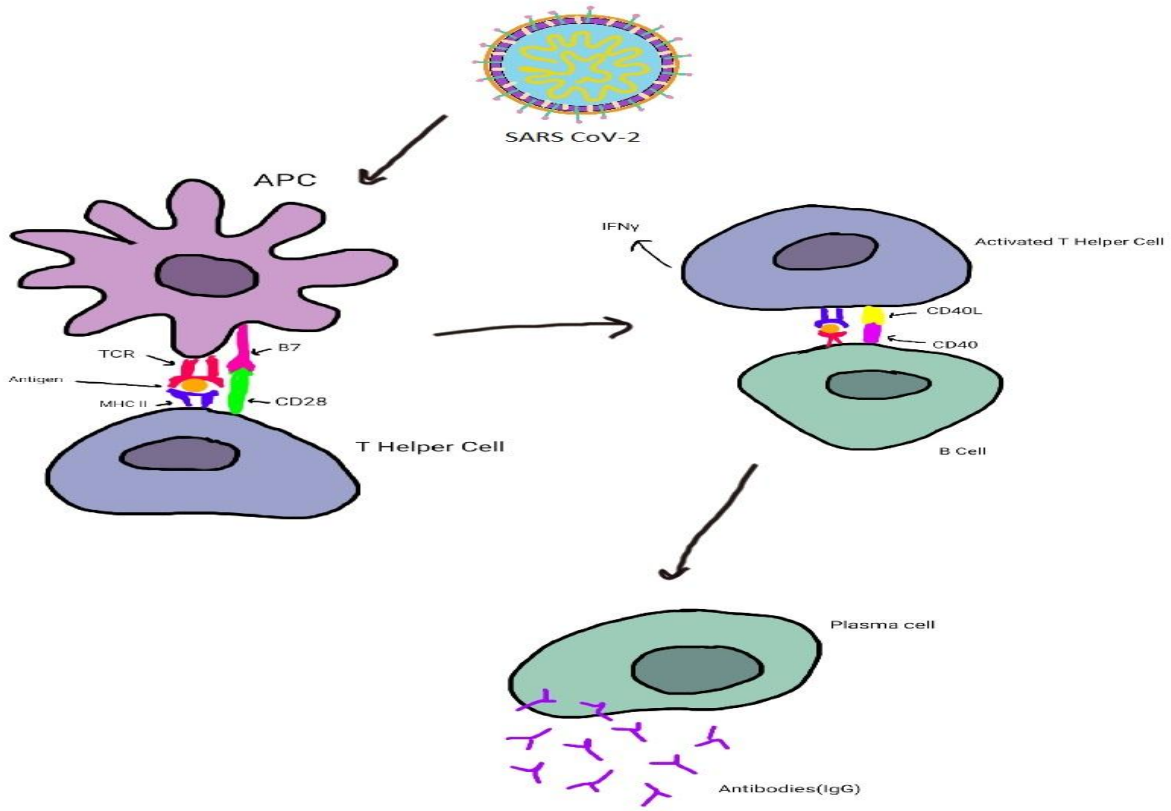
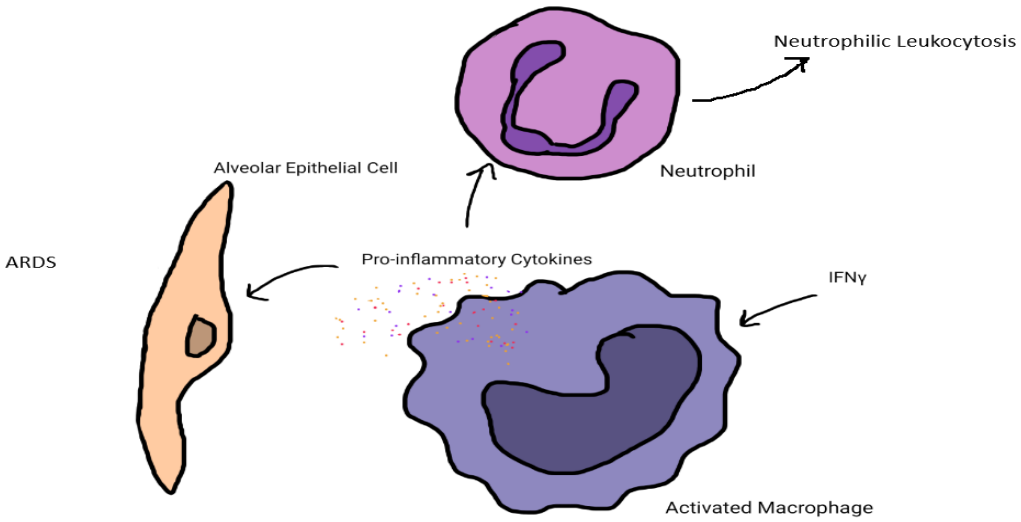



Fig. Effects of Cytokine dysregulation




Pro-Inflammatory Cytokines released by macrophages to cause cytokine storm:

TNF-α
IL-1
IL-6
IL-17

**Human inborn errors of immunity could be a determining factor of contracting corona virus infection**

Since human inborn errors of immunity can alter the course of different viral infection, so it is expected that any genetic variant which gives rise to dysregulated or exaggerated immune response may give rise to the severe manifestation of COVID-19. It is proposed that deficient/decreased Type 1 IFN production may give rise to severe disease course in SARS COV infection from many studies [61,62,63] and population studies have identified single nucleotide polymorphism (SNPS) and susceptibility to SARS CoV disease progression [64,65]. So also the replication is inhibited by giving exogenous Type 1 IFN. So it is assumed that any genetic mutation regarding dysregulation of Type 1 IFN predispose to COVID-19 disease progress. Also the clinical outcome is influenced by alteration of PRR and immune signaling pathways involved in recovery of SARS-COV-2. Also the effect or function of Type 1 and 2 if Janus Kinase (JAK) signal transporter and activator of transcription stat pathway.

Activation of the complement system is thought to contribute to the lung pathology of COV-2.[66,67] So targeting complement protease (C5) inhibition is postulated as an effective therapeutic intervention as Mannose binding lectin (MBL) is a recognition molecule. So MBL, despite its presence in serum, causes increased susceptibilities for SARS COV patients. In several studies it has been found after comparing CVID (common variable immunodeficiency) and pure agammaglobulinemia; that agammaglobulinemia has milder disease but CVID affected persons experience more severe disease suggesting immune dysregulation with abnormal B immune cell phenotype and excessive IL-6 production in COVID-19 patients.[68]

Also of the T cells role in protecting COVID-19 severity is stated Severe T cell lymphopenia appears to increase risk of severe viral infection. But conclusive evidence for T cell are being assessed.[69]

For COVID-19 pathogenesis and pathways, the potential susceptibility gene might be involved in immune dysregulation, auto inflammation and pathways in cytokine and TLR signaling cascade especially those associated with IL-1 and IL-6 synthesis and production. Genetic variation may be anticipated to aggravate coagulopathy and thrombotic events.[70,71,72]

As we know the HLA (Major Histocompatibility Complex Antigen loci) influences host susceptibility to infectious disease, No conclusive evidence for COVID-19 is yet there.[73] But it is predicted that variants in the molecule resulting in decreased binding specifities for SARS CoV-2 pedtides would confer a more severe COVID-19 disease.[74]

**Therapeutics**

No specific therapeutic protocols for SARS COV-2 has been formulated but some therapeutic trials with antivirals like Remdesivir, Lopinavir, Ritonavir and repurposive drugs like Chloroquine, Hydroxychloroquine, Ivermectin and IFN β has been used. Remdesivir so far[75,76,77] has been found to have the most promising antiviral activity against COVID-19 and other Coronaviruses like SARS and MARS. Although initially no significant results were found, larger trials of Remdesivir showed significant shortening of the hospital stay in severely affected COVID-19.[78,79]

Also trials with the repurposive drugs like Chloroquine/Hydroxychloroquine with or without Macrolides has not been found to have significant outcome but Hydroxychloroquine is still being evaluated by WHO. Drugs like cellular protease inhibitor Camostat Mesylate used in Japan for pancreatitis and post-operative esophagitis is on evaluation in Denmark.[80,81,82] The agents blocking either IL-1 or IL-6 like Anakinra and Tocilizumab respectively are being used in severely affected COVID-19 patients has considerable importance due to the well-established role of the cytokines in immunopathology and is associated with poor clinical outcome.[47] Different manufacturers like Pfizer Biontech and Oxford Astrazeneca has produced and sent their vaccines to the UK and other European countries. Also by now, USA, Canada and other countries are primarily authorizing different vaccines. We have to wait for another couple of months to know the outcomes and potential effectiveness of these vaccines.

## CONCLUSION

COVID-19 is still a raging bull across the continents. The host genetics is a very important issue in predicting and adopting strategy for severity of the disease itself. The fast changing nature of the virus due to its alteration in its genome is making us quite intrigued. Even some strains in the UK and South Africa are 70% more infectious but some patients having varied blood groups with its protectivity, their HLA antigen getup with ACE-2 and TMPRSS-2 and their interactions correlate well with Covid outcome. The observations and research must go on.

## REFFERENCES

1. WHO Coronavirus Disease (Covid-19) Dashboard-UB, 2021; 01: 08.
2. Houldcrof CJ, Kellam P. Host genetic of Epstein-Barr infection latency and disease. Rev. Med. Virol, 2015; 71-84.
3. Chapman SJ, Hill AV. Human genetic susceptibility to infectious disease. Nature Reviews Genetics, 2012; 13: 175-188.
4. Dean M, Carrington M, Winkler C, et al. Genetic restriction of HIV-1 infection and progression to AIDS by a deletion allele of the CKR5 structural gene. Hemophilia Growth and Development study, Multi- center AIDS Cohort study, Multicenter

Hemophilia Cohort study, San Francisco City Cohort, ALIVE study. Science, 1996; 273: 1856-1862.
5. Samson M, Libert F, Doranz BJ, et al Resistance to HIV-1 infection in Caucasian individuals bearing mutant alleles of the CCR-5 chemokine receptor gene. Nature, 1996; 382: 722-725.
6. Netea MG, Wijmenga C, O, Neill LA. Genetic variation in Toll-like receptors and disease susceptibility. Nature Immunology 13: 535-542.
7. Wang Z, Zhang A, Wan Y, Liu X, Qiu C, Xi X, et al. Early hypercytokinemia is associated with interferon-induced transmembrane protin-3 dysfunction and predictive of fatal H7N9 infection. Proc Nat1 Acad Sci USA, 2014; 111: 769-74.
8. Everitt AR, Clare S. Pertel T, John SP, Wash RS, Smith SE, et al. IFITM3 restricts the morbidity and mortality associated with influenza. Nature, 2012; 484: 519-23.
9. Woo PC, Huang Y, Lau SK, Yuen KY. Coronavirus genimics and bioinformatics analysis. Viruses, 2010; 2: 1804-20. doi: 10.3390/v2081803
10. Woo PC, Lau SK, Lam CS Lau CC, Tsang AK, Lau JH, et al. Discovery of seven novel Mammalian and avian coronaviruses in the genus deltacoronavirus supports bat coronaviruses in the alphacoronavirus and betacoronaviruses and avian coronaviruses as the genesource of gammacoronaviruses and deltacoronaviruses. J Virol, 2012; 86: 3995-4008. doi: 10.1128/ JVI.06540-11
11. Lu R, Zhao X, Li J, Niu P, Yang B, Wu H, et al. Geneomic characterisation and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding. Lancet, 2020; 395: 565-74. doi: 10.1016/ S0140-6736(20)30251-8
12. Zhou P, Yang XL, Wang XG, Hu B, Zhang W, et al. A pneumoinia outbreak associated with a new coronavirus of probable bat origin. Nature, 2020; 579: 270-3. doi: 10.1038/s41586-020-2012-7.
13. Li X, Zai J, Zhao Q, Nie Q, Li Y, Foley BT, et al. Evolutionary history, potential intermediate animal host, and cross-species analyses of SARS-CoV-2, J Med Virol, 2020; 92: 602-14. doi: 10.100/jmv.25731.
14. Andersen KG, Rambaut A, Lipkin WI, Holemes EC, Garry RF. The proximal origin of SARS-CoV-2. Nat Med, 2020; 26: 450-2. doi 10.1038/s41591-020-0820-9
15. Thevrajan I, Buisng KL, Cowie Bc Clinical presentation and management of covid-19 Med Jaust, 2020; 213(3): 134-139.
16. Management of patients with confirmed 2019-Ncov/CDC. Updated December 8, 2020.
17. Coronavirus Genomic and Bioinformatics Analysis. Woo.P.C.Y, Huang Y, Lau. S. K. P, Yuen. K-Y. Viruses, 2020; 2: 1804-1820. doi: 10.3390/v2081803
18. Woo, P.C.; Lau, S.K.; Lam, C,S; Lai, K.K.; Huang, Y.; Lee, P.; Luk, G.S.; Dyrting,K.C.; Chan, K.H.; Yuen, K.Y. Comparative analysis of complete genome sequences of three avian coronaviruses reveals a novel group 3c coronavirus.J. Virol, 2009; 83: 908-917.
19. Mihindukulasuriya, K.A.; Wu,G.; St Leger, J.; Nordhausen, R.W.; Wang, D. Identification of a novel coronavirus from a beluga whale by using a panviral microarray. J. Virol, 2008; 82: 5084-5088.
20. Lai, M.M.; Perlman, S.; L.; A. Coronaviridae. In Fields virology, Knipe, D.M.; Howley, P.M., Eds.; Lippincott Williams and Wilkins: Philadelphia, PA.USA, 2007; 5: 1305-1335.
21. QBRI Insights: Influence of Host and Viral Genome Variation on COVID-19. Vaikat NN, Asfar SS, Masbour NK, et al, 2020.
22. New insights into genetic susceptibility of COVID-19: an ACE2 and TMPRSS2 polymorphism analysis. Hou Y, Zhao J, Martin W, Kallianpur A, Chung K M, Jehi L, 2020; 18: 26. https://doi.org/10.1186/s12916-020-01673-z
23. Shirato k, Kawase M, Matsuyama S, Wild-type human coronaviruses prefer cell-surface TMPRSS2 to endosomal cathepsins for cell entry. Virology, 2018; 517: 9-15.
24. Matsuyama S, Nagata N, Shirato K, Kawase M, Takeda M, Taguchi F. Efficient activation of the sever acute respiratory syndrome coronavirus spike protein by the transmembrane protease TMPRSS2. J Virol, 2010; 84: 12658-64. Doi: 10.1128/JVI.01542-10
25. Shulla A, Heald-Sargent T, Subramanya G, Zhao J, Perlman S, Gallagher T. A transmembrane serine protease is linked to the severe acute respiratory syndrome coronavirus receptor and activates virus entry. J Virol, 2011; 85: 873-82. Doi: 10.1128/JVI. 02062-10
26. Yang XH, Deng W, Tong Z, Liu YX, Zhang LF, Zhu H, et al. Mice transgenic for human angiotensin-converting enzyme 2 provide a model for SARS coronavirus infection. Comp Med, 2007; 57: 450-9
27. Wrapp D, Wang N, Corbett KS, Goldsmith JA, Hsieh CI, Abiona O, et al. Cryo-EM structure of 2019-nCoV spike in the prefusion conformation. Science, 2020; 367: 1260-3. Doi: 10.1126/science.abb2507
28. Hoffmann M, Kleine-Weber H, Schroeder S, Kruger N, Herrler T, Erichsen S, et al. SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. Cell, 2020; 181: 271-80.e8. doi: 10.1016/j.cell.2020.02.052
29. Lan J, Ge J, Yu J, Shan S, Zhou H, Fan S, et al. Structure of the SARS-CoV-2 Spike receptor-binding domain bound to the ACE2 receptor. Nature, 2020; 581: 215-20. Doi: 10.1038/s41586-020-2180-5
30. Kirchdoerfer RN, Wang N, Pallensen J, Wrapp D, turner HI, Cottrell CA, et al. Stabilized coronavirus spike are resistant to conformational change induce

by receptor recognition or proteolysis. Sci Rep, 2008; 8: 15701. Doi:10.1038/s41598-018-36918-8
31. Yu J, Ouyang W, Chu MLK, Xie C, SARS-CoV-2 transmission in patients with cancer at a tertiary care hospital in Wuhan. China JAMA Oncol, 2020. https://doi.org/10.101/jamaoncol.2020.0980
32. Schuler A, Habermann C, Plosa J, et al. Age- related expression of SARS-CoV-2 primining protease TMPRSS2 in the developing lugh, 2020. https://doi.org/10.1101/2020.05.22.111187
33. Li Y, Chen M, Cao Y, Zhu Y, Zheng J, Zhou H. Extraordinary Gu- rich single- strand RNA identified from SARS coronavirus contributes an excessive innate immune response. Microbes infect, 2013; 15: 88-95. doi: 10.1016/j.micinf.2012.10.008
34. Kawasaki T, Kawai T. Toll-like receptor signalling pathways. Front Immunol, 2014; 5: 461. doi: 10.3389/fimmu.2014.00461
35. Totura AL, Whitmore S, Schafer A, Katze MG, Heise MT, et al. Toll-like receptor 3 signaling via TRIF contributes to a protective innate immune response to severe acute respiratory syndrome coronavirus infection. mBio, 2015; 6: e00638-15
36. Gralinski LE, Menachery VD, Morgan AP, Totura AL, Beall A, Kocher J, et al. Allelic variation in the toll-like receptor adaptor protein Ticam2 contributes to SARS –coronavirus pathogenesis in mice. G3, 2017; 7: 1653-63. Doi: 10.1534/g3.117.041434
37. Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, et al. Clinical characteristics of 138 hospitalized patients with 2019. novel coronavirus-infected pneumonia in Wuhan, China. JAMA, 2020; 323: 1061–9. doi: 10.1001/jama.2020.1585
38. Zalinger ZB, Elliott R, Rose KM,Weiss SR. MDA5 is Critical to Host defense during infection with Murine Coronavirus. J Virol, 2015; 89: 12330-40. Doi 10.1128/JVI.01470-15
39. Barnes BJ, Adrover JM, Baxter-Sroltzfus A, Borczuk A, Cools- Lartigue J, Crawford JM, et al. Targeting potential drivers of COVID-19: Neutrophil extracellular traps. J Exp Med, 2020; 217: e20200652. doi: 10.1084/jem.20200652
40. Zuo Y. Yalavarthi S, Shi H, Gockman K, Zuo M, Madism JA, et al. Neutrophil extracellular traps in COVID-19. JCI Insight, 2020; 5: 11. Doi: 10.1101/2020.04.30.20086736
41. Blanco-Melo D, Nilsson- Payant BE, Liu WC, Uhl S. Hoagland D, Moller R, et al. Imbalanced host response to SARS-Cov-2 drives development of COVID-19. Cell, 2020; 181: 1036-45.e9. doi: 10.1016/j.cell.2020.04.026
42. Channappanvar R, Zhao J, Perlman S, T cell-mediated immune response to respiratory coronaviruses. Immunol Res, 2014; 59: 118-28. doi. 10.1007/s12026-014-8534-z
43. Li CK, Wu H, Yan H, Ma S, Wang L, Zhang M, et al. T cell responses to whole SARS coronavirus in humans. J Immunol, 2008; 181: 5490-500. Doi: 10.4049/jimmunol.181.8.5490
44. Hsueh PR, Huang LM, Chen PJ, Kao CL, Yang PC. Chronological evolution of IgM, IgA, IgG and neutralisation antibodies after infection with SARS-associated coronavirus. Clin Microbiol Infect, 2004; 10: 1062–6. doi: 10.1111/j.1469-0691.2004.01009.x
45. Qin C, Zhou I, Hu Z, Zhang S, Yang S, Tao Y, et al. Dysregulation of immune response in patients with COVID-19 in Wuhan, China, China. Clin Infect Dis, 2020. Doi: 10.1093/cid/ciaa248. [Epub ahead of print]
46. Pedersen SF, Ho YC. SARS-CoV-2: a storm is raging. J Clin Invest, 2020; 130: 2202-5. Doi: 101172/JCI137647
47. Huang C, Wang Y, Li X, Ren I, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China, Lancet, 2020; 395: 497-506. Doi: 10.1016/S0240-6736 (20)300183-5
48. Long QX, Liu BZ, Deng HJ, Wu GC, Deng K, Chen YK, et al. Antibody responses to SARS-CoV-2 in patients with COVID-19. Nat Med, 2020; 26: 845–8. doi: 10.1038/s41591-020-0897-1
49. Channappanavar R, Fett C, Zhao J, Meyerhoiz DK, Perlman S. Virus specific memory CD8 T cells provide susbstantial protection from lethal severe acute respiratory syndrome coronavirus infection, J Virol, 2014; 88: 11034-44. doi: 10.1128/JVI.01505-14
50. Channappanavar R, Fehr AR, Vijay R, Mack M, Zhao J, Meyerholz DK, et all. Dysregulated type i interferon and inflammatory monocyte-macrophage responses cause lethal pneumonia in SARS-CoV-infected Mice. Cell Host Microbe, 2016; 19, 181-93. doi: 10.1016/j.chom.2016.o1.007
51. Wolfel R, Corman VM, Guggemos W, Seilmaier M, Zange S, Muller MA, et al. Virological assessment of hospitalized patients with COVID-2019. Natuer, 2020; 581: 465 -69.doi: 10.1038/s41586-020-2196-x
52. Hsueh PR, Hung LM, Chen PJ, Kao CL, Yang PC. Chronological evolution of IgM, IgA, IgG and neutralisation antibodies after infection with SARS-associated coronavirus. Clin Microbiol infect, 2004; 10: 1062-6. Doi 10.1111/j.1469-0691.01009.x
53. Zhu M. SARS immunity and vaccination. cell Mol Immunol, 2004; 1: 193-8.
54. Li G, Chen X, Xu A, Profile of specific antibodies to the SARS- associated coronavirus. N Engl J Med, 2003; 349: 508-9. Doi: 10.1056/NEJM200307313490520
55. Kellam P, Barclay W. The dynamics of humoral immune responses following SARS-CoV-2 infection and the potential. J Gen Virol, 2020. Doi: 10.1099/jgv.0.001439
56. Long QX, Liu BZ, Deng HJ, Wu GC, Deng K, Chen YK, et al. Antibody responses to SARS-CoV-2 in patients with COVID-19. Nat Med, 2020; 26: 845-8. Doi: 10.1038/s41591-020-0897-1
57. Ezekowitz RA. Role of the mannose-binding lectin in innate immunity. J Infect Dis, 2003; 187(2): S335–9. doi: 10.1086/374746

58. Ziegler T, Matikainen S, Ronkko E, Osterlund P, Sillanpaa M, Siren J, et al. Severe acute respiratory syndrome coronavirus fails to activate cytokine-mediated innate immune responses in cultured human monocyte-derived dendritic cells. J Virol, 2005; 79: 13800-5. Doi: 10.1128/JVI.79.21.13800-13805.2005
59. Law HK, Cheung CY, Ng HY, Sia SF, Chan Yo, Luk W, et al. Chemokine up-regulation in SARS-coronavirus-infected, monocyte-derived human dendritic cells. Blood, 2005; 106: 2366-7. Doi: 10.1182/blood-2004-10-4166
60. Hamano E, Hijikata M, Itoyama S, Quy T, Phi NC, Long HT, et al. Polymorphisms of interferon-inducible genes OAS-1 and MxA associated with SARS in the Vietnamese population. Biochem Biophys Res Commun, 2005; 329: 1234-9. Doi: 10.1016/j.bbrc.2005.02.101
61. He J, Feng D, de Vlas SJ, Wang H, Fontanet A, Zhang P, et al. Association of SARS susceptibility with single nucleic acid polymorphisms of OASI and MxA genes: a case-control study. BMC Infect Dis, 2006; 6: 106. Doi:10.1186/1471-2334-6-106
62. Sonc WC, FitzGerald GA. COVID-19, microangiopathy, hemostatic activation, and complement. J Clin Invest, 2020. Doi: 10.1172/JCI140183
63. Bosmann M. Complement activation during critical illness current findings and and outlook in the era of covid-19. Am J Respir Crit Care Med, 2020. Doi: 10.1164/rccm.202005-1926ED.
64. Kulasekararaj AG, Lazana I, Large J, Posadas K, Eagleton H, Villajin JL, et al. Terminal complement inhibition dampens the inflammation during COVID-19. Br J Haematol, 2020. Doi/ 10.1111/bjh.16916.
65. Ezekowitz RA. Role of the mannose –binding lectin in innate immunity. J Infect Dis, 2003; 187(1.2): S335-9. Doi: 10.1086/374746
66. Ip WK, Chan KH, Law Hk, Tso GH, Kong WH, et al. Mannose-binding lectin in severe acute respiratory syndrome coronavirus infection. J Infect Dis, 2005; 191: 1697-704. Doi: 10.1086/429631
67. Quinti I, Lougaris V, Milito C, Cinetto F, Pecoraro A, Mezzaroma I, et al. A possible role for B cells in Covid-19? Lesson from patients with agammaglobulinemina. JJ Allergy Clin Immunol, 2020. Doi: 10..1016/j.jaci.2020.04.013.
68. Dauly N. Potential impact of covid-19 in people living with HIV: experience from previous 21st century coronaviruses epidemics. AIDS, 2020; 34: 1255-6. Doi: 10.1097/QAD.0000000000002555
69. Beigel JH, Tomashek KM, Dodd LE, Mehta AK, Zingman BS, Kalil AC, et al. Remdesivir for the treatment of Covid-19 - preliminary report. N Engl J Med, 2020; doi: 10.1056/NEJMoa2007764.
70. Goldman JD, Lye DCB, Hui DS, Marks KM, Bruno R, Montejano R, et al. Remdesivir for 5 or 10 days in patients with severe Covid-19. N Engl J Med, 2020. doi: 10.1056/NEJMoa2015301
71. FOIPAN. Camostat Mesilate Tablets Information Sheet. Osaka: Ono Pharmaceutical CO., Ltd.
72. Matzaraki V, Kumar V, Wijmenga C, Zhernakova A. The MHC locus and genetic susceptibility to autoimmune and infection diseases. Genome Biol, 2007; 18: 76. Doi: 10.1186/s13059-017-1207-1
73. Shi Y, Wang Y, Shao C, Huang J, Gan J, Huang X, et al. COVID-19 infection: the perspectives response. Cell Death Differ, 2020; 27: 1451-4. Doi: 10.1038/s41418-020-0530-3
74. (FDA) USFDA. Corona Virus Disease 2019. (covid-19). (2020). Available online at: https://www.fda.gov/emergency-preparedness-and-response/ counterterrorism-and-emerging-threats/coronavirus-desease-2019-covid-19 (accessed December, 2020; 6.
75. EMA. Coronavirus Disease (Covid-19). (2020). Avilable online at: https://www.ema.europa.eu/en/human-regulatory/overview/public-health-threats/coronavirus-disease-covid1-19, 2020; 15.
76. WHO. "Solidarity" Clinical Trial for covid-19 Treatments. (2020). Available online at: https://www.who.int/emergencies/disease/nobel-coronavirus-2019-non/solodarity-clinical- trial-for-covid-19-treatment, 2020; 10.
77. Beigel JH, Tomashek KM, Dodd LE, Mehta AK, Zingman BS, Kalil AC, et al Remdesivir for the treatment of Covid-19-prelimminary report. N Eng J Med, 2020. doi: 10.1056/NEJMoa2007764.
78. Goldman JD, Lye DCB, Hui DS, Marks KM, Bruno R, Montejano R, et al, Remdesivir for 5 or 10 days in patients with severe Covid-19. N EngL J Med, 2020. doi: 10.1056/NEJMoa2015301
79. FOIPAN. Camostat Mesilate Tablets information aheet. Osaka: Ono Pharmaceutical CO., Ltd.
80. Ramsey ML, Nuttall J, Hart PA. A phase ½ trial to evaluate the Pharmacokinetics, safety, and efficacy of NI-03 in patients with chronic pancreatitis study protocol for a randomized controlled trial on the assessment of camostat treatment chronic pancreatitis (TACTIC). Trials, 2020; 20: 501. Doi:10.1186/s13063-019-3606-y
81. Clinicaltrials.gov. The Impact of Camostat Mesilate on COVID-19 Infection (CamoCo-19). NCT04321096: Clinicaltrials.gov; (2020) Available online at https://clinicaltrials.gov/ct2/show/NCT04321096?term=Camostat$+$mesylate&draw=2&rank=1 (accessed December 15th, 2020).
82. Zhou Y, Vedantham P, Lu K, Agudelo J, Carrion R Jr., et al. Protease inhibitors targeting coronavirus and filovirus entry. Antiviral Res, 2015; 116: 76–84. doi: 10.1016/j.antiviral.2015.01.011